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Case Report

Pythium insidiosum: A Rare Necrotizing Orbital and Facial Infection

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Pythium insidiosum, also known as "swamp cancer," has been long known for its destructive effects on plants and animals. Infections with this fungus-like organism typically occur in temperate, tropical, and subtropical regions [1]. Human infection with *P insidiosum*, although exceedingly rare, is characterized by invasion of the cornea, cutaneous, subcutaneous, and orbital tissues with eosinophilic, tumor-like masses demonstrating arterial tropism [1, 2]. In most cases, patients have a history of recent exposure to wet environments [1]. If left untreated, *P insidiosum* is fatal, because it is an angioinvasive organism that leads to thrombosis and tissue ischemia. Reports of most human cases are from Thailand, with only 4 well documented orbital cases to date in the United States and Australia [1, 3, 4].

Key words. diagnosis; orbital cellulitis; *pythium insidiosum*; treatment; vaccine.

CASE REPORT

A 10-year-old, healthy female developed progressive left eyelid swelling unresponsive to amoxicillin-clavulanate. She presented with fever (101°F), leukocytosis (14 400), and mild eosinophilia (11%), and had no antecedent history of trauma, sinus infection, or travel outside the United States. Physical examination of the patient revealed soft tissue edema of the periorbital area with no surface excoriation. A computed tomography scan of the orbits revealed a nonspecific infiltrate in the preseptal tissues, extending into the inferior orbit (Figure 1*A*). Paranasal sinuses were clear. Despite 72 hours of intravenous clindamycin and ceftriaxone, the patient's facial swelling progressed to chemosis with restriction of motility (Figure 1*B*). An orbital biopsy revealed a nodular fibrotic infiltrate. Initial pathologic evaluation demonstrated intense inflammation with predominantly eosinophilic infiltrate. Parenteral steroids were started for possible orbital pseudotumor. Forty-eight hours later, the Gomori Methenamine Silver stain on the specimen revealed scattered branching and septate fungal hyphae with vascular invasion suggestive of *Aspergillus*. Liposomal amphotericin B and voriconazole were started and steroids were stopped. A specimen was sent for fungal culture from subsequent debridement procedures.

The patient was found to be human immunodeficiency virus negative and to have normal results on testing for chronic granulomatous disease. She was also found to have a normal hemoglobin A1C. Infection with *Pythium insidiosum* was suspected because this patient had no predisposing conditions for invasive fungal infection. There had been a patient diagnosed with *P insidiosum* at this institution approximately 10 years earlier. Tissue, serum, and organism growing in the fungal culture were sent to a research laboratory at Michigan State University where the infectious organism was identified as *P insidiosum* (Figure 2, *B–D*) by culture, serology (enzyme-linked immunosorbent assay), and polymerase chain reaction. Antifungal susceptibility testing was performed at the Fungus Testing Laboratory in San Antonio, TX. The results were as follows: amphotericin B > 16, caspofungin > 16, flucanozole > 64, itraconazole 1.0, voriconazole 1.0, posaconazole 0.125, and terbinafine 0.03.

Once the diagnosis was known, the patient's therapy was changed to itraconazole and terbinafine due to previous success with this regimen. Despite this treatment, rapid, relentless progression across her face and scalp occurred within 3 weeks of admission. Emergency, compassionate Institutional Review Board and US Food and

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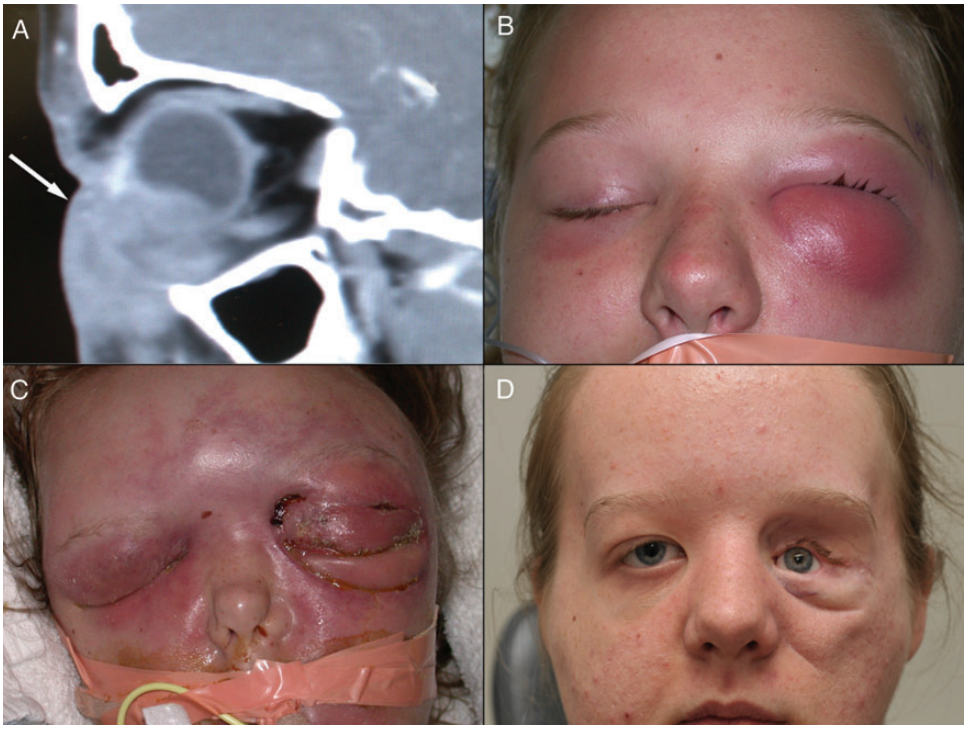

Figure 1. The clinical panel is illustrated. (*A*) Sagittal section of the left orbit with a massive dense inferior preseptal and orbital infiltrate on initial presentation. (*B*) Taught edema, erythema centered on the lower eyelid 3 days after initial presentation and immediately prior to the first orbital biopsy. (*C*) Massive facial swelling after 3 doses of the immune vaccine against *Pythium insidiosum*. The patient is intubated secondary to the oropharyngeal swelling. (*D*) Five years after initial presentation, a prosthesis is in place with tremendous loss of orbital and facial volume especially in the cheek and temporal fossa, secondary to missing soft tissue and musculature on the left side.

Drug Administration approvals were obtained to use *P insidiosum* immunotherapy in this patient. The immunotherapeutic, consisting of *P insidiosum* protein extracts, was created at Michigan State University and was licensed for use in animals with pythiosis. This therapy had been successfully used to treat human *P insidiosum* arteritis in Thailand [6]. The patient initially received serial injections of decreasing dilutions of the therapeutic agent of the following doses of *Pythium insidiosum* extract: day 1, intradermal injection of 0.1 mL extract at 1:10 dilution and 1:2 dilutions. On day 2, she received 0.1 mL full-strength extract intradermally. She had no significant reaction to the intradermal doses. On day 3, she received 0.5 mL subcutaneously. After this first dose, she experienced a significant increase in pain, edema, and erythema of the facial and periorbital tissues, which was both expected and desired. She received her second of 4 full-dose injections on day 10 with some increase in the local inflammatory response again. A third dose was given on day 17. A fourth dose was planned but held due to progressive pain, swelling, and respiratory distress after the third dose. She developed severe facial swelling (Figure 1*C*) and acute respiratory distress syndrome (ARDS), necessitating mechanical ventilation and continuous veno-venous hemofiltration in the intensive care unit 21 days after initiation of immunotherapy. She ultimately recovered and was discharged from the hospital on posaconazole, which had more reliable gastric absorption than voriconazole.

Despite temporary recovery, she had disease progression over the next few months with posterior spread of woody edema over her scalp associated with episodes of severe pain, necessitating hospital admission. Out of concern for ongoing infection, she was further treated with an immune-stimulatory treatment, first granulocyte-monocyte colony-stimulating factor and then interferon-γ in addition to antifungals. She developed severe head and neck swelling again, which required placement of a gastrostomy tube for nutrition and a tracheostomy for upper airway obstruction. When she could no longer tolerate immune stimulation, interferon-γ was discontinued. High-dose steroids were started to curtail the excessive immune response, with the hope that the organism had finally been killed. She remained on antifungals, parenteral voriconazole, throughout this admission. She tolerated this well and was able to be discharged after approximately 2 months of hospitalization. Her swelling and pain continued to flare with attempted steroid tapers. She was treated with methotrexate as a steroid-sparing agent until she could be

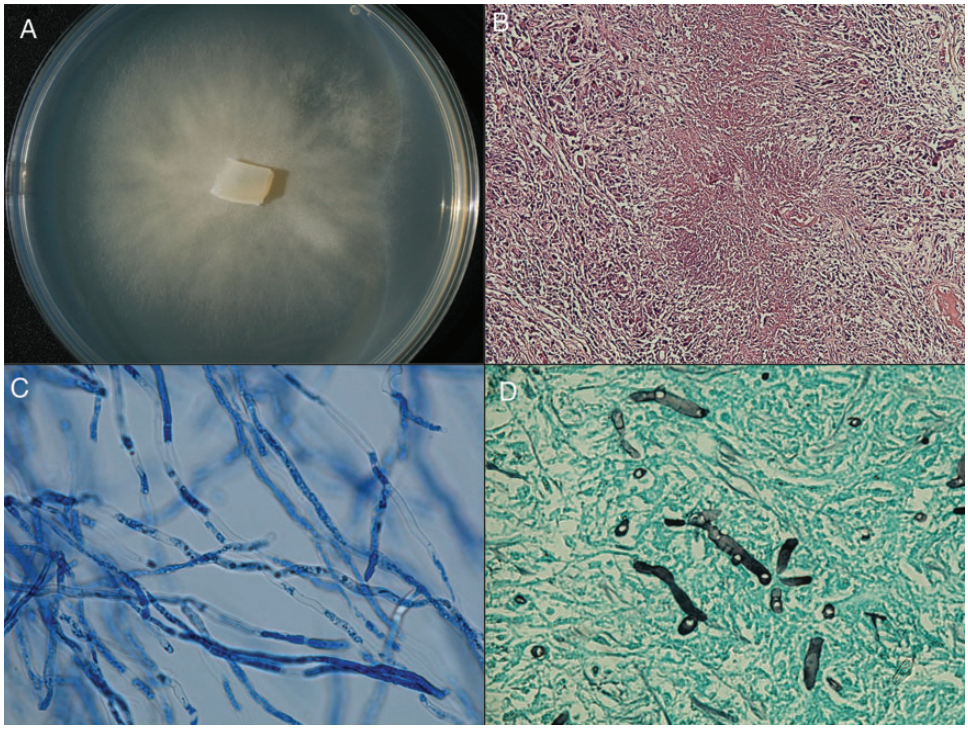

Figure 2. The pathological panel is illustrated. (*A*) *Pythium insidiosum* culture plate. (*B*) Numerous eosinophilic microabscesses containing small fragments of hyphae (at the center of the microabscesses), necrotic foci, some giant cells, numerous eosinophils, and mast cells. *Pythium insidiosum* is known to stain poorly on regular hematoxylin and eosin staining, in contrast with hyphae of the Zygomycetes (*Aspergillosis*) from which the differential diagnosis has to be established. Hematoxylin and eosin stain, magnification × 100. (*C*) Microscopy reveals sparsely septate, branching hyphae. Lactophenol cotton blue stain, magnification × 400. (*D*) Histologic examination shows numerous fungal elements. Gomori methenamine-silver stain, magnification × 400.

completely weaned off immunosuppressive therapy approximately 6 months after initiation.

Multiple biopsies were performed with pathological evaluation during the multiple admissions. Two specimens were sent to Dr. Mendoza, who specifically looked for *Pythium* organisms: the second orbital biopsy was performed 5 days after admission, and a cheek biopsy was done 2.5 months after treatment. All initial biopsies revealed fungal elements, surrounded by massive eosinophilic infiltrate, necrosis with microabscess formation. The biopsy negative for fungal elements and specifically for *Pythium* was 2.5 months after admission.

Approximately 10 months after her illness onset, she presented with worsening dyspnea and was found to have bilateral pleural effusions, determined to be chylous. She was treated with parenteral nutrition, but effusions recurred with any enteral feeding including Portagen (medium chain triglyceride formula). On exploration of her pleural space, she was found to have leakage of lymph from intercostal lymphatics. Pleurodesis was eventually performed and was curative. The pleural fluid and pleural tissue were not cultured; however, no fungal elements were seen on histopathology. The pathology revealed an organizing fibrin with acute and chronic inflammation.

One year after admission, the patient developed a blind, painful, nonfunctioning eye that had to be enucleated. The globe was sent to histopathologic examination, revealing focal acute and chronic inflammation within the globe as well as periorbital and episcleral large areas of necrosis with associated acute and chronic inflammation surrounding the scattered fungal elements. The patient also had residual bilateral facial nerve palsies. She recovered sufficient bulbar function to have her gastrostomy tube and tracheostomy removed 18 months after the illness onset. She has undergone multiple reconstructive surgeries performed by our ophthalmic plastic team in attempt to create a more normal appearing orbit and face (Figure 1*D*). She remains in great spirits and has just graduated from high school.

DISCUSSION

Pythium insidiosum is a destructive, underrecognized infection of orbital and subcutaneous tissues that occurs in endemic (warm or wet) climates [1]. Pythiosis is frequently mistaken for aspergillosis based on the similar appearance of hyphal elements [1]. A high index of suspicion is required to diagnose pythiosis. Is should be suspected in

immunocompetent patients with history of exposure to wet environments who present with a head or neck mass with relentless spread along tissue planes and are nonresponsive to conventional antimicrobial therapy. Biopsies should be obtained, and identification of the pathogen by culture and nonculture techniques should be undertaken, especially if vascular invasion by fungus is documented. Immunomodulatory treatment has been used for patients with vascular pythiosis in Asia. To our knowledge, this is the first patient with orbital pythiosis to receive the immunomodulatory vaccine. The vaccine, approved for use in animals and consisting of hyphal elements and culture filtrate antigens of *P insidiosum*, has been found to be curative in approximately 50% of cases [5]. The disease usually creates an eosinophilic inflammatory reaction consistent with a T-helper (Th)2 immune response that is not microbicidal. The vaccine is theorized to switch the host's immune response to the Th1 response that is microbicidal. In this case, the vaccine elicited a fulminant host immune response, creating a systemic inflammatory response syndrome and ARDS.

Multispecialty and interinstitutional collaboration, the use of a novel vaccine, and powerful antifungal and immunomodulatory agents averted this patient's demise. However, the relentless evolution of this disease was difficult to control, leaving the patient with permanent disfigurement.

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Potential conflicts of interest. L. L. M. had a patent on the vaccine against *Pythium insidiosum*, for which his institution received royalties in the past.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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