

Invasive infection with *Trichosporon inkin* in 2 siblings with chronic granulomatous disease

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A 9-year-old girl with autosomal recessive chronic granulomatous disease (CGD) presented with asymptomatic bilateral pulmonary infiltrates on routine computed tomography. Fine-needle aspirate of the infiltrates was obtained and showed fungal cells resembling *Trichosporon inkin*. The specimen grew in culture, and testing by means of both API 20C and PCR amplification confirmed the diagnosis of *T inkin*. The infiltrates increased in size, despite sequential therapy with voriconazole, liposomal amphotericin B, caspofungin, and posaconazole. The patient required resection of the infected lung tissue, after which she recovered completely. While she was undergoing therapy, her 13-year-old brother, also with CGD, was given a diagnosis of bilateral *T inkin*-induced pulmonary infection. He also required bilateral pulmonary resection for cure. These cases demonstrate the predisposition of patients with CGD to have invasive infections with unusual fungal organisms, such as *T inkin*. They also illustrate the difficulty of treating invasive *T inkin* infections with antifungal agents alone. There are 9 previously reported cases of invasive infections caused by *T inkin*, 3 of which are in patients with CGD. All patients required removal of infected prosthetic devices or surgical resection of infected tissue for cure. (J Allergy Clin Immunol 2004;114:1418-24.)

Key words: Neutrophil dysfunction, posaconazole, voriconazole, caspofungin, amphotericin

CASE PRESENTATIONS

Case 1

A 9-year-old African American girl was given a diagnosis of autosomal recessive chronic granulomatous

Abbreviations used

CAPD: Continuous ambulatory peritoneal dialysis
CGD: Chronic granulomatous disease
CT: Computed tomography
MIC: Minimum inhibitory concentration
phox: Phagocyte oxidase

disease (CGD) caused by p47^{phox} (phagocyte oxidase) deficiency at the age of 3 years during family screening. Subsequently, she had pneumonia caused by *Burkholderia cepacia*. Additionally, she had several scalp abscesses caused by *Trichophyton tonsurans*. She presented in January 2003 for a routine outpatient visit without complaints. Her medications included 80 mg of trimethoprim/400 mg of sulfamethoxazole twice daily, 400 mg of cefixime daily, 200 mg of itraconazole daily, and 50 µg/m² IFN-γ administered subcutaneously 3 times weekly. Laboratory examination showed a white blood cell count of 7570/µL with 47% segmented forms and an erythrocyte sedimentation rate of 47 mm/h. A routine computed tomographic (CT) scan of the chest showed new lingular and right perihilar infiltrates (Fig 1, A). She was admitted to the hospital. A CT-guided fine-needle aspirate sample of the lingular infiltrate did not show any pathogen, and culture results were negative. Intravenous trimethoprim/sulfamethoxazole and ceftriaxone and oral voriconazole were begun empirically. A CT scan on hospital day 13 showed a slight increase in both infiltrates. Repeat fine-needle aspiration showed small forms that were not initially identified but were thought to resemble *Pneumocystis jiroveci*. However, the results of both immunofluorescent mAb staining and PCR for *P jiroveci* were negative. No microbiologic diagnosis was made. Because the patient continued to do well clinically, she was discharged to home on intravenous trimethoprim/sulfamethoxazole, ceftriaxone, and oral voriconazole.

Two weeks after discharge, she returned without complaints. A chest CT scan showed progression in both infiltrates, despite continued antimicrobial therapy (Fig 1, B). The white blood cell count was 9300/µL with 51%

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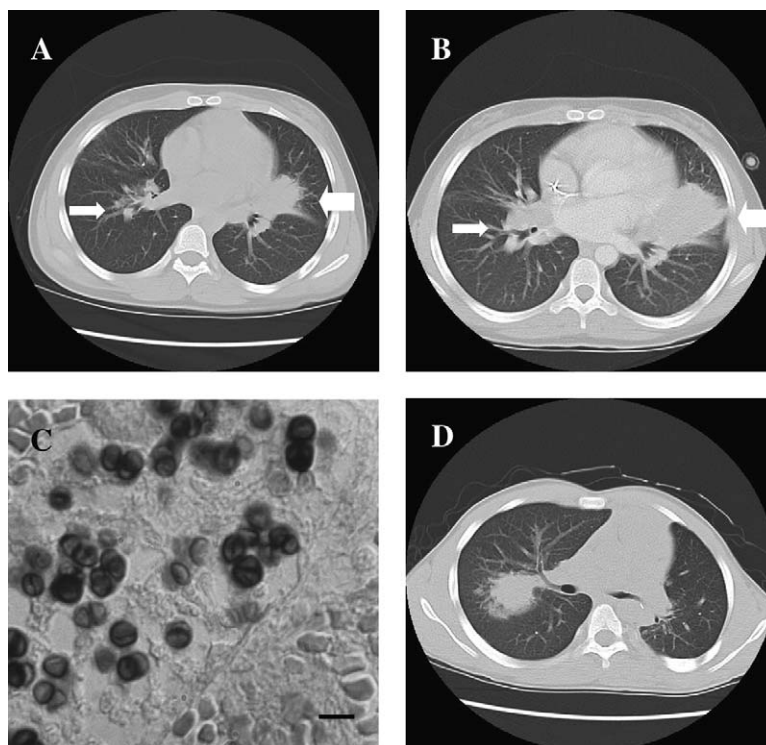


FIG 1. A, Case 1: CT scan of chest indicating new lingular (large arrow) and right perihilar (small arrow) infiltrates. B, Follow-up CT scan 4 weeks later showed progression of both infiltrates. C, Cell block section of the repeat needle aspirate stained with Grocott Methenamine Silver showing clusters of *T inkin* cells (bar = 6 μ m). D, Case 2: CT scan indicating new right midlung infiltrate.

segmented forms, and the erythrocyte sedimentation rate was 79 mm/h. A repeat CT-guided fine-needle aspirate sample of the lingular infiltrate showed oblong to globose fungal cells on Grocott Methenamine Silver staining (Fig 1, C), morphologically resembling the agents of chromoblastomycosis, as well as sarcinae, of *Trichosporon inkin* (*Sarcinosporin inkin*).¹ The hematoxylin and eosin-stained cellblock section, however, showed no pigment in the cell wall, which is more consistent with sarcinae of *T inkin*. Antibiotics and voriconazole were discontinued, and the patient was started on liposomal amphotericin B and daily granulocyte infusions. CT scans on hospital days 15 and 22 showed an increase in the infiltrates. On hospital day 23, she underwent resection of the superior segment of the left upper lobe (lingula). Surgical pathology showed fungal cells morphologically consistent with *T inkin*, and *T inkin* grew in pure culture. The *T inkin* isolate had a reported minimum inhibitory concentration (MIC) of 0.03 μ g/mL at 24 hours and 0.06 μ g/mL at 48 hours for itraconazole and voriconazole and an MIC of 0.03 μ g/mL at 24 hours and 0.06 μ g/mL at 48 hours for posaconazole.

After surgery, caspofungin was added, and liposomal amphotericin B was continued. On hospital day 36, CT scans showed no change in the right perihilar infiltrate. Liposomal amphotericin B was stopped, and posaconazole was started. On hospital day 37, she underwent resection of the right medial basilar segment of the right

lower lobe. The surgical pathology was again consistent with an infection caused by *T inkin*.

Because of the robust failures of all antifungal therapies and the apparent success of the bilateral thoracotomies, the patient was discharged to home on no antifungal therapy. Two months after discharge, the patient had pancreatitis and a new right-lower-lobe infiltrate. A CT-guided fine-needle aspirate sample of the infiltrate grew *Serratia marcescens* only. However, fungal cells morphologically consistent with sarcinae of *T inkin* were again seen on special stains. The patient was treated with intravenous meropenem and sulfamethoxazole/trimethoprim alone, and no antifungal therapy was initiated. The pancreatitis and pneumonia resolved completely. Repeat chest CT scanning 8 weeks later showed no residuum of the pneumonias from which the *T inkin* had been obtained.

Case 2

The 13-year-old brother of the patient described in case 1 also had autosomal recessive CGD caused by p47^{phox} deficiency diagnosed at age 7 years during family screening. Infections included pneumonia caused by *Cladophialophora bantiana* that was treated with amphotericin B, flucytosine, and left-lower-lobe wedge resection. In 1999, he had pneumonia caused by *T inkin* that was successfully treated with amphotericin B and left

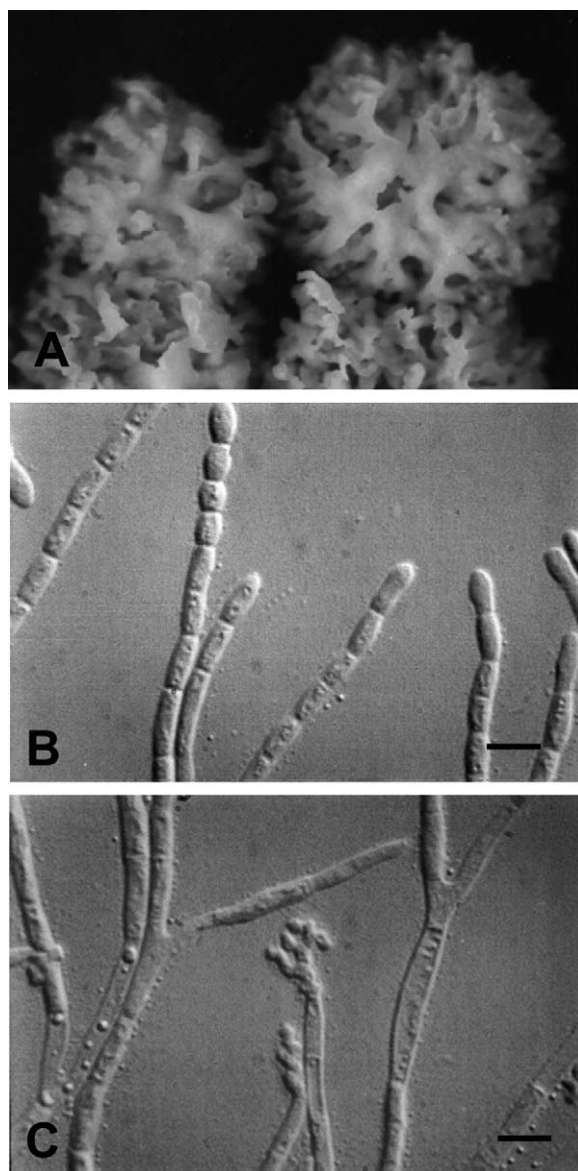


FIG 2. A, Five-day-old colonies of *T inkin* (from the patient described in case 1) grown on potato dextrose agar at 30°C, showing a highly wrinkled dry surface (2×). B, Arthroconidia (bar = 6 μm). C, Appressoria produced at the tip of the hyphae (bar = 6 μm).

upper lobe wedge resection. At the time of this presentation, in March 2003, he had no complaints. His medications included 200 mg of itraconazole daily, 80 mg of trimethoprim/400 mg of sulfamethoxazole twice daily, 400 mg of cefixime daily, and 500 mg of levofloxacin daily. The white blood cell count was 4680/μL with 57% segmented forms, and the erythrocyte sedimentation rate was 35 mm/h. A routine CT scan showed a new large infiltrate in the right midlung field (Fig 1, D) and a pleural-based nodule at the left base. A fine-needle aspiration biopsy specimen of the right-sided infiltrate yielded a yeast-like organism resembling *T inkin*. He was initially

started on intravenous trimethoprim/sulfamethoxazole, ceftriaxone, and oral voriconazole. After identification of *T inkin*, antimicrobial agents, including voriconazole, were stopped, and the patient was started on posaconazole. CT scans on hospital days 10 and 16 showed an increase in the right lung infiltrate. On hospital day 17, he underwent right upper lobe posterior segmentectomy. Surgical pathology was identical to that in case 1, and *T inkin* grew in pure culture. The *T inkin* isolate had a reported MIC of 0.03 μg/mL at 24 hours and 0.06 μg/mL at 48 hours for posaconazole. CT scanning on hospital day 31, after 24 days of posaconazole, showed an increase in the left basilar nodule. Resection of the left-lower-lobe nodule was performed on hospital day 38. Pathology from this surgery showed sarcinae consistent with *T inkin*, and a strain of *T inkin* morphologically indistinguishable from that seen in case 1 grew in pure culture. The patient was continued on posaconazole and was doing well at 9 months of follow-up.

DIFFERENTIAL DIAGNOSIS

CGD is a rare inherited disorder resulting in defective production of toxic oxygen metabolites by phagocytes. Inheritance can be X-linked, with mutations affecting the membrane-bound gp91^{phox}, or autosomal recessive, with mutations in the genes encoding p47^{phox}, p67^{phox}, and p22^{phox}.² The disease is characterized by granuloma formation in several organ systems and frequent, often life-threatening infections. Patients are particularly susceptible to infections caused by catalase-producing organisms, such as *Staphylococcus*, *Burkholderia*, *Serratia*, *Nocardia*, and *Aspergillus* species.³ Patients are routinely started on prophylaxis with trimethoprim/sulfamethoxazole, itraconazole, and IFN-γ. Despite these measures, the mortality caused by CGD is 2% to 5% per year.³

Review of a registry of 368 patients with CGD revealed that 79% of these patients had been given diagnoses of pneumonia at least once in their lifetime.³ The most common organisms to cause pneumonia in these patients were *Aspergillus* species (33%), *Staphylococcus* species (9%), *Burkholderia* species (7%), *Nocardia* species (6%), and *Serratia* species (4%). Therefore when the patient described in case 1 was given a diagnosis of bilateral infiltrates, her initial empiric coverage was broad and included coverage of all of these organisms. Although these are the most common organisms to cause pneumonia in patients with CGD, there are many other organisms also reported to cause pneumonia, although at much lower rates: *Mycobacteria* species, *Klebsiella* species, *Francisella philomiragia*, *Chromobacterium violaceum*, *Paecilomyces* species, and other species. In most cases tissue or biopsy specimens must be obtained to make a definitive diagnosis. Therefore fine-needle biopsy was pursued immediately in both cases. Direct visualization of the fungus in tissue, as well as mycologic testing, helped make the diagnosis of invasive infection with *T inkin*.

LABORATORY AND OTHER TESTING PROCEDURES

Biopsy specimens of the lung tissue obtained from both patients were cultured on various mycologic media and incubated at 30°C. Small dry colonies of a yeast-like fungus grew from the specimens in 24 hours. The colonies were cream to light yellow in color and became highly convoluted by 5 days' incubation (Fig 2, A). Colony characteristics of the isolates obtained from the 2 patients were identical, without notable variations with changes in media or growth temperature. The isolates grew faster at 37°C than at 30°C and continued to grow at 42°C, although it took 72 hours before growth became evident. Slide cultures prepared with corn meal agar revealed chains of oval or barrel-shaped to cylindrical arthroconidia resembling that of *Trichosporon* species (Fig 2, B). Occasional hyphae bearing terminal or lateral appressoria (infectious structures of fungi) indicative of *T inkin* were also observed (Fig 2, C). The assimilation reactions obtained with the API 20C (BioMerieux Vitek, St Louis, Mo) were consistent with the analytic profile of *T inkin* for both isolates. Because *T inkin* has rarely been isolated from the lungs, further studies with molecular techniques were carried out. The sequences of small-subunit ribosomal DNAs were amplified by using the PCR primers (1, 5'-AGAGGCCTACCATGGTATCA-3'; 2, 5'-TAAGACC-CAATAGAGCCCTA-3') for generic identification of *Trichosporon* species.⁴ DNA of *Trichosporon mucoides* was used as the positive control, whereas *Candida albicans*, *Saccharomyces cerevisiae*, *Cryptococcus neoformans*, and *Candida glabrata* were used as the negative controls. The PCR reaction amplified a single 170-bp DNA band only from *T mucoides*, the positive control, and the isolates from the 2 siblings (Fig 3). To confirm the species status of the isolates, the divergent domain at the 5' end of the large-subunit ribosomal DNA (D1/D2 of the 26S) was amplified with the primer set NL-1 and NL-2.⁵ The PCR clones thus obtained were sequenced, and the sequences of multiple clones were identical. The D1/D2 sequences were aligned with those in the database by using the MacVector computer program. The sequences of the D1/D2 regions of the 2 isolates were identical and matched with that of *T inkin*.

TENTATIVE DIAGNOSIS WITH DISCUSSION OF PATHOGENESIS

These patients were both given diagnoses of *T inkin* on the basis of mycologic testing of the biopsy specimens. *Trichosporon* Behrend is a genus of basidiomycetous yeast capable of causing superficial infections, as well as deep-seated infection, in certain immunocompromised hosts. There are 6 medically relevant species: *Trichosporon asahii*, *Trichosporon asteroides*, *Trichosporon cutaneum*, *T inkin*, *Trichosporon mucoides*, and *Trichosporon ovoides*.⁶

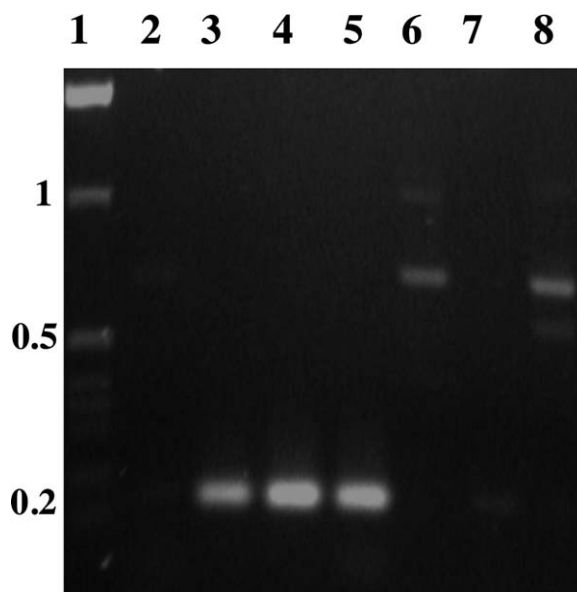


FIG 3. PCR amplification products (170-kb fragment) of the small subunit ribosomal DNA of various yeasts. Lane 1, Molecular weight marker (kb); lane 2, *Candida albicans*; lane 3, *T mucoides*; lane 4, *T inkin* from case 2; lane 5, *T inkin* from case 1; lane 6, *Candida glabrata*; lane 7, *Cryptococcus neoformans*; lane 8, *Saccharomyces cerevisiae*.

T inkin is the causative agent of white piedra, a fungal infection of the hair shaft, in the genital area and has also been reported to cause several invasive infections. Table 1⁷⁻¹⁵ outlines the cases of invasive infection with *T inkin* reported in the literature, as well as the 2 cases in this report. Previous cases include prosthetic mitral and aortic valve endocarditis in 2 patients,^{7,8} continuous ambulatory peritoneal dialysis (CAPD) catheter-associated peritonitis in 3 patients,⁹⁻¹¹ implanted venous catheter-related infection in a patient undergoing ablative chemotherapy,¹² and 3 cases of pulmonary infection in patients with CGD.¹³⁻¹⁵ With the 2 cases reported here, the total reported cases are 11, 5 of which have been in patients with CGD. Of note, our patient reported in case 2 had a pulmonary infection with *T inkin* 4 years earlier, which was not reported. Most important, the patients described in these cases were treated with a variety of antifungal agents, but common to all successful treatment was the removal of infected devices or infected tissue.

We have reviewed the methods that were used to establish mycologic diagnoses of *T inkin* in these cases, and we consider 3 of the diagnoses to be questionable because they lack definitive histology or molecular sequencing. *T inkin* can be misidentified in the routine diagnostic laboratory if only an API 20C AUX strip is used for identification because neither version of this strip distinguishes between *T inkin* and *T ovoides*. Similarly, histology can only be used to distinguish *T inkin* from *T ovoides* if sarcinae are present. Sarcinae are the result of incomplete separation of cells after division and are characteristic of *T inkin*. In the reported case of *T inkin*–

TABLE I. Infections caused by *T inkin*

Year, reference	Age (y), sex	Underlying disease/ risk factor	Clinical syndrome	Treatment	Outcome	Mycology
1990, Kenney et al ¹³	18, M	CGD	Pneumonia	● Surgical resection ● Amphotericin B and WBC transfusions, followed by oral itraconazole	Cure	Reliable
1996, Chaumentin et al ⁷	46, F	Prosthetic mitral valve	Endocarditis	● Valve replacement ● Amphotericin B, followed by oral itraconazole	Cure	Inconclusive*
1997, Lopes et al ⁹	45, M	Renal failure, CAPD	Peritonitis	● Catheter removal ● Oral fluconazole	Cure	Reliable
1998, Mussa et al ¹⁴	9, F	CGD	Pneumonia, paraspinal mass	● Ketoconazole	Death	Reliable
2000, Piwoz et al ¹⁵	9, M	CGD	Lung abscess	● Surgical resection ● Liposomal amphotericin, rifampin, miconazole, and WBC transfusions	Cure (death soon after from unrelated cause)	Reliable†
2001, Moretti-Branchini ¹²	42, M	Acute myelogenous leukemia, ablative chemotherapy	Catheter infection	● Catheter removal ● Oral fluconazole	Cure	Reliable
2003, Crowther et al ¹⁰	45, M	Renal failure, CAPD	Peritonitis	● Catheter removal ● Oral fluconazole and flucytosine	Cure	Inconclusive‡
2003, Madariagi et al ¹¹	49, F	Renal failure, CAPD	Peritonitis	● Catheter removal ● IV caspofungin	Cure	Inconclusive§
2004, Ramos et al ⁸	52, M	Prosthetic aortic valve	Endocarditis	● No surgery or antifungal therapy; patient died before diagnosis was made	Death	Reliable
Case 1	9, F	CGD	Pneumonia	● Surgical resection ● Intravenous voriconazole, liposomal amphotericin, WBC transfusions, caspofungin, posaconazole	Cure	Reliable
Case 2	13, M	CGD	Pneumonia	● Surgical resection ● Posaconazole	Cure	Reliable

WBC, White blood cell.

*Histology not diagnostic of *T inkin*; serology not validated as a diagnostic tool for infections caused by *T inkin*.†API 20C AUX not reliable for identification of *T inkin*. However, subsequent review of histology confirms *T inkin*.‡No information given regarding method of diagnosis of *T inkin*.§API 20C AUX not reliable for identification of *T inkin*.

induced lung abscess in a boy with CGD,¹⁵ histologic examination demonstrated “intracellular yeast forms with rudimentary hyphae.” Without evidence of sarcinae, this alone is not diagnostic of *T inkin*. Furthermore, the API 20C AUX strip used to identify *T inkin* is not reliable as a sole identifier. However, review of the slides (generously provided by Dr Cunningham-Rundles) did show sarcinae to be present, confirming this as a true case of *T inkin* infection. In the case of *T inkin*-induced mitral valve endocarditis,⁷ *T inkin* was diagnosed by means of culture on the basis of septate hyphae with arthrospores and yeasts, which is not definitively diagnostic of *T inkin*.

Serology was also used to support the diagnosis of *T inkin*, but use of specific antibodies has not been validated to be reliable in distinguishing infection caused by *T inkin* from closely related *Trichosporon* species, such as *T ovoides*. In the case of *T inkin*-induced peritonitis in a 49-year-old African-American woman,¹¹ the diagnosis is unreliable because an API 20C AUX strip was used to identify *T inkin*, with no mention of sarcinae being seen on culture or molecular sequencing being performed. Finally, in the case of *T inkin*-induced peritonitis in a patient returning from the Caribbean,¹⁰ no information is given regarding the microbiologic diagnosis of *T inkin*.

Of the 6 reported cases with reliable mycologic diagnoses, 4 can be considered truly invasive infection: prosthetic aortic valve endocarditis,⁸ pneumonia,¹³ pneumonia with paraspinous mass,¹⁴ and lung abscess.¹⁵ The additional 2 cases of reliable mycologic diagnoses were catheter-related infections: peritonitis related to CAPD catheter⁹ and line-related infection.¹² With the exception of the case of prosthetic aortic valve endocarditis, the truly invasive infections all occurred in patients with CGD.

The 2 cases reported here are typical for CGD. Both patients were asymptomatic, and infiltrates were only discovered on routine screening CT scans. Both patients were receiving itraconazole prophylaxis when they had the infections. Despite aggressive attempts to isolate a pathogen, the diagnosis in case 1 was elusive and required 3 fine-needle aspirates before *T inkin* was identified. The diagnosis in case 2 was facilitated by proximity in time to case 1, allowing for easier recognition of *T inkin*. An unusual aspect of these cases is that the patients were siblings and lived in the same home. It is unclear what common exposure these siblings might have shared that led to their infections. Another brother with CGD living in the same home has not had an infection with *T inkin*.

FINAL DIAGNOSIS AND TREATMENT-MANAGEMENT PLAN

Both of these patients with CGD were given definitive diagnoses of invasive *T inkin* infections. There is very little information published about the treatment of invasive infection caused by *T inkin*. All successfully treated cases have required surgical resection for cure. The patient described in case 1 was initially treated with voriconazole, a broad-spectrum azole. Like other azoles, it inhibits cytochrome P450 14 α -lanosterol demethylase, an enzyme necessary for the production of ergosterol, a component of the fungal cell wall. Despite susceptibility testing that indicated sensitivity to voriconazole, the patient described in case 1 showed a progression of disease while receiving this agent.

Her antifungal therapy was then changed to liposomal amphotericin B, a polyene that binds to sterols in the fungal cell membrane and disrupts the osmotic stability of the membrane. Again, there was progression of disease. Therefore the patient underwent surgery and was then started on caspofungin. Caspofungin is a member of a new class of antifungals, echinocandins, that work by blocking the synthesis of the fungal cell wall component 1,3- β -D-glucan, resulting in osmotic instability. There was no improvement on this medication. Therefore posaconazole, an investigational azole antifungal agent, was started, and the patient underwent a second operation.

The patient described in case 2 was given his diagnosis after the first patient had shown progression of disease despite treatment with 3 classes of antifungals. He was therefore started on posaconazole in the hope that it would effectively inhibit the growth of *T inkin*. Susceptibility testing showed the *T inkin* isolate from the patient to be

sensitive to posaconazole, but his infiltrate increased with this therapy, and he too required surgery.

The most common risk factors for disseminated trichosporonosis are abnormalities involving neutrophils, either in number or function. Patients with CGD have impaired neutrophil activity and are at increased risk for infection, especially by organisms that produce catalase, such as *Trichosporon* species. In an effort to better understand host defense mechanisms against *Trichosporon* species, Lyman et al¹⁶ examined the functional responses of normal neutrophils and monocytes to *Trichosporon beigeli* (synonym *Trichosporon cutaneum*). After serum opsonization, the percentage of organisms phagocytosed was significantly lower for *T beigeli* than for *Candida albicans*. In addition, fungicidal activity of neutrophils and monocytes was significantly impaired against *T beigeli* compared with *Candida albicans*. The authors speculated that higher levels of effector/target ratios might be necessary to control *T beigeli*. It follows that impaired neutrophil function, as in CGD, is a risk for infection with *Trichosporon* species. A recent report of spontaneous disseminated trichosporonosis in a murine model of CGD confirms the critical role of the reduced nicotinamide adenine dinucleotide phosphate oxidase in this infection.¹⁷

Management of these patients was challenging. Both patients had progression of disease despite aggressive therapy spanning the major therapeutic antifungal agents, including those predicted to be of value by means of susceptibility testing. The patient described in case 1 underwent 4 weeks of therapy with voriconazole, followed by 5 weeks of treatment with liposomal amphotericin, in addition to daily granulocyte infusions. Despite these, her infiltrates increased. She also received 2 weeks of caspofungin in addition to liposomal amphotericin B after resection of the lingula. Still, the right perihilar infiltrate increased in size and required resection. The patient described in case 2 was treated with posaconazole for 16 days, with progression of bilateral infiltrates. After 24 days of therapy, he had progression of disease in the left lower lobe, and *T inkin* continued to grow in culture. Therefore *T inkin* infection in CGD appears to be resistant to amphotericin B, liposomal amphotericin B, caspofungin, itraconazole, voriconazole, posaconazole and granulocyte transfusions.

SUMMARY STATEMENT

The treatment of invasive *T inkin* infections is difficult. There is very little information about *in vivo* response to antifungal therapy, and *in vitro* susceptibility testing can be misleading. It is clear from the reported cases that treatment of *T inkin* infection requires removal of infected prosthetic material or surgical resection of involved tissue. The patient with mitral valve endocarditis who underwent surgery did well after valve replacement,⁷ and the patients with peritonitis recovered after removal of the CAPD catheters.⁹⁻¹¹ The patient with the venous catheter infection also did well after removal of the catheter.¹² In 2 of

the 3 cases of pulmonary infection in CGD,^{13,15} as well as in the 2 cases reported here, the patients did well with surgical resection, regardless of the antifungal therapy. The 2 reported fatalities caused by *T inkin* (mitral valve endocarditis and pneumonia with spinal mass)^{8,14} were in patients who did not undergo surgery. Current antifungal therapy is not sufficient to treat invasive infection caused by *T inkin*. Removal of infected devices or tissue remains the only proved means by which to cure these infections.

CLINICAL PEARLS

- Invasive *T inkin* infection should be considered in the differential diagnosis in patients with CGD and pulmonary infiltrates.
- *T inkin* must be identified by the presence of sarcinae on histology or by means of molecular sequencing. Identification of *T inkin* cannot be made with an API 20C AUX strip alone.
- Invasive *T inkin* infection cannot be treated with antifungal therapy alone. Removal of infected prosthetic devices or infected tissue is required for cure.

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