Unusual Fungal Pathogens in Leg Ulcers at a North Carolina Wound Center

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Abstract: Over a 7-month period (October 2008–April 2009), 150 patients were seen at a North Carolina wound care center, two of whom presented with unusual fungal infections—Rhodotorula and Chromblastomycosis. Both patients responded to topical antifungal therapy, and in one case, a unique combination of silver and miconazole. The authors were unable to locate a reference to this treatment combination in the literature. Fungal infections, particularly in combination with bacteria, may prove to be an emerging problem, and should encourage wound care center specialists to check for fungal infections in cases of refractory ulcers.

Keypoints
- Fungal infections in leg ulcers are rare
- Only 20 articles have been published on fungal infections in leg ulcers over the last 40 years

Case Reports

Case 1. A 62-year-old black man who was a retired textile worker with multiple comorbidities presented with diabetes mellitus, end-stage renal disease (on hemodialysis), coronary artery bypass, and was a former smoker. He presented on October 27, 2008 with a 3-week history of a blister, which had broken to form an irregular pretibial ulcer. The patient did not have a history of trauma or insect bites.

Examination revealed an ulcer measuring 1.6 cm x 3 cm with a black
eschar, no odor, and greenish exudate. Pathology on the debrided tissue showed invasive fungal elements most consistent with Phialophora, which is a form of Chromoblastomycosis associated with severe gangrenous changes. Escherichia coli was also cultured.

The E coli was treated with oral ciprofloxacin. Initially, the ulcer was treated with a 7-day silver-coated antimicrobial dressing (Acticoat 7™, Smith & Nephew Wound Management, Hull, UK) and a multilayer compression bandage system. The wound was debrided on November 13 and November 28, 2008 to remove eschar. The ulcer continued to increase in size. A subsequent pathology report showed fungus was present in the debridement tissue. At that point, miconazole and the antimicrobial dressing were applied simultaneously.

The patient was evaluated for deep venous thrombosis and venous disease, both of which were negative. A CT angiogram showed no occlusive arterial disease. Once the combination of miconazole and silver-coated antimicrobial dressing were applied, the ulcer progressively decreased in size until it eventually healed on January 2, 2009 (Figure 1). There has been no recurrence or any problems since that time.

In this patient’s case, the Infectious Disease consultation recommended itraconazole for the fungus component, but unfortunately the medication was too expensive for the patient. A compromise was made to address the problem with topical medications only, but even so, a gratifying response with this therapy was achieved.

Case 2. An 88-year-old white woman, who was a retired mill worker, was referred to the authors’ wound center on April 2, 2008. The patient presented with swelling and a painful rash on the lower part of both legs of 2 weeks’ duration. Comorbidities consisted of goiter history and peptic ulcer disease.

Examination showed an area on the left leg 31 cm x 21 cm and on the right leg 15 cm x 18.5 cm with a yeasty odor. Initially, the patient was treated with miconazole, triamcinolone, and Unna boots. She was given Diflucan 150 mg/day for 7 days. However, 1 week later the rash worsened and proceeded to spread to the abdomen and thighs. She also had conjunctivitis. A dermatology consultation revealed the patient had xerosis cutis, intertrigo, and stasis dermatitis.

Meanwhile, the culture of the patient’s skin eventually grew Rhodotorula mucilaginosa, and the treatment was changed to a combination of clotrimazole and triamcinolone. One item of interest was the fact that both clotrimazole and miconazole are imidazoles—synthetic anti-fungal agents that inhibit the enzyme cytochrome P450 14 alpha demethylase; however, the patient seemed to respond better to the clotrimazole than to the miconazole. The patient’s white cell count was 7.8 K/µL; the remainder of the laboratory work was unremarkable.

The rash rapidly improved with clotrimazole treatment. The infection was completely cleared by May 7, 2008, and 2 years later the patient remains disease- and problem-free.

Discussion

Sonck reported on yeast cultures from 11,700 human skin samples. He found that most were Candida species, but did isolate Rhodotorula rubra in 115 cases. He also noted combinations of infecting yeast species.

Merkur and Hodge found that Rhodotorula was a contaminant in most cases. In their opinion, human disease resulting from this organism is rare. They went on to describe a case of Rhodotorula in an HIV-positive man. They also stated, “it is becoming increasingly important to clinically recognize and consider such opportunistic organisms.” Similarly, Anatoliotaki et al also commented on the emergence of Rhodotorula as an opportunistic pathogen. Their review of literature spanning from 1960–2001 disclosed 47 cases of Rhodotorula fungemia.

Tuon, who noted the majority of those were associated with catheter placement and cancer, reviewed Rhodotorula infections reported in the literature. In the studied patient population, 79% had fungemia, 7% had an eye infection, and 5% had a peritoneal infection. According to Zaas et al, treatment remains controversial;
however, Rhodotorula is usually a fungus with low virulence from which most patients recover. In the present cases, the topical clotrimazole and triamcinolone treatment was sufficient in addition to being a well-established pharmaceutical strategy.

Conversely, Chromoblastomycosis can be difficult to eradicate. Antibiotics are recommended for any bacterial infection and itraconazole for the fungal component. Unfortunately, in the present case, the medication was too expensive; hence, the patient was treated with a topical combination of miconazole and silver-coated antimicrobial dressing. The response to the combination of silver and miconazole was satisfactory and the ulcer steadily decreased in size. The authors were unable to locate a reference in the literature regarding the use of this drug combination, although Codd reported the use of miconazole and chlorhexidine to treat oral candidiasis.

In retrospect, the patient in Case 1 fits the classic clinical picture for Chromoblastomycosis. Usually, the initial trauma that causes the infection is not recognized immediately, after which the infection grows over a period of a few years until small red papules appear. Complications arise such as the fungus spreading into the blood and lymphatic system. Multiple nodules may appear on the same limb, and a secondary bacterial infection may sometimes cause lymphatic obstruction. The central portion of the region may heal or it may ulcerate, as it did in Case 1. Apart from Japan, Chromoblastomycosis is rare in developed countries. In Portugal, for example, less than 10 cases have been reported.

It is interesting to note that in the case of Chromoblastomycosis (Case 1), the patient was co-infected with E coli, which led to the conjecture that the two organisms acted synergistically. This is a relatively new concept—an infectious collaboration of bacteria and fungi. Xu et al found that in the case of Candida, a peptidoglycan from bacteria causes the conversion of otherwise harmless C albicans to its infectious, virulent form. Anaissie et al also commented on the fact that fungi, such as Fusarium species, which were originally thought to represent harmless colonization, are now being recognized as serious pathogens.

**KEYPOINTS**
- Fusarium species, originally thought to be harmless, are now being recognized as serious pathogens

**Conclusion**
In cases of patients with unusual skin lesions, it would seem prudent to check for fungal infections via biopsy or culture, especially in view of the concept that fungi are emerging pathogens. Although treatment can be difficult, a pharmaceutical combination of topical antifungal agents was proved effective in the two cases presented. The combination of silver and miconazole provided a gratifying outcome and may be the first time that this combination has been used to treat fungal infections.

**References**