

Case Report/Case Series

Trichosporon inkin as an Emergent Pathogen in Patients With Severe Pemphigus

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IMPORTANCE To our knowledge, these are the first reports of bloodstream infections by *Trichosporon inkin* in patients with pemphigus.

OBSERVATIONS *Trichosporon inkin*, a novel organism causing bloodstream infection, was detected in 2 patients with pemphigus. An elderly man with pemphigus foliaceus died despite treatment with liposomal amphotericin B, 3 mg/kg/d, and a young girl with pemphigus vulgaris responded to treatment with voriconazole, 8 mg/kg/d, for 24 days. One of the *T inkin* isolates had a minimal inhibitory concentration of 2 mg/L against amphotericin B, suggesting resistance to the drug.

CONCLUSIONS AND RELEVANCE Delayed suspicion of invasive infection by *T inkin* may result in a poor outcome in patients with severe forms of pemphigus. This opportunistic infection is highly refractory to conventional potent antifungal treatment.

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Treatment for pemphigus relies on systemic corticosteroids, usually administered with other immunosuppressant agents. Treatment controls disease activity but may lead to severe infections.¹ Mortality rates can reach 80% to 100% in patients with pemphigus who develop septicemia.^{2,3}

Trichosporon inkin is the etiologic agent of white piedra, a benign disease of hair shafts.⁴ Invasive fungal infection caused by this species was described⁴ in patients with predisposing factors, such as oncohematologic diseases and neutropenia. Recently, invasive fungal infection caused by *T inkin* was reported in patients in our hospital who underwent solid organ transplantation.⁵ Our aim is to report what we believe to be the first cases of deep-seated infections related to *T inkin* in patients with pemphigus.

Positive blood cultures (obtained using Bactec Plus Aerobic/F; Becton Dickinson and Company) were plated (CHROMagar Candida; Becton Dickinson and Company), and phenotypic identification was carried out by urease test, slide culture, and the carbon assimilation panel (API 20AUX; bioMérieux). To confirm species identification, double-strand sequencing of the ribosomal DNA intergenic spacer 1 region was performed⁶; sequences were then compared with those in the GenBank database (<http://www.ncbi.nlm.nih.gov>). Antifungal susceptibility testing for amphotericin B, fluconazole, itraconazole, and voriconazole was carried out using the recently revised European Committee on Antimicrobial Susceptibility Testing microdilution method for yeasts.⁷

Report of Cases

Case 1

A 71-year-old man who had developed pemphigus foliaceus 6 months before the hospital consultation had disseminated erythematous, desquamative skin lesions and pustules restricted to his buttocks and lower extremities. He was receiving systemic treatment with prednisone, 1 mg/kg/d. Laboratory evaluation results showed (1) pemphigus foliaceus with secondary impetiginization (Figure 1A), (2) intraepidermal intercellular IgG and C3 deposits (Figure 1B), and (3) intercellular intraepidermal staining (titer, 1:5120) (Figure 1C).

The prednisone dose was increased to 1.5 mg/kg/d, and cephalexin, 2 g/d for 14 days, was prescribed for treatment of a secondary bacterial skin infection. The patient had persistent hyperglycemia, which was treated with insulin. Although his skin lesions improved, the patient developed fever and respiratory symptoms due to right-sided pneumonia 30 days after the prednisone dose was increased. Despite antimicrobial therapy with piperacillin sodium-tazobactam sodium, 16 g/d, and vancomycin hydrochloride, 2 g/d, the infection progressed, and the patient developed septic shock, respiratory failure, and renal failure. He was transferred to the intensive care unit and underwent mechanical ventilation and hemodialysis. On day 34, 2 sets of blood cultures that were collected on the patient's admission to the intensive care unit revealed budding yeast cells that were identified as *Candida*

Figure 1. Clinical and Histopathologic Findings From Case 1



A, Pemphigus foliaceus extending from the patient's back to his lower extremities. B, Histopathologic findings demonstrate subcorneal cleavage in pemphigus foliaceus (hematoxylin-eosin, original magnification $\times 100$). C, Direct immunofluorescence shows intraepidermal intercellular IgG deposits (hematoxylin-eosin, original magnification $\times 200$).

albicans (day 38). Therapy with liposomal amphotericin B, 3 mg/kg/d, was started. On day 39, the patient developed a new episode of septic shock. A primary culture of tracheal aspirates yielded yeast cells interpreted as "colonizing agents." Skin scrapings collected from the patient's face and anterior abdomen on the same day also showed abundant yeast cells and arthroconidia (Figure 2). The patient died 2 days later.

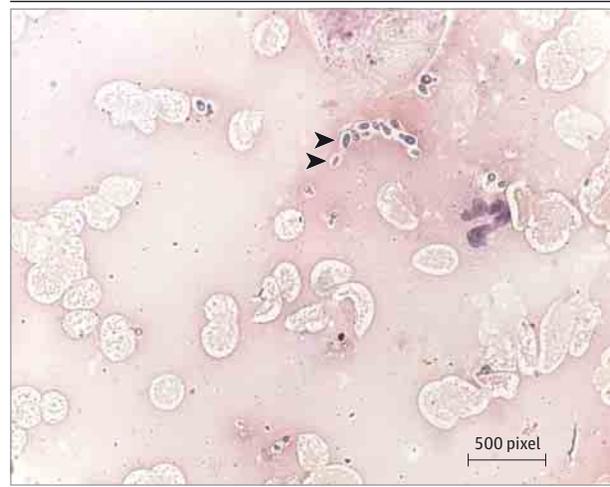
Three consecutive sets of blood cultures collected during amphotericin B treatment on days 39, 40 (through the central venous catheter), and 41 were positive, with budding and arthrosporic fungal elements on Gram stain. *Trichosporon inkin* was identified in the 3 samples.

Case 2

A 9-year-old girl with pemphigus vulgaris was hospitalized with fever and worsening skin lesions. She was receiving oral prednisone, 1 mg/kg/d. Physical examination revealed extensive oral mucosal erosions and ulcerations with superficial bullae on her trunk as well as her upper and lower limbs. Laboratory evaluation results showed (1) suprabasal epidermal acantholysis, clefting, and blister formation; (2) intercellular IgG and C3 deposits at the lower layers of the epidermis; and (3) intercellular intraepidermal staining, titer 1:2560.

Bacterial infection of the skin was treated with vancomycin, 1 g/d, and piperacillin-tazobactam, 6.75 g/d. Blood cultures collected on admission were negative for organisms; the prednisone dose was increased to 1.5 mg/kg/d and then was replaced by betamethasone sodium phosphate, 6 mg/d. On day 5, the patient experienced a new episode of

Figure 2. Skin Scraping From the Patient With Pemphigus Foliaceus



Yeastlike cells and arthroconidia (arrowheads) are suggestive of *Trichosporon* (hematoxylin-eosin, original magnification $\times 1000$).

fever. Subsequent blood cultures showed budding yeast cells on direct examination, and *T inkin* was identified 2 days later. Fluconazole, 300 mg/d, was prescribed. Despite antimicrobial and antifungal therapy, the fever persisted. On day 15, treatment was switched to voriconazole, 8 mg/kg/d, which was maintained for 24 days. The patient was discharged after 112 days of hospitalization.

Discussion

The 2 urease-positive isolates were initially identified as *T inkin*. Ribosomal DNA intergenic spacer 1 region sequencing confirmed the species identification. Antifungal susceptibility testing revealed that the isolate of *T inkin* from the patient in case 1 had a minimal inhibitory concentration (MIC) of 2.0 mg/L for amphotericin B, suggesting resistance to this drug. The *T inkin* isolates in both patients had 100% similarity to a sequence available in GenBank (FJ153608.1). The MICs for cases 1 and 2, respectively, were amphotericin B, 2.0 and 0.5 mg/L; fluconazole, 2.0 and 1.0 mg/L; voriconazole, 0.03 and 0.03 mg/L; and itraconazole, 0.06 and 0.25 mg/L.

Opportunistic infections in pemphigus, although not rare, are seldom reported. In one study,⁸ *Nocardia*, cytomegalovirus, *Legionella*, and *Listeria* were the most frequent organisms linked to opportunist infections, affecting elderly patients as well as those receiving prophylaxis for *Pneumocystis jirovecii*. Although neutropenia is the major predisposing risk factor for invasive trichosporonosis, both of our patients had white blood cell counts within the reference range.⁹ The severity of cutaneous/mucosal involvement and development of diabetes mellitus, which were present in our patients, are also risk factors for infections in patients with pemphigus vulgaris.²

Features shared by our patients were previous antibiotic therapy, indwelling catheters, and breakthrough infection during amphotericin B or fluconazole therapy. Cultures obtained from wounds, respiratory tract samples, and intravenous cath-

eters are often positive for *Trichosporon* before or during the episode of invasive infection.¹⁰ In the present report, the patient in case 1 demonstrated yeast in the tracheal aspirate skin sample collected on the same day as the first blood culture that identified *T inkin*. Despite belonging to the normal microbiota of the human gastrointestinal tract, respiratory tract, and skin, *T inkin* is potentially acquired through the hospital environment.¹¹ Neither of our patients had hair lesions compatible with white piedra. Our cases therefore were nosocomial infections of unknown sources caused by *T inkin*.

Clinical breakpoints have not been defined for *Trichosporon* species, and the MICs cannot be reliably interpreted as indicating resistance or susceptibility.^{7,12} *Trichosporon asahii* is the most commonly isolated species in invasive trichosporonosis, and a high percentage of these isolates have MICs above 1.0 mg/L, suggestive of resistance to amphotericin B.¹³ Among the few clinical isolates of *T inkin* tested, some MICs above 1.0 mg/L for amphotericin B have been described. One of our isolates had an MIC of 2.0 mg/L for amphotericin B. Among theazole derivatives, voriconazole seems to have the strongest in vitro activity against *Trichosporon* isolates.¹³

Conclusions

The identification of yeasts from nonsterile sites, such as the respiratory tract and skin, may cause suspicion of *T inkin* infection in patients with pemphigus. In such instances, voriconazole therapy should be promptly initiated.

ARTICLE INFORMATION

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NOTABLE NOTES

Magic of the Skin

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The earliest record of magic as a performing art is that of the magician Dedi in ancient Egypt in 2700 BC. Over time, magicians developed a vast array of tricks using craftsmanship, showmanship, thrill, and intrigue.

The skin has often been an important element of a magician's illusions. Coins can be hidden in skin folds. By pouring rubber cement on the skin, it becomes sticky and small objects like a pen can be hidden. Fake skin is used in tricks where body parts are sawed off. The American magician Harry Houdini was notable for his extraordinary escape acts in which he would free himself from handcuffs, restraints, straitjackets, and locked objects. When Houdini was young, he studied lock picking, and it is speculated that Houdini would occasionally hide lock picks in the calluses of his feet.¹ The modern day magician David Blaine uses a trick whereby a needle repeatedly inserted through the skin of the arm over many years creates a tunnel of scar tissue into which small objects can be hidden.

Lying on a bed of nails is a magic trick dating to meditation practices in ancient India. In this trick, a person lies between 2 boards of nails while another individual uses a sledgehammer to break a concrete cinder block located on the top board. The person between the boards is unharmed owing to the inertia of the concrete cinder block and energy spent in deconstructing it.² Although the individual nails are sharp, the skin is not pierced because the force of each nail on the skin is reduced by spreading body weight over the total number of nails and area in contact with the skin. Another magic trick creates the illusion of fire-proof skin. The trick is performed by soaking a cotton ball in a mixture of water and rubbing alcohol and lighting it on fire while it is in the magician's hand. While water

prevents the cotton from igniting, the alcohol concentrates on the outside of the ball due to its high vapor pressure and burns, creating the illusion that the magician is holding a ball of fire.

In the "rubber-hand illusion" described by Ehrsson et al,³ the subject views a fake, rubber hand as his or her own. When the subject strokes a rubber hand while his or her own hand is hidden from view and stroked simultaneously, an illusion is created that the rubber hand belongs to the subject. Information obtained through cutaneous sensory receptors integrates with the visual information about the body.

These tricks depict how the skin, as the boundary between the mind-body connection and external surroundings, is an organ that has been used by magicians to deceive and entertain audiences throughout time.

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