**Pythium insidiosum** Pleuropericarditis Complicating Pneumonia in a Child with Leukemia

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We describe a 12-year-old boy with acute myeloid leukemia who developed pleuropericarditis while he was neutropenic and was receiving intravenously administered antibiotic and antifungal therapy for pneumonia. A KOH preparation of the purulent material from an extensive diagnostic and therapeutic pleuropericardial drainage procedure revealed multiple irregularly septate hyphae, and cultures yielded the organism *Pythium insidiosum*. After completing a 12-month course of intravenously administered liposomal amphotericin B (AmBisome; Fujisawa Healthcare) and itraconazole, the patient remained alive, in clinical remission, and symptom free.

*Pythium insidiosum* is a well-known funguslike plant and animal pathogen that is an emerging pathogen in humans, primarily in tropical and subtropical regions of the world [1, 2], and it has been reported only rarely in North America [3, 4]. Pythiosis usually presents in humans as cutaneous, subcutaneous, vascular, or ophthalmic disease. The organism is aquatic, produces motile zoospores, and has a strong tropism for skin, hair, and plant leaves. We report a case of pythiosis in a 12-year-old boy with acute myeloid leukemia who developed purulent pleuropericarditis while receiving intravenously administered antibiotics and liposomal amphotericin B (AmBisome; Fujisawa Healthcare) for an episode of prolonged fever, neutropenia, and pneumonia.

**Case report.** A 12-year-old boy, born in the United States to Pakistani parents, had acute myeloid leukemia (M4 myelomonocytic subtype) diagnosed in January 2001, after the onset of fever, lethargy, and bone pain. He had no prior medical or family history of note. Initial remission-induction therapy consisted of 4 courses of intensive chemotherapy, and complete remission was subsequently confirmed by bone marrow aspiration and lumbar puncture. Consolidation chemotherapy was completed on 3 May 2001. The patient was prescribed oral nystatin and trimethoprim-sulfamethoxazole for fungal and *Pneumocystis carinii* prophylaxis, respectively.

The patient presented to the emergency department of Memorial Sloan-Kettering Cancer Center (New York) on 8 May 2001, after he experienced onset of fever (temperature, 38.8°C), sore throat, and mild shortness of breath. Physical examination revealed pallor and a mildly erythematous throat but no clear focus of infection. A complete blood count revealed a hemoglobin level of 80 g/L, a total WBC count of $3 \times 10^9$ cells/L (absolute neutrophil count, $0.1 \times 10^9$ neutrophils/L), and a platelet count of 64 × 10^9 platelets/L. A chest radiograph demonstrated a small area of consolidation at the left base, consistent with pneumonia.

The patient was admitted to the hospital and started receiving broad-spectrum antibiotics intravenously, including ticarcillin-clavulanate, amikacin, and vancomycin. He was also given granulocyte-colony-stimulating factor, 5 μg/kg/day s.c. The occurrence of intermittent high fever spikes (maximum temperature, 40.0°C) and the persistence of neutropenia during the 10 days after admission necessitated several changes in antibiotic coverage. Daily therapy with liposomal amphotericin B, 3 mg/kg, was initiated on day 7 of hospitalization. A CT scan of the chest cavity obtained on day 10 of hospitalization revealed persistence of the left lower lobe infiltrate, which now had a nodule with a 5-mm diameter within the lobe, and a small, left-side pleural effusion. The results of successive cultures of blood, sputum, urine, and stool continued to be negative. The patient’s fever slowly dissipated as his neutropenia resolved, with the first absolute neutrophil count $>0.5 \times 10^9$ neutrophils/L documented on day 21 of hospitalization. He remained afebrile and symptom free after gradual removal of all antimicrobials, including liposomal amphotericin B.

A follow-up chest radiograph obtained on day 25 of hospitalization showed that, in addition to persistence of left lower lobe consolidation and left-side pleural effusion, a new and extensive air-fluid level within an enlarged pericardial sac had developed (figure 1). The patient was asymptomatic at this time, and he had no respiratory or cardiovascular abnormalities de-
tected at the time of physical examination. CT of the chest revealed, within the area of previous consolidation in the left lower lobe of the lung, a cavity consistent with an abscess and erosion into the pericardium, which now contained both air and fluid in the pericardial space. An echocardiogram demonstrated a pericardial effusion of moderate size, with evidence of loculation and adhesions. Ventricular function was normal, with an ejection fraction of 55%, and there was no suggestion of cardiac tamponade.

The patient subsequently underwent left-side thoracotomy with wedge resections of 2 pulmonary abscesses, pericardial biopsy and window formation, and pericardial drainage. After the removal of >200 cc of seropurulent material and the breakdown of numerous fibrinous adhesions that were causing loculation, an open pericardial window was created to facilitate continued drainage. The patient's immediate postoperative recovery was uneventful. Microbiological examination of a KOH preparation of the drained fluid and of pericardial, epicardial, and lung tissue specimens revealed numerous irregularly septate hyphae (figure 2). Histologic examination of the lung tissue revealed an acute and chronic organizing pneumonia with evidence of abscess formation, and the presence of many fungal hyphae was noted. Pericardial biopsy showed a fibrinous pericarditis, fibrosis, and granulation tissue.

Cultures of epicardial and pericardial tissue yielded growth of a mold with thin septate hyphae on sheep blood, chocolate, brain-heart infusion, and charcoal yeast extract (CYE) agars after 3 days of incubation at 37°C. Growth was better at 37°C than at 30°C on all media. After 5 days of incubation at 37°C, colonies of subcultures to sheep blood agar were white to yellowish white and had an undulated surface (figure 3A). Colonies on CYE agar were fluffy and white, becoming powdery and gray (figure 3B). Lactophenol cotton blue wet preparations of the mold on CYE agar showed thin, irregularly septate hyphae, and globose to subglobose zoosporangia that contained numerous zoospores (figure 3C). Mold placed into water and incubated overnight yielded zoospores with germ tubes (figure 3D).

Antimicrobial susceptibility testing of the *P. insidiosum* iso-
late recovered was performed by Dr. Michael G. Rinaldi at the Fungus Testing Laboratory at the University of Texas Health Science Center (San Antonio), according to the macro broth dilution method of the National Committee for Clinical Laboratory Standards. MICs at 24 h were 0.25 µg/mL for amphotericin B, >64 µg/mL for flucytosine, 1 µg/mL for ketoconazole, >64 µg/mL for fluconazole, 2 µg/mL for itraconazole, and 0.3 µg/mL for terbinafine. The patient was given broad-spectrum antimicrobials intravenously, including liposomal amphotericin B (5 mg/kg/day) and itraconazole (400 mg/day for 4 days, followed by 200 mg/day), and he had an uneventful recovery.

Follow-up CT scans of the chest obtained 1 and 2 weeks after surgery showed resolution of the pneumopericardium, with a significant decrease in the amount of pericardial fluid. A follow-up echocardiogram also showed complete resolution of the pericardial collection with maintenance of the normal ventricular function. Antibacterial therapy was subsequently discontinued. The patient was discharged from the hospital 18 days after undergoing thoracotomy. He successfully completed chemotherapy and remains in complete remission. Fourteen months after discharge from the hospital, the patient remained completely symptom free, having completed 12 months of therapy with intravenously administered amphotericin B (5 mg/kg/day) and 8 months of therapy with intravenously administered itraconazole (200 mg/day), followed by 4 months of therapy with orally administered itraconazole, 200 mg twice daily.

Discussion. All patients who undergo chemotherapy are immunosuppressed and have an increased risk for opportunistic infections, including both fungal and bacterial infections. Infection is a particular risk for patients with acute myeloid leukemia who are receiving intense chemotherapy to achieve and maintain remission status. P. insidiosum, which was the cause of infection in the child described in the present report, is an aquatic, filamentous organism, the taxonomy of which has been controversial. The organism is funguslike, but it probably belongs to the kingdom Stramenopila, which includes organisms characterized by the formation of motile spores [5]. The genus Pythium comprises

Figure 3. *Pythium insidiosum*. A, Growth of the organism on sheep blood agar incubated at 37°C for 5 days. B, Growth on charcoal yeast extract agar at 37°C for 5 days. C, Wet mount showing zoosporangia containing zoospores. D, Wet mount showing zoospores with germ tubes.
~85 species, primarily plant and fish pathogens. The species *P. insidiosum* is principally a pathogen of horses, cattle, dogs, and cats, but rarely humans. The organism forms biflagellate, motile, asexual zoospores, which appear to have a strong tropism for both animal and human skin and hair, in addition to water lilies and grasses of the usual swampy environs of the organisms [6]. The spores may subsequently enter the skin or mucous membranes, encyst, and produce hyphae that penetrate tissues. Although the organism then grows as a mycelium in tissue, it is not a true fungus, lacking several characteristics of fungi, including the ergosterol component of the cell wall.

Pythiosis ("swamp cancer") is a well-described veterinary condition that most often manifests as chronic, progressive cutaneous granulomas. It is usually seen in tropical and subtropical regions, although sporadic cases have been reported in cooler areas. *P. insidiosum* infections in humans were first reported as chronic nonfatal subcutaneous granulomas in the 1980s. Approximately 30 cases have been documented (most of which have occurred among patients with thalassemia in Thailand), and they have predominantly involved entry of the organism into the cutaneous and subcutaneous tissues after skin trauma [7–9]. To our knowledge, this is the first report of isolation of *P. insidiosum* in cultures of lung and pericardial tissue specimens obtained from humans. It is also only the third reported case of pythiosis in humans in North America; 2 previously reported cases involved a 4-year-old boy in Texas [3] and a 2-year-old boy in Tennessee [4], both of whom had extensive and deeply invasive facial infections. The patients were free of the infection at the time of report, one after undergoing successive surgical debridements and the other after receiving a prolonged course of treatment with terbinafine and itraconazole.

The source of infection in our patient remains unclear. The patient had experienced no apparent injury, and no contact with high-risk aquatic habitats, such as swamps, temperate river water, hot pools, or muddy water, could be identified. He had never resided in a tropical zone, having lived briefly in Chicago, Illinois, and Westchester County, New York, before moving to Staten Island, New York, ~5 years before the hospital admission reported here. His family had never owned pets, and he had experienced minimal contact with domestic animal species. Apart from having traveled to Pakistan several times to visit family over the years, the patient had no other history of travel and had never been to a tropical destination. Furthermore, the organism’s portal of entry into the pleural space and the timing of the infection are open to conjecture. We surmise that the breakdown of the mucus membrane barrier known to occur in association with the receipt of intensive chemotherapy probably contributed to both the entry of the organism and the spread of infection. However, the patient may well have had subclinical infection before receiving chemotherapy, with the resulting severe immunosuppression leading to an extensive opportunistic infection. It remains undetermined whether this infection was the result of direct invasion along the respiratory tract or via the gastrointestinal tract (as has been described in animals), with hematogenous spread occurring subsequently.

Successful treatment of pythiosis in humans has involved the use of potassium iodide [8], administration of an immunotherapeutic vaccine [10], and, usually, surgical excision of the infected tissue [8]. *P. insidiosum* does not contain ergosterol in the cell membrane; therefore, successful treatment with either amphotericin B alone or the azole fungicides might not be expected. However, one patient with deeply invasive facial infection was successfully treated with a combination of terbinafine and itraconazole [4], and peri-orbital subcutaneous pythiosis responded to amphotericin B therapy [11]. For our patient, given the site and nature of the infection, surgical debridement with removal of all grossly infected tissue was considered essential, and restoration of the patient’s immune function was probably necessary. Results of in vitro susceptibility tests suggested that use of amphotericin B and itraconazole might be warranted; however, these results should be interpreted with caution, both because the tests are not standardized for the filamentous fungi and because prediction of clinical correlations is difficult as a result of the pharmacokinetics and interaction of the drugs. Consideration of aspergillosis, pseudallescheriasis, and fusariosis in the differential diagnosis for our patient, who was not responding to treatment with liposomal amphotericin B, 3 mg/kg/day, and whose surgical specimens revealed septate hyphae, suggested that it was prudent to increase the dosage of intravenously administered liposomal amphotericin B to 5 mg/kg/day and to commence therapy with intravenously administered itraconazole.

Fourteen months after the procedure was performed, the patient continued to do well and had no clinical, radiographic, or echocardiographic evidence of continued infection. We are therefore optimistic that the infection was successfully treated and that, given continued remission of underlying leukemia, the patient’s outlook remains good. This report broadens the clinical spectrum of disease caused by this emerging pathogen and serves to remind all those who deal with immunosuppressed patients that unusual and novel opportunistic infections remain a constant threat.

**References**