Successful Medical Therapy for Deeply Invasive Facial Infection Due to Pythium insidiosum in a Child


Pythiosis occurs in animals and humans who encounter aquatic habitats that harbor Pythium insidiosum. Drug therapy for deeply invasive infections with this organism has been ineffective in humans and animals; patients have been cured only by radical surgical debridement. A 2-year-old boy developed periorbital cellulitis unresponsive to antibiotic and antifungal therapy. The cellulitis extended to the nasopharynx, compromising the airway and necessitating a gastrostomy for feeding. P. insidiosum was isolated from surgical biopsy specimens of the affected tissue. On the basis of in vitro susceptibility studies of the isolate, the patient was treated with a combination of terbinafine and itraconazole. The infection resolved over a period of a few months. The patient remained well 1.5 years after completing a 1-year course of therapy. Cure of deep P. insidiosum infection is feasible with drug therapy.

Pythium species, excluding Pythium insidiosum, have long been recognized as plant pathogens. P. insidiosum is the only member of its genus that has been implicated in human and animal infections [1, 2]. P. insidiosum is a cosmopolitan aquatic organism that has an ecological preference for swampy environments and that produces biflagellate, motile zoospores. These asexual propagules appear to be chemotactically attracted to plant leaves, certain grasses, or human/animal hairs and likely serve as infectious particles.

See article on related topic by Thitithanyanout et al. on pages 1394–400.

The taxonomy, classification, and nomenclature of this genus and its species have undergone several revisions over the years and continue to be controversial. Pythium species originally were considered to be oomycetous members of the kingdom Fungi, but the discovery and elucidation of zoosporogenesis and oosporogenesis resulted in their reclassification to the kingdom Prototista. More recent molecular studies have suggested that Pythium species belong to the kingdom Stramenopila—organisms that form motile spores and differ from true fungi in at least six biological characteristics [3, 4].

Disease in animals was first reported in India in 1884 by a veterinarian who described bursautee in horses and noted that the disease could be transmitted to healthy animals by inoculation of infected tissue [5]. Other synonyms for pythiosis include “swamp cancer,” “Florida horse leech,” “equine phycomycosis,” and “hyphomycosis destructus” [1, 2]. P. insidiosum infection of humans is rare; only one case in North America has been reported [6], and ~20 reported cases have occurred in Thailand, almost exclusively in patients with thalassemia [7–11]. There have been reports of limited response of human cutaneous pythiosis to potassium iodide therapy [8]. In addition, there is a report of two young, immunocompetent Australian males with peri-orbital subcutaneous pythiosis who responded to amphotericin B therapy [12]. However, cure of deeply invasive human infections has invariably required extensive surgical debridement. Likewise, successful drug therapy for invasive pythiosis in animals has not been described. The single case of pythiosis reported from the United States, involving a child who presented with characteristics remarkably similar to those of the patient reported herein, required incapacitating surgical debridement to arrest his infection [6]. We describe a child with deeply invasive P. insidiosum infection of the head and...
Case Report

A 2-year-old boy was admitted to the hospital for treatment of periorbital cellulitis and fever. There was no history of trauma. He had been playing in mud in an area with standing water. Physical examination revealed moderate swelling, erythema, and tenderness of the left periorbital area. The WBC count was 14,700/mm³, with 51% neutrophils, 35% lymphocytes, and 10% monocytes. Blood cultures were sterile. CT of the face yielded findings compatible with left preseptal cellulitis with opacification of the left maxillary antrum (figure 1A). He was treated with intravenous cefotaxime for presumed bacterial cellulitis. After 3 days, his treatment was changed to oral administration of trimethoprim-sulfamethoxazole, and he was discharged with the clinical impression of nominal improvement of the cellulitis.

The periorbital swelling increased markedly over the next day (figure 2A), and he was readmitted. Repeated CT of the face revealed increased preseptal soft-tissue swelling without liquefaction (figure 1B), as well as partial aeration of the left maxillary sinus. Intravenous vancomycin, clindamycin, and cefotaxime were administered but no improvement was noted. A biopsy of the periorbital region revealed grossly visible microabscesses and nonspecific granulomatous inflammation, with hyphae seen on a silver-stained preparation. The patient became febrile, and the periorbital swelling gradually spread to the adjacent cheek and paranasal area. Findings of a second biopsy of the infraorbital region were again suggestive of zygomycotic infection. Fungal, bacterial, and mycobacterial cultures of both biopsy specimens were sterile. There was no response to high-dose amphotericin B after 6 weeks of administration.

The patient remained febrile, and the left-sided facial swelling gradually progressed to involve the right forehead and periorbital area and the left-lower cheek and jaw. Oral itraconazole was prescribed, but intake was severely limited because of progression of the cellulitis into his pharynx, with massive swelling of his tongue and resulting dysphagia (figure 1C). MRI revealed marked retropharyngeal and parapharyngeal swelling that impinged upon his airway (figure 1D). Moderate respiratory distress was managed with bilateral nasal trumpet airways.

Hemoglobin electrophoresis, serum immunoglobulins, and complement values were normal, as were nitroblue tetrazolium dye reduction test findings and T cell function. Neutrophil opsonophagocytosis was marginally diminished initially; results of subsequent testing were normal. Recombinant IFN-γ was administered empirically without response.

On the basis of this child’s clinical course and the histopathologic findings, immunodiffusion tests for P. insidiosum antibodies were recommended and performed by Dr. L. Kaufman at the Centers for Disease Control and Prevention (CDC), with use of undiluted specimens of patient sera, a 1:2 dilution of P. insidiosum culture filtrate antigen, and undiluted reference rabbit P. insidiosum antisera [13]. This reference serum produces six precipitin bands; formation of one or more lines of identity of the test serum specimen with the reference precipitates is considered diagnostic. A serum specimen obtained 6 weeks after onset of facial cellulitis yielded two precipitin bands of identity with reference P. insidiosum precipitates. Over the next 2 months, three additional serum specimens each yielded three lines of identity (figure 3).

On hospital day 65 a third infraorbital biopsy was performed, and findings were similar to those of the previous two biopsies (figure 4). Because conventional methods had twice failed to yield an organism and few organisms were present histologically in previous biopsies, an aliquot of the third tissue biopsy specimen was dispersed in saline with use of a sterile, disposable tissue grinder (Sage Products, Crystal Lake, IL). The specimen was inoculated onto 10 agar plates of brain-heart infusion with gentamicin (100 µg/mL).

Hyphal growth was observed on three of the 10 brain-heart-infusion agar plates after 1 day’s incubation at 30°C. Microscopically, branched, occasionally septate hyphae were observed. No conidia were observed on the original agar plates or on subsequent inoculation to Sabouraud dextrose, Czapek, tomato-vegetable juice, or potato dextrose agars. The hyphae were wide and extensively branched, with some terminal swellings. An aliquot of agar was placed in a petri dish with sterile water at 35°C. After overnight incubation, extensive sporangia, sporangia with motile zoospores, and free zoospores characteristic of P. insidiosum were observed with an inverted microscope. Identity of the isolate was confirmed by mycologic examination at the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio and at the CDC by the exoantigen method [14].

The presence of P. insidiosum in the biopsy tissue specimen was also confirmed by fluorescein isothiocyanate–labeled rabbit antitribulbino to P. insidiosum, rendered specific by adsorption with cells of Pythium diclinum and Pythium graminicola [14]. The staining of hyphae in tissue obtained at biopsy with use of fluorescent antibody indicated that the hyphae were those of P. insidiosum.

Broth macrodilution and checkerboard synergy antimicrobial susceptibility testing was performed with RPMI-1640 at the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio. The patient’s isolate was resistant to amphotericin B, flucytosine, miconazole, and griseofulvin (table 1). Itraconazole had moderate activity (table 1). Neither rifampin nor flucytosine affected the activity of amphotericin B or itraconazole (data not shown). Terbinafine was active as a single agent and had an additive effect when used with itraconazole but not with fluconazole (table 1). Independent replicate analysis (2–4×) yielded concordant results for each antimicrobial tested, and standard control tests against.
Figure 1. Serial CT and MR images of a 2-year-old boy presumed to have bacterial cellulitis. A, Initial study. Axial noncontrast section shows preseptal left-sided soft-tissue swelling and opacity of the left maxillary antrum. B, 16 days later. Enhanced axial CT section at same level shows clearing of left maxillary sinus but further extension of cellulitis across the midline and into the left temporal soft tissues. C, 1 month after B. Enhanced CT section demonstrates solid induration of the lower lip across the midline and left juxtamandibular cellulitis lateral to the left side of the tongue (T). Note endotracheal tube (arrow) placed for the procedure but normal retropharyngeal and parapharyngeal soft tissues. Bilateral cervical lymphadenopathy was also present (N). D, MR image 26 days after C. Contrast-enhanced, T1-weighted spin-echo image (TR, 700; TE, 19 milliseconds) shows enhancing high-signal-intensity swelling of the face, left floor of the mouth, and parapharyngeal and retropharyngeal soft tissues, deforming the pharyngeal air column (T = tongue).
a reference organism yielded results within specified ranges in each assay.

Because of the patient’s inability to swallow, a gastrostomy tube was placed. An investigational itraconazole suspension (Janssen Pharmaceuticals, Titusville, NJ) was administered via the gastrostomy tube at a dosage of 60 mg twice daily (8 mg/[kg \( \cdot \) d]). Serum levels of itraconazole with use of this suspension ranged from 1.0 \( \mu \)g/mL to 2.1 \( \mu \)g/mL. Administration of terbinafine (Sandoz Research Institute, East Hanover, NJ)—obtained on a compassionate-use basis—was begun on hospital day 84 at a dosage of 125 mg twice daily (32 mg/[kg \( \cdot \) d]). Both of these agents were tolerated with no adverse effects.

Over the next several weeks, there was a gradual decrease in the facial swelling and a marked reduction in the swelling of the tongue. After discharge on hospital day 118, the patient’s condition continued to improve, and he now has no residual edema, erythema, or tenderness of the left-lower cheek (figure 2B). He does have mild residual weakness of the left side of his face. Therapy was discontinued after administration of itraconazole for \( \sim \)13 months and terbinafine for \( \sim \)12 months. There was no evidence of recurrence 1.5 years after discontinuation of therapy.

Discussion

The first cases of invasive pythiosis in humans were described in 1989 in Thailand [7]. Five patients with thalassemia had invasive pythiosis of the lower extremities, characterized by the gradual onset of intermittent claudication, pain, and local temperature changes. Histologically, the infection was distinguished by a purulent arteritis. A variety of antifungal agents, including amphotericin B and potassium iodide, were administered without apparent benefit. All patients required extensive surgical debridement, and two died. Since this initial report, several additional cases of invasive infections due to \( P. \) insidiosum in Thai patients with thalassemia have been described, and rare cases of infection due to \( P. \) insidiosum in patients without thalassemia have been reported [7–10, 12]. In addition, nine cases of keratitis have been reported [15].
Table 1. Results of in vitro susceptibility testing of the *Pythium insidiosum* isolate from the 2-year-old patient with deeply invasive facial infection.

<table>
<thead>
<tr>
<th>Drug tested</th>
<th>MIC (µg/mL)</th>
<th>MLC* (µg/mL)</th>
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<tbody>
<tr>
<td>Amphotericin B</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Fluconosine</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.125†</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Terbinafine + fluconazole</td>
<td>0.5 - 0.125</td>
<td>0.5 - 0.125</td>
</tr>
<tr>
<td>Terbinafine + itraconazole</td>
<td>0.008 - 0.015</td>
<td>0.03 - 0.015</td>
</tr>
</tbody>
</table>

* MLC = minimal lethal concentration.
† 24-Hour reading; at 48 hours, 0.5 µg/mL.

The only reported case of invasive pythiosis in North America occurred in Texas in an otherwise healthy 4-year-old boy, who required repeated and extensive orbital and facial surgical debridement, including enucleation of his right eye, before the infection was cured [6]. Although two young Australian males with peri orbital subcutaneous pythiosis responded to amphotericin B therapy [12], our patient’s disease progressed despite a 6-week course of amphotericin B at doses as high as 1.5 mg/(kg · d). To our knowledge, no deeply invasive infection due to this organism has responded satisfactorily to drug therapy alone.

At the time our patient’s condition was diagnosed, surgical debridement was no longer an option because of involvement of the eyes, the mid-face, the tongue, and the parapharyngeal tissues. Empirical trials of marketed antifungal agents were clinically ineffective. In vitro testing of the patient’s *P. insidiosum* isolate demonstrated that two antifungal agents, itraconazole and terbinafine, were active, and, when combined, their activities were additive, approaching synergistic interaction. The patient had not responded to itraconazole administration alone; however, because of swelling of his pharynx, delivery of the drug could not be ensured.

Placement of a gastrostomy tube, the use of a liquid form of itraconazole with monitoring of drug levels, and the addition of terbinafine slowly reversed the disease progression, resulting in only residual left-facial-nerve damage and minimal edema of the left face at the end of a 1-year course of therapy. There was no indication of recurrence 1.5 years after the end of therapy. To our knowledge, this is the first case of invasive pythiosis in a human that was successfully managed with drug therapy alone.

Our patient had no injury, unusual exposure, or predisposing factor to account for this infection that occurs rarely in humans. He did play in an area with standing water, which may have been the source of infection. Normal findings of an extensive immunologic evaluation, combined with his benign history, indicated lack of immunodeficiency. His hemoglobin electrophoresis value was normal, eliminating hemoglobinopathy as a possible explanation for the *P. insidiosum* infection. Thus, inordinate host susceptibility did not appear to be a key factor in this case.

Prompt recognition and treatment of this infection are critical since the natural progression of deeply invasive disease is fatal hemorrhage due to arteritis. Immunodiagnosis is valuable for establishing an early diagnosis. Our experience with this patient suggests that drug therapy can be guided by in vitro susceptibility testing and that pharmacological cure of this dreaded disease is feasible.
Acknowledgments

The authors thank Drs. David Ragland, Douglas McGaw, and Susan Hillebert for their support of the efforts to diagnose and treat this boy’s infection.

References