

Trichosporon pullulans infection in 2 patients with chronic granulomatous disease: An emerging pathogen and review of the literature

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Background: Chronic granulomatous disease is a genetically determined primary immunodeficiency disease in which phagocytic cells are unable to kill certain bacteria and fungi after ingestion. Manifestations include recurrent pyogenic infections caused by catalase-positive microbes. *Trichosporon* species are emerging as opportunistic agents that cause systemic disease in immunocompromised patients. Typically disease has been described in association with *T beigelii* in patients with secondary immunodeficiency, such as underlying malignancy.

Objective: The objective was to report the first 2 cases of *T pullulans* infection in 2 male children with chronic granulomatous disease.

Methods: The records of the 2 patients were reviewed. In addition, all cases of *T pullulans* infection reported in the English language literature are presented.

Results: This report brings to 7 the total number of cases of *T pullulans* reported and the first in patients with chronic granulomatous disease, one with invasive pneumonia and the other with an infected paronychia and localized cellulitis. In the 5 additional cases malignancy was the principal risk factor.

Conclusion: *T pullulans* has rarely been reported as a fungal pathogen. The most prominent risk factor for the development of trichosporonosis is immunocompromise most notably with neutropenia. Abnormally functioning neutrophils, such as with chronic granulomatous disease, may also predispose individuals to this opportunistic pathogen. (J Allergy Clin Immunol 2003;111:1370-4.)

Key words: Chronic granulomatous disease, *Trichosporon pullulans*, emerging pathogen

Trichosporon pullulans is a yeast-like fungus that belongs to the genus *Trichosporon*, family Sporidiobolaceae, order Sporidiales, and phylum Basidiomycota. Within the genus *Trichosporon*, *T beigelii* (formerly known as *T cutaneum*) accounts for the majority of infections reported in both pediatric and adult populations.^{1,2}

Abbreviations used

BAL: Bronchoalveolar lavage

CGD: Chronic granulomatous disease

NADPH: Nicotinamide dinucleotide phosphate

Trichosporonosis is a rare infection and is most frequently encountered in patients with underlying malignancy, especially those with neutropenia, and manifests primarily as sepsis, catheter-related bloodstream infection, and pneumonia.³ *T pullulans* has more recently been recognized as a human pathogen⁴; however, given its rare occurrence, there is a paucity of reports in the medical literature describing infection attributable to this fungal pathogen.⁵⁻⁷ *T pullulans* has been described as causing skin and soft tissue infection,⁴ pneumonia,⁵ and fungemia.^{6,7} In immunocompromised patients, trichosporonosis is associated with significant mortality, including patients with *T pullulans* infection.⁸

Chronic granulomatous disease (CGD) is an inherited immunodeficiency in which the patient's phagocytes have impaired functioning of the nicotinamide dinucleotide phosphate (NADPH) oxidase system.⁹ The result is an inability to produce superoxide and hydrogen peroxide efficiently with impaired microbial killing of intracellular pathogens. Consequently, these patients are at increased risk for suppurative infections primarily caused by catalase-positive bacteria and fungi such as *Staphylococcus aureus*, *Aspergillus* spp, and *Burkholderia cepacia*. *Aspergillus* spp are the most prevalent fungal pathogen followed by *Candida* spp.¹⁰ Isolated reports of infection with *Rhizopus*, *Fusarium* spp, *Paecilomyces* spp, and *Exophiala* spp have also been described.¹⁰ Given that trichosporonosis is more prevalent in patients with neutropenia and measures to improve neutrophil function have been associated with an improved outcome in a murine model,¹¹ it follows that patients with impaired phagocyte function, such as those with CGD, will be susceptible to infection with this pathogen.

We report 2 male patients, second-degree relatives, with underlying CGD and documented *T pullulans* infection. Both were receiving antifungal therapy at the time of the infection. There was a successful outcome in each case. To our knowledge these are the first reports of *T pullulans* infection in this population of susceptible hosts.

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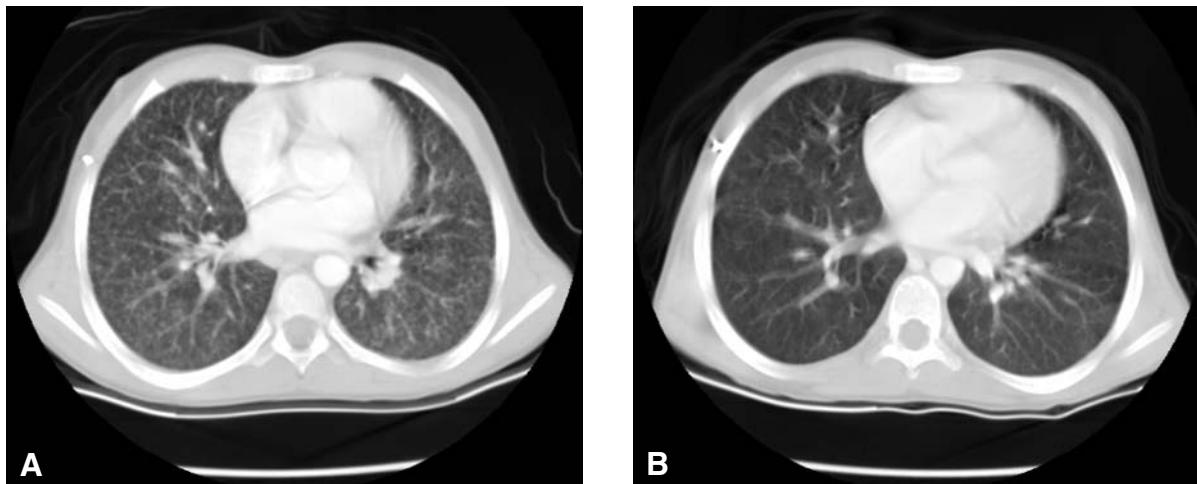


FIG 1. A, Case 1, contrast-enhanced computed tomography of the chest indicating extensive bilateral micronodular infiltrates. B, Case 1, follow-up computed tomography 1 month after initiation of liposomal amphotericin B indicating significant improvement in the previously noted bilateral nodular pneumonic process.

CASE REPORTS

Case 1

A 9-year-old Latin-American boy with a history of X-linked recessive CGD, diagnosed at 4 months of age as a result of recurrent pyogenic infections, presented in September 1999 with a 4-day history of fever to 101°F, nonproductive cough, pleuritic chest, and back pain. He was receiving prophylactic trimethoprim-sulfamethoxazole and itraconazole, as well as IFN- γ (50 $\mu\text{g}/\text{m}^2$) subcutaneously 3 times weekly. Previous infectious complications included *Nocardia caviae* pneumonia (1994), *Salmonella arizonae* bacteremia (1995), *Serratia marcescens* hepatic abscess (1996), and *Aspergillus fumigatus* pneumonia (1997).

Initial laboratory evaluation showed white blood cell count of 10,500/ mm^3 with 82% segmented forms and an erythrocyte sedimentation rate of 91 mm/h. Chest radiograph performed on admission showed a diffuse parenchymal abnormality with reticulonodular densities. Computed tomography also showed worsening interstitial nodular pneumonia (Fig 1, A). The patient was empirically commenced on broad-spectrum antibiotic therapy (ticarcillin/clavulanate and gentamicin) and underwent bronchoscopy and transbronchial biopsy on hospital day 3. The lung biopsy material obtained was inadequate for histopathology examination, and bronchoalveolar lavage (BAL) fluid was sent for culture. On hospital day 14 the patient underwent an open lung biopsy in an effort to diagnose the infectious agent. In addition, he persisted with intermittent fever despite broad-spectrum antibiotic therapy. Histopathologic examination of the lung tissue obtained by the open procedure showed multiple granulomas of varying size (Fig 2) with evidence of small fragmented hyphae within the granulomas. At 6 weeks *T pullulans* was isolated from the BAL fluid; however, cultures of lung tissue obtained by open biopsy remained sterile. After the open biopsy antibiotics were discontinued, and the patient was commenced on liposomal amphotericin B. He completed 90 days of therapy without significant complication. Follow-up chest imaging at 1 month showed almost complete resolution of the nodular infiltrates (Fig 1, B). In vitro susceptibility data were available for the isolate as performed at the fungus testing laboratory at University of Texas Health Center at San Antonio. Minimum inhibitory concentration at 24, 96, and 120 hours for amphotericin B and itraconazole was 0.25 and 0.5 $\mu\text{g}/\text{mL}$, respectively; minimum lethal concentration for amphotericin B was 0.25 $\mu\text{g}/\text{mL}$ at 24 hours.

Case 2

A 7-year-old Latin-American male patient with X-linked recessive CGD (diagnosed during the neonatal period as a result of a positive family history) was hospitalized in January 2001 for ongoing management of *Emmericella nidulans* pneumonia, originally diagnosed in August 2000. At the time of admission he was receiving therapeutic doses of liposomal amphotericin B, voriconazole, caspofungin, as well as linezolid for previous *Nocardia* spp pneumonia. In addition, the patient was receiving subcutaneous IFN- γ (50 $\mu\text{g}/\text{m}^2$) 3 times weekly.

Three months into the hospital admission the patient developed recurrent inflammation of the right hallux with surrounding cellulitis. Routine cultures performed on the purulent drainage failed to isolate a pathogen. Because of the persistent nature of the infection/inflammation the patient underwent surgical wedge resection of the right hallux toenail. *T pullulans* was isolated from miscellaneous as well as fungal cultures of the resected tissue. No bacterial pathogens were identified. Given the extensive antifungal therapy the patient was receiving at time of the resection, no alteration was made to his regimen. The local infection resolved after surgical resection without recurrence.

In each of the above 2 cases *T pullulans* was identified by using the VITEK yeast biochemical card (bioMérieux Vitek, Durham, NC) with 99% certainty.¹²

DISCUSSION

Trichosporon is a yeast-like fungus isolated from soil, water samples, vegetables, mammals, and birds. In addition to being part of the normal flora of the mouth, skin, and nails, it is the causative agent of superficial and deep infections in humans. To date, *T beigelii* is the most prevalent pathogen in the genus. In a report by Anaissie et al,¹³ *T beigelii* was described as an emerging fungal pathogen that was responsible for 26 cases of serious fungal infection during a 10-year period in a large cancer center. Infections reported included systemic infection, pulmonary infection, and fungemia alone.¹³

T pullulans is also recognized as a human pathogen but with significantly less frequency. Table I outlines cases of infection with *T pullulans* as reported in the cur-

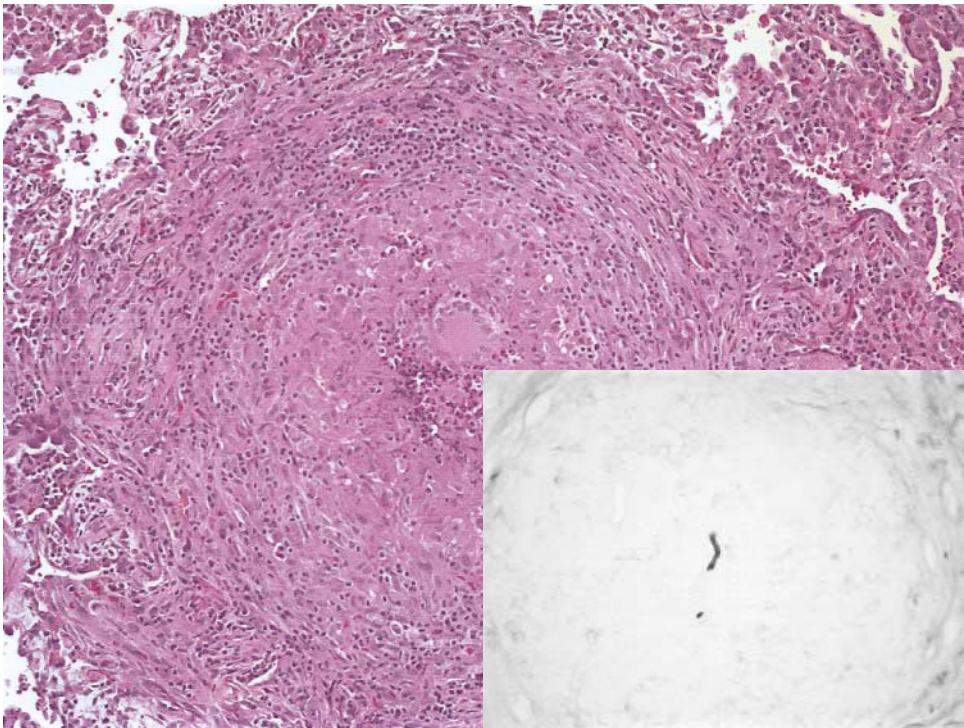


FIG 2. Numerous small necrotizing granulomas composed of epithelioid cells and occasional Langerhans-type giant cells were present throughout the lung (hematoxylin-eosin stain; original magnification $\times 125$). **Insert.** Silver staining of a representative granuloma revealed a few fragmented hyphal forms, some with segmentation, located in the center (methenamine silver stain; original magnification $\times 320$).

TABLE I. Clinical characteristics of systemic and local infections due to *Trichosporon pullulans*

Case no.	Reference, year	Age (y), Sex	Underlying disease or risk factors	Site of infection	Clinical syndrome	Treatment	Outcome
1	4, 1988	56, Male	Renal transplant, insulin-dependent diabetes mellitus, immunosuppressive drugs	Hallux and ankle	Cellulitis and osteomyelitis	Amphotericin B and amputation	Cure
2	5, 1991	78, Male	T-cell leukemia	Lungs	Reticulonodular pneumonia	Fluconazole and miconazole	Death
3	7, 1996	65, Female	Ovarian cancer, central venous catheter	Blood, catheter-related infection	Fungemia	Amphotericin B and removal of catheter	Death
4	7, 1996	63, Male	Non-Hodgkin's lymphoma, central venous catheter	Blood, catheter-related infection	Fungemia	Amphotericin B and removal of catheter	Death related to underlying primary illness
5	7, 1996	55, Male	Acute myelogenous leukemia	Blood	Fungemia	Amphotericin B	Death
6	Present report, case 1	9, Male	Chronic granulomatous disease	Lungs	Reticulonodular pneumonia	Amphotericin B	Cure
7	Present report, case 2	7, Male	Chronic granulomatous disease	Hallux	Lateral sub-ungual onychomycosis	Surgical debridement*	Cure

*Patient already receiving amphotericin B, voriconazole, and caspofungin for *Emmericella nidulans* pneumonia.

rent medical literature (n = 5) in addition to the 2 cases in this report. Comparable to our 2 cases, there have been previously documented cases of pneumonia as well as

nail and skin infection caused by *T pullulans*. A 78-year-old male patient with new onset adult T-cell leukemia developed fatal *T pullulans* pneumonia cultured from

bronchial washings.⁵ In addition, a 56-year-old male patient with diabetes mellitus and status post renal transplant developed toe pain, cellulitis and tender nodules on his ankle; *T pullulans* was cultured from purulent drainage material from the toe.⁴ *T pullulans* infection appears to have significant associated mortality, with 3 of 5 (60%) patients succumbing to deep-seated infection. In addition, 6 of the 7 (86%) reported cases occurred in male patients. Underlying immunodeficiency is a consistent finding in all reported cases.

In case 1 outlined in this report, clinical and laboratory findings suggested new onset lung infection. *T pullulans* alone was isolated from BAL fluid, and septated hyphal elements were noted within pulmonary granuloma on histopathology specimens (Fig 2). Neither *Candida* nor *Aspergillus* species were isolated from any pathologic specimens. In addition, reticulonodular pneumonia, as was noted in this case, has been previously described in association with *Trichosporon* species.^{5,14} Case 2 represents soft tissue infection in an immunocompromised host caused by *T pullulans*. In the absence of any identifiable bacterial pathogens and the isolation of the fungal pathogen from surgically obtained specimens, this case presumably represents infection rather than colonization, because *T beigelii* has been identified in a recent review of onychomycosis as the second most commonly isolated pathogen.¹⁵ In addition, Pontes et al¹⁶ identified *Trichosporon* spp as the pathogen most frequently associated with distal lateral subungual onychomycosis.

Each episode of *T pullulans* infection occurred in the face of antifungal medication, prophylaxis in case 1 and extensive antifungal therapy in case 2. Kunova et al⁷ reported fatal *T pullulans* breakthrough infection in 3 patients receiving itraconazole prophylaxis. Each patient was receiving oral therapy, and in each case the isolate was only moderately susceptible to amphotericin B. Therapy with amphotericin B failed in each case. In addition, a recent study by Paphitou et al¹⁷ suggested a superiority of the newer second generation azoles to amphotericin B as antifungal agents against *Trichosporon* species. Breakthrough trichosporonosis has also been described during prophylactic therapy with caspofungin acetate.¹⁸

Trichosporonosis is principally a disease of the immunocompromised host, most notably those with underlying neutropenia. Cases have primarily been described in cancer patients but also in neonates, most notably those born prematurely.¹⁹ Impaired neutrophil function is common to the latter groups of patients. Patients with CGD have immunodeficiency as a result of impaired phagocytic function. As a result of a genetically inherited defect, these individuals have abnormally functioning NADPH-oxidase with resultant defective superoxide and hydrogen peroxide production and ineffective intracellular killing. Lyman et al²⁰ attempted to define the role of polymorphonuclear leukocytes and monocytes in host defense against *T beigelii* infection. After serum opsonization, *Trichosporon* organisms were minimally phagocytosed despite similar phagocytic indices in comparison to *Candida albicans*. In addition, fungicidal activ-

ity of both neutrophils and monocytes was significantly impaired against *T beigelii* compared with that of *C albicans*.²⁰ Because granulocytopenia is a recognized major risk factor for disseminated *Trichosporon* infection, extremely high effector: target ratios may be necessary to efficiently control this organism. From these data it follows that patients with impaired neutrophil function such as patients with CGD should be at an increased risk for trichosporonosis. In addition, *Trichosporon* species are catalase-positive organisms, further contributing to the increased risk among CGD patients given the net loss of endogenous hydrogen peroxide production, a key element for successful intracellular killing. Muranaka et al¹¹ reported similar data with improved survival in a murine model of trichosporonosis pretreated with granulocyte-stimulating cytokines.

To our knowledge this is the first report of *T pullulans* infection in patients with underlying CGD. In a recent review of non-*Aspergillus* fungal infections in patients with CGD *Trichosporon* spp were not among those reported.²¹ In the past these unusual fungal pathogens may have been considered contaminants. Given the significant mortality associated with trichosporonosis especially in association with *T pullulans*, it appears prudent to consider all fungi isolated from patients with CGD as probable pathogens until proven otherwise. Trichosporonosis may be diagnosed by isolation of the organism from blood culture or alternatively from other normally sterile or surgically obtained specimens. Optimal empirical therapy remains elusive because 2 of the 5 patients in this review in whom amphotericin B was initiated died as a result of the infection. Therefore, antifungal susceptibility testing should be performed for all clinically relevant isolates of *Trichosporon* spp because the susceptibility patterns are unpredictable.^{17,19} Favorable survival rates are associated with early initiation of appropriate antifungal therapy in addition to surgical debridement where indicated and removal of potentially infected central venous catheters.

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