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

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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 cavitary 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 leukocyte count of 0.3×10^9/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 afebrile, the chest X-ray showed significant improvement, and the leukocyte count had increased to 3.1×10^9/liter with a normal differential and no evidence of leukemic blasts. She was discharged home in good condition on oral fluconazole. 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 leukocytes, 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 afebrile 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 cavitary 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 suppurative 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 fibrinous 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

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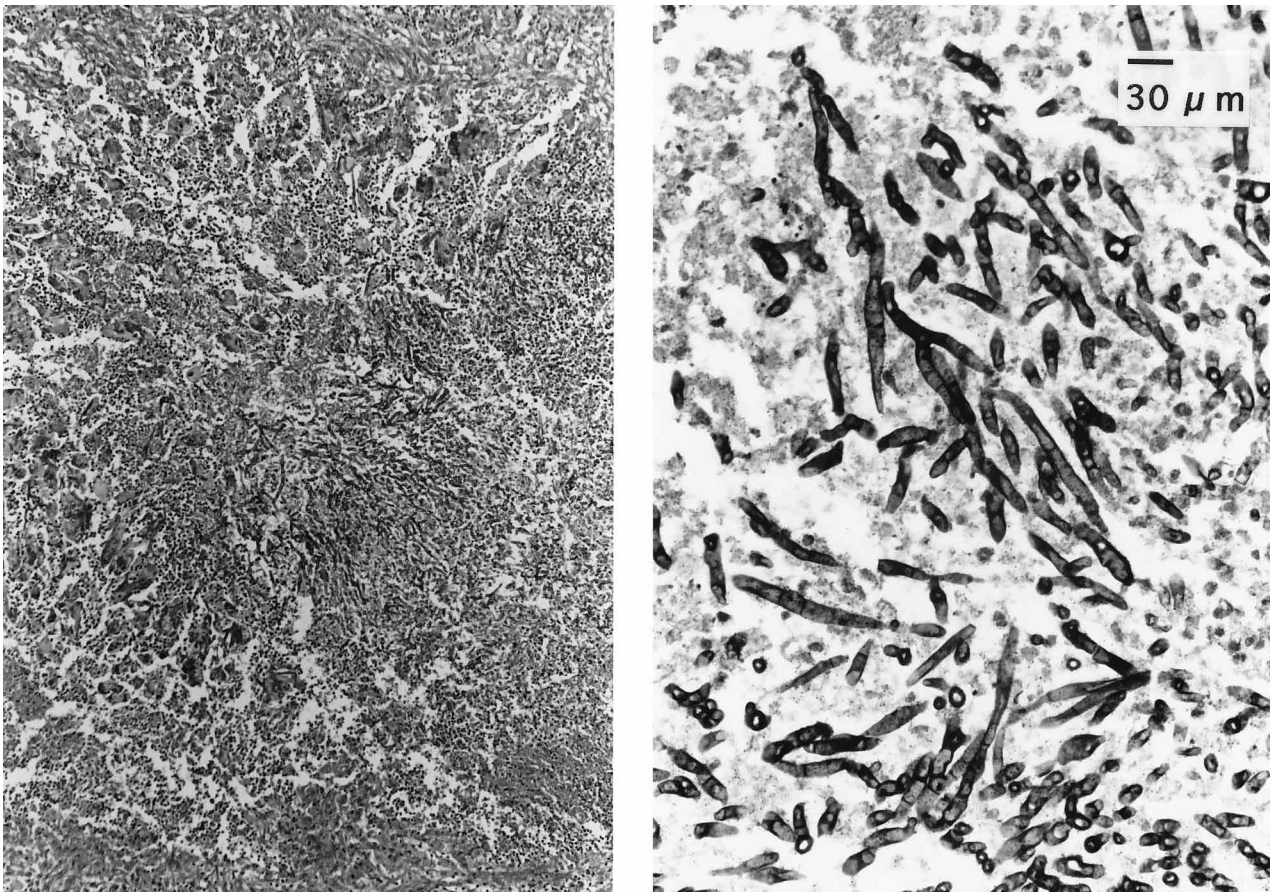

FIG. 1. Histology of nodular lung lesion showing suppurative granulomatous inflammation (PAS) (left panel) involving septate branching fungal mycelia (Grocott methenamine silver) (right panel). Magnification, ×40 (left) and ×400 (right).

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, which was thought to have been a result of laboratory contamination and was therefore not identified or saved. No bacterial or mycobacterial growth resulted from tissues obtained at autopsy. For fungal cultures, postmortem tissue specimens from pericardium, myocardium, endocardium, lungs, liver, spleen, and brain were chopped finely under aseptic conditions and inoculated onto antibiotic-free SDA plates. These were incubated at 30 and 37°C for 6 weeks. After 48 h, cultures of lung tissue and pericardium at both temperatures showed heavy pure growth of a white mold which became blue-green over the next 24 h. Colonies were radially sulcate, reaching 20 mm at 7 days at 30°C. The mycelium was white peripherally and grayish orange at the center of the colony, with dull gray-turquoise conidial masses. The surface was velutinous with floccose areas at the center and yellow-brown exudate. The reverse of the colony was yellow-brown, with no pigment production. Hyphae were hyaline, 1.9 to 2.5 mm wide, septate, and regular. Conidiophores were borne from surface hyphae, with stipes 100 to 200 μm long, smooth walled, and single or more commonly biverticillate. Divergent terminal metulae were of equal length, 12 to 15 μm long in whorls of three to five. Phialides were mostly 7 to 8 μm long, ampulliform, bearing well-defined chains of spherical to subspherical conidia 2.5 to 3.0 μm in diameter, with walls smooth or finely roughened (Fig. 2). The fungus 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-

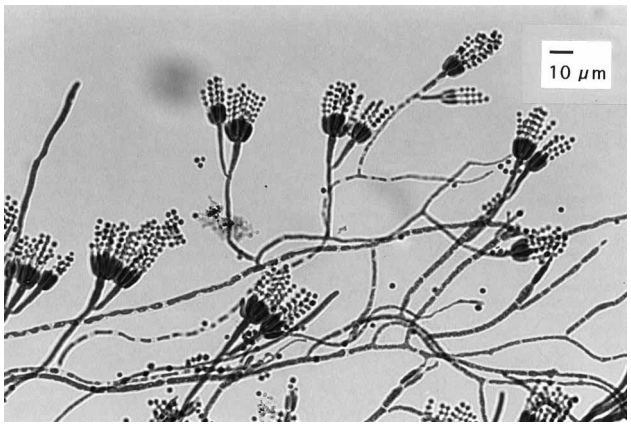

FIG. 2. Septate branching hyphae of *P. citrinum* showing ampulliform phialides and spherical conidia (lactophenol blue). Magnification, ca. ×100.

tizing esophagitis (5) and endophthalmitis (2), and *P. commune*, causing fungemia (6). *P. marneffei*, a dimorphic fungus in Southeast Asia, is reported to be the third most common opportunistic pathogen in patients with AIDS in Northern Thailand (12).

We believe that our patient died from a *P. citrinum* infection for the following reasons. (i) Although two cases of *C. incongruus* pneumonia and pericarditis have been reported previously (1, 14) and *C. incongruus* was isolated from an initial sputum culture, evidence to confirm that this was a true infection was lacking in our patient. (ii) Only a single colony of *C. incongruus* was isolated on the one occasion, despite repeated attempts to reculture this organism during the patient's treatment and from postmortem tissue. (iii) In contrast, not only was a *Penicillium* species cultured from the sputum, but *P. citrinum* was isolated in pure culture from both lung and pericardial autopsy tissue with histological confirmation of tissue invasion with numerous branching septate hyphae. (iv) Broad, aseptate or sparsely septate hyphae, said to be characteristic of tissue invasion with *C. incongruus* (7), were not found despite careful examination of all tissue sections.

This patient was immunocompromised and had chest X-ray findings compatible with fungal pneumonia. Despite receiving amphotericin B during her febrile episodes and oral fluconazole when afebrile and regenerating a normal bone marrow, our patient died from fungal infection. The apparent clinical response to antifungal therapy, as judged by resolution of fever and improvement in radiological findings, suggested that the patient was receiving appropriate antimicrobial therapy. While we recognize the current limitations of antifungal sensitivity testing methodology, the results of the postmortem in vitro sensitivity tests on the *P. citrinum* isolate may explain why this fungal infection persisted, and we speculate that the intermittent use of antifungal drugs in this patient may have contributed to the selection of a resistant strain. With the human immunodeficiency virus pandemic and the increasing use of more intensive myelosuppressive cytotoxic chemotherapy with or without bone marrow transplantation, immunocompromised 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).

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