Cutaneous Infection by *Fusarium* Species in Healthy and Immunocompromised Hosts: Implications for Diagnosis and Management

Marcio Nucci and Elias Anaissie

1University Hospital, Universidade Federal do Rio de Janeiro, Brazil; and 2University of Arkansas for Medical Sciences, Little Rock

Infections by *Fusarium* species frequently involve the skin, either as the primary or the metastatic site. To better understand the pathophysiology of these infections, 43 new patients with fusariosis were evaluated, and the literature was reviewed. A total of 259 patients (232 immunocompromised and 27 immunocompetent) were identified. Skin involvement was present in 70% of patients, particularly in immunocompromised patients (72% vs. 52%; $P = .03$). In immunocompetent patients, cutaneous infections were characterized by preceding skin breakdown, localized involvement, slow pace of progression, and good response to therapy. In contrast, skin involvement in immunocompromised patients was only occasionally preceded by skin breakdown and typically was presented as rapidly progressive disseminated lesions at various stages of evolution. Metastatic skin lesions were associated with fungemia, neutropenia, and death. Skin was the single source of diagnosis for the majority of immunocompromised and immunocompetent patients. Recommendations for the prevention of fatal fusariosis originating from skin are presented.

Fungal infections represent an important complication for immunosuppressed patients and are associated with high morbidity and mortality [1, 2]. The limited diagnostic tools available usually delay the diagnosis and treatment of these infections. Therapy is complicated further by the variable susceptibilities of pathogens to antifungal agents [3]. Thus, any clue to the early diagnosis of infection with a specific pathogen may lead to changes in antifungal therapy and may be critical for an improved outcome. *Fusarium* species have long been recognized as a cause of localized infections in immunocompetent individuals [4] and disseminated infections among those who are severely immunocompromised [5]. *Fusarium* species now represent the second most frequent mold-causing invasive fungal infections in this latter population [5, 6].

One of the most frequent aspects of infection by *Fusarium* species is the development of skin lesions, which are frequently the only source of diagnostic material. Therefore, it is important to characterize the clinicopathological features of skin infection involvement in fusariosis and to establish their role in the diagnosis and management of this infection. We describe the characteristics of fusarial skin infections in immunocompetent and immunocompromised hosts and make practical recommendations for management.

PATIENTS AND METHODS

A computerized search of MEDLINE from January 1966 to October 2001 was performed; we used the keywords “*Fusarium*” and “fusariosis.” In addition, 45 previously unpublished cases of fusariosis from Brazil were included in our analysis [7]. We selected studies that provided a detailed description of the clinical presentation, treatment, and outcome. Reports with limited...
disseminated infection was defined as the presence of 1 lesion in noncontiguous sites. Categorical variables were analyzed by $\chi^2$ or Fisher’s exact test. Registration and analysis of data were performed by EpiInfo 6.04 software (Centers for Disease Control and Prevention). $P \leq .05$ was considered to be statistically significant.

RESULTS

There were 157 reports describing fusarial infections between 1970 and 2001. Cases described in 31 reports were excluded because of publication in languages other than English ($n = 15$), lack of detailed clinical description ($n = 12$), and duplicate publication ($n = 4$). Thus, we examined 126 publications reporting 216 patients with fusariosis [5, 8–131]. Forty-three previously unpublished cases of fusarial infections from a multicenter Brazilian study [7] also were included, for a total of 259 patients. The 259 evaluated patients included 232 who were immunocompromised (90%) and 27 who were immunocompetent (table 1). Skin involvement by fusariosis was present in 181 patients (70%) and was more common among immunocompromised patients (72% vs. 52%; $P = .03$).

**Table 1. Underlying conditions in 259 cases of fusariosis in immunocompromised and immunocompetent patients.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. (%) of patients</th>
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<tbody>
<tr>
<td>Immunocompromised</td>
<td>232 (88)</td>
</tr>
<tr>
<td>Cancer</td>
<td>205 (80)</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Solid-organ transplantation</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Renal</td>
<td>4</td>
</tr>
<tr>
<td>Heart and lung</td>
<td>1</td>
</tr>
<tr>
<td>Heart and liver</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2)</td>
</tr>
<tr>
<td>AIDS</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Chronic neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>1</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>27</td>
</tr>
<tr>
<td>None</td>
<td>15 (56)</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Renal failure, chronic ambulatory dialysis</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Burns</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Heatstroke</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Injection drug abuse</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

**Type of skin lesions in immunocompetent hosts.** Thirteen of the 14 immunocompetent patients with fusarial skin involvement presented with localized lesions (figure 1). The majority of these patients ($n = 10$) had a history of recent skin breakdown at the site of the fusarial infection, either as a result of trauma (7 patients) or of preexisting onychomycosis (3 patients). Fusarial infection presented as cellulitis among these latter 3 patients. The 7 patients who developed infection after trauma presented with nercrotic lesions of the skin and soft tissues after a motor vehicle accident (2 patients) [35]; cellulitis with necrosis after severe burns (2 patients) [10, 18]; chronic, painful toe ulcer that developed 1 year after surgery on the same toe [19] (1 patient); subcutaneous abscess after direct trauma, 1 year earlier, with a small bamboo chip (1 patient) [84]; and a plaque with several vesicles and pustules and a central superficial ulcer on a finger 3 weeks after minor trauma (1 patient) [32]. In 3 patients, a history of skin breakdown or trauma was not reported. Two of the latter patients presented with ulcerated lesions resembling chromoblastomycosis. One patient had 1 large ulcerated lesion extending from the left shoulder to the upper forearm, as well as another circular indurated ulcer on the right forearm, which had evolved over years [28]. The second patient had 2 large, deep ulcers covering the entire skin surface of the dorsum of both feet, which had been present for 1 year [56]. A third patient without a history of skin breakdown had a $5 \times 5$ mm erythematous pustule on the dorsum of the hand [12]. The single case of disseminated metastatic skin lesion occurred in a child with fever, pulmonary infiltrates, multiple erythematous papules and nodules, and several blood cultures yielding *Fusarium* species. The results of an extensive workup for an underlying immunosuppressive illness were negative [7].

**Type of skin lesions in immunocompromised hosts.** Of 167 patients, localized cutaneous lesions occurred in only 20 (12%), of whom 11 had a recent history of skin breakdown. The most frequent lesion among the latter 11 patients was cellulitis at the site of preexisting onychomycosis (8 patients). The skin lesions in the remaining 3 patients were nercrotic lesions on the feet after local trauma (2 neutropenic patients with acute lymphoid leukemia) [7] and an abscess on the left calf (a bone marrow transplant recipient with acute lymphoid leukemia) [42]. Among the 9 patients without a history of skin breakdown,
the skin lesions included periorbital cellulitis (4 patients with sinusitis) and ulcerative lesions (2 patients): a leg ulcer in a patient with diabetes [16], and a left heel ulcer in a kidney transplant recipient [91]. One patient with chronic granulomatous disease developed a keratotic lesion on the cheek that evolved over 6 months [8]. One renal transplant recipient presented with a subcutaneous abscess on the dorsum of the foot [121], and 1 patient with acute lymphoid leukemia developed a single 2 × 2–cm erythematous, tender, raised lesion on the forearm [48]. Ten of 12 patients with cellulitis were neutropenic, and 4 of the 5 patients with ulcers or abscesses had adequate neutrophil counts (P = .02).

The most frequent skin lesions among patients with disseminated disease were multiple painful erythematous papular or nodular lesions with (87 patients) or without (58 patients) central necrosis. Most necrotic lesions had an ecthyma gangrenosum appearance.

Figure 1. Type and extent of skin lesions caused by Fusarium species, according to immune competence of host. Among the 65 immunocompromised patients without skin lesions, infections included fungemia (37 patients), pneumonia (10 patients), sinusitis (9 patients), brain abscess (2 patients), arthritis (1 patient), liver involvement (1 patient), and endophthalmitis (1 patient). No data were available for the remaining 4 patients. Infections among 13 immunocompetent patients without skin involvement included peritonitis following peritoneal dialysis (3 patients), sinusitis (2 patients), pneumonia (2 patients), arthritis following motor vehicle accident (2 patients), endophthalmitis (2 patients [1 injection drug user]), and fungemia following heat stroke and allergic bronchopulmonary fusariosis (1 patient each).
Figure 2. Lower extremity involvement, with several *Fusarium* skin lesions of different types and ages. A, Small macular lesions. B, Papular lesions of different sizes. C, Two target lesions: central necrosis surrounded by an erythematous base, an area of normal skin, and an outer rim of thin erythema (arrows). Patient was a 32-year-old woman with relapsed leukemia who had undergone allogeneic bone marrow transplantation and developed disseminated and fatal fusarial infection.

grenosum-like appearance (71 patients), whereas target lesions (a thin rim of erythema of 1–3 cm in diameter surrounding the above-mentioned papular or nodular lesions) were reported in the remaining 16 patients (figure 2). One patient developed bullae in addition to nodular lesions (figure 3). These lesions involved practically any skin site, with predominance in the extremities. The lesions evolved rapidly, usually over a few days (range, 1–5 days). Lesions at different stages of evolution were

Figure 3. A, Paranasal cellulitis in a 15-year-old girl with aplastic anemia who presented with *Fusarium* sinusitis with subsequent development of cutaneous nodules on the face (A), extremities (B), and chest (C) caused by *Fusarium* species. Note the appearance of bullae in some fusarial lesions (B). The chest lesion became necrotic (C); the patient developed endophthalmitis with blindness and died a few days later. Panels B and C are reprinted with permission from [65].
described in 51 patients (usually a combination of papules, nodules, and necrotic lesions; figure 1), and myalgias (suggesting muscle involvement) were reported in 23 patients.

Among 16 patients with metastatic skin lesions, a recent history of cellulitis at the site of onychomycosis (11 patients; figures 4 and 5), local trauma (3 patients), or an insect bite (2 patients) were reported, suggesting that skin was the primary site of infection that led to disseminated fusariosis in these 16 patients. Only 2 patients with metastatic skin lesions did not have papular or nodular lesions. In these 2 patients, a fusarial cellulitis developed in one toe after trauma and was followed by cellulitis at another toe in the other foot [45, 46]. The pattern of skin lesions did not appear to be associated with any particular Fusarium species.

Compared with nonneutropenic immunocompromised patients, patients with neutropenia had a higher rate of skin lesions (78% vs. 45%; \(P < .0001\)), and these lesions were disseminated more frequently (94% vs. 41%; \(P < .0001\)). Patients.
Table 2. Differentiating features of cutaneous infection with *Fusarium* species between immunocompetent and immunocompromised hosts.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Immunocompetent host</th>
<th>Immunocompromised host</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue breakdown (trauma, onychomycosis, insect bite)</td>
<td>Very common (&gt;70%); may precede infection by up to 1 year</td>
<td>Uncommon (&lt;10%)</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>Adequate</td>
<td>Usually immediately before infection; neutropenia</td>
</tr>
<tr>
<td>Type of skin lesion</td>
<td>Necrosis, cellulitis, ulcer, abscess, rarely chromoblastomycosis-like</td>
<td>Multiple, painful erythematous papules or nodules with necrosis; some with evolution into target lesions; different stages of evolution; less commonly, cellulitis (usually site of tissue breakdown)</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>Marked</td>
<td>Scant</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Variable</td>
<td>Marked</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>No</td>
<td>Abundant</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Abundant</td>
<td>No</td>
</tr>
<tr>
<td>Hyphae</td>
<td>Few</td>
<td>Abundant</td>
</tr>
<tr>
<td>Extent</td>
<td>Localized</td>
<td>Disseminated</td>
</tr>
<tr>
<td>Pace of clinical progression</td>
<td>Slow, over months</td>
<td>Rapid, over days</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>Negative</td>
<td>Positive (50%)</td>
</tr>
<tr>
<td>Skin cultures, histopathology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Treatment</td>
<td>Local debridement; systemic antifungal therapy; perhaps local antifungal therapy</td>
<td>Perhaps systemic antifungal therapy with newer agents; perhaps granulocyte transfusion</td>
</tr>
<tr>
<td>Mortality</td>
<td>Very low</td>
<td>Very high, unless immunosuppression can be resolved promptly</td>
</tr>
</tbody>
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with disseminated lesions also were more likely to have blood cultures positive for *Fusarium* species than those whose lesions were localized (57% vs. 7%; *P* < .0001).

**Contribution of cutaneous infection to the diagnosis of fusariosis.** Skin lesions were the single source of diagnosis of fusarial infection in the majority of patients (100 [55%] of 181), including in the 148 patients whose skin lesions were disseminated. Of these 148 patients, 78 had blood cultures negative for *Fusarium* species, and the skin was the only source of diagnostic material in all except 2 patients (sinus was the source in 2 patients). Detailed information on the timing of positive blood cultures and the occurrence of skin lesions was provided for 18 of the remaining 71 patients whose blood cultures yielded *Fusarium* species.

In these latter patients, skin lesions preceded fungemia in 11 patients by a median of 5 days (range, 1–10 days), occurred on the same day (4 patients), and did not appear until after the diagnosis of fungemia was made (3 patients, at 3, 5, and 13 days after diagnosis). Seventy-six of the 82 patients for whom information on histopathologic examination was available had hyaline acute-branching septate hyphae invading the skin. Hyphal invasion extended into the blood vessels, with thrombosis and skin necrosis in those patients with metastatic lesions.

**Patient outcome in relation to cutaneous involvement.** The overall death rate of patients with fusarial infections was 66% (170 of 259 patients), with a 100% mortality among persistently neutropenic patients, compared with only 30% among those who ultimately recovered from immunosuppression (*P* < .0001). A higher mortality also was observed among patients with skin lesions (70% vs. 56%; *P* = .04), particularly among those whose lesions were disseminated (76% vs. 39%; *P* < .0001). However, a stratified analysis of patients with metastatic lesions by neutrophil count revealed that the higher mortality rate remained significant only among those who had an adequate neutrophil count throughout the course of their illness. In this group of patients with persistently adequate neutrophil counts, the mortality rate was 67% for those with metastatic lesions and 21% for those with localized lesions (*P* = .03). The mortality among neutropenic patients was high, regardless of whether the lesions were localized or metastatic (64% vs. 77%; *P* = .33), respectively, which reflects the contribution of severe immunosuppression to the fatal outcome.
DISCUSSION

This is the first attempt to characterize the cutaneous involvement in infections with Fusarium species in immunocompetent and immunosuppressed hosts and to compare the findings in these 2 patient populations. Our analysis yielded several findings. First, skin lesions represent a frequent manifestation (>50%) of infection by Fusarium species, especially among immunocompromised patients, in contrast to the rare cutaneous involvement (<10%) in infection with other opportunistic fungi, such as Candida species or Aspergillus species. Second, skin is the primary site of disseminated and life-threatening infections among a subset of highly immunocompromised patients. Third, skin is also the most common source of diagnostic material (and frequently the only one). Fourth, distinct patterns of skin involvement by Fusarium species exist, depending on the immune status of the host (Table 2). Fifth, the mortality rate among neutropenic patients is high, regardless of whether fusarial skin lesions are localized or disseminated. This is in contrast to the immunocompromised patients with adequate neutrophil count and in whom localized skin lesions are associated with a lower mortality rate. We also describe the first patient with skin bullae as a manifestation of disseminated fusariosis.

Among immunocompetent individuals, skin lesions typically are localized and develop after skin breakdown at the site of infection later became disseminated and involved multiple organs, including the skin (B).

Figure 6. Black necrotic hard palate ulcer (A) caused by Fusarium species in a 29-year-old patient with leukemia and fusarial sinusitis and pneumonia. The infection later became disseminated and involved multiple organs, including the skin (B).

Figure 7. Multiple cutaneous fusarial skin lesions on the face and scalp (A) and abdomen (B) of an 8-year-old girl who experienced relapse of leukemia. The infection started as paranasal sinusitis, which was followed by pneumonia and skin lesions. Patient died 30 days later with persistent fusariosis and leukemia. Courtesy of Dr. Flavio Queiroz-Telles, University Hospital, Universidade Federal do Paraná, Curitiba, Brazil.
infection. It is of note that skin breakdown may precede infection by up to 1 year. Cutaneous infections in these immunocompetent hosts present most commonly as necrotic lesions that complicate extensive wounds (burns and trauma), cellulitis secondary to underlying onychomycosis, or chronic ulcers and abscesses. Skin infection may rarely resemble chromoblastomycosis, an infection caused by dematiaceous fungi.

By contrast, the majority of immunocompromised patients have disseminated skin lesions that evolve over a much shorter period of time, particularly among neutropenic patients. Lesions in these patients typically consist of multiple painful erythematous papules or nodules with necrosis, occur among neutropenic patients, and are associated frequently with cultures positive for *Fusarium* species (blood and skin) and death. These disseminated lesions may result from a skin breakdown in some patients with preexisting onychomycosis. When such patients undergo severely immunosuppressive therapy, toe or finger cellulitis develops at the site of the onychomycosis and is followed by disseminated infection (figures 4 and 5). It is likely that the preexisting skin damage allows for entry of these pathogenic fungi into the underlying soft tissues, which leads to the development of cellulitis and subsequent dissemination in a manner reminiscent of bacterial infections. The nasal sinuses are yet another primary site of fusarial infections that may lead to dissemination after severe immunosuppression (figures 6 and 7).

Our study is limited by its retrospective nature and, thus, may underestimate the true incidence of some of our findings, such as the history of previous trauma and the presence of lesions at different stages of evolution. However, the consistency of findings across various reports from different institutions and over a long period of time suggests that our analysis is an accurate reflection of the nature of the cutaneous involvement in infection by *Fusarium* species.

Our findings have several implications for the clinical management of immunocompromised patients. Because skin may be the source for disseminated and frequently life-threatening fusarial infections, we recommend that patients likely to undergo severely immunosuppressive therapy undergo a thorough skin evaluation before commencing immunosuppressive therapy (table 3). All areas of tissue breakdown should be identified and suspicious skin lesions cultured, and a biopsy should be performed. The histopathological findings of infection with *Fusarium* species (branching hyaline hyphae) cannot be distinguished from those caused by infection with other opportunistic molds, such as *Aspergillus* species. Because of these remarkable similarities and the differences in susceptibility to antifungal agents between *Fusarium* species and various hyaline molds, identification by culture is critical.

Local debridement should be performed and topical antifungal agents (e.g., natamycin and amphotericin B) considered if *Fusarium* species are identified. In addition, severely immunocompromised patients with skin or other exposed tissue breakdown should avoid exposure to environmental sources of *Fusarium* species, such as tap water. Indeed, we have shown that hospital water may be contaminated with *Fusarium* species and may lead to patient infection [132].

Because infection with *Fusarium* species is more likely to involve the skin than infections by *Candida* species or *Aspergillus* species and because skin is the most likely source of diagnostic material, the presence of skin lesions in immunocompromised patients should raise the index of suspicion for this infection. Because of the relatively high yield of blood cultures among patients with fusarial skin lesions, immunocompromised patients with skin lesions should have blood samples collected and cultured. Identifying the specific pathogen is critical, because *Fusarium* species have variable susceptibilities to the antifungal agents that are currently used. Newer antifungal triazole agents that may have good activity against *Fusarium* species have become available. These include itraconazole, voriconazole, and posaconazole [133–139]. The development of these new antifungal drugs with activity against *Fusarium* species and the promising role of granulocyte transfusions in severely neutropenic patients undergoing severely immunosuppressive therapy are discussed in a later section.

Table 3. Prevention of fusarial infections during severe immunosuppression.

<table>
<thead>
<tr>
<th>Educate patients about need to avoid the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities associated with increased risk of skin breakdown</td>
</tr>
<tr>
<td>Contact of areas with skin breakdown (onychomycosis, dermato- mycosis, or other) with tap water</td>
</tr>
<tr>
<td>History and physical examination before commencing immuno- suppression should ascertain the following:</td>
</tr>
<tr>
<td>History of skin lesions during previous immunosuppression</td>
</tr>
<tr>
<td>Presence of areas of skin breakdown (onychomycosis, derma- tomycosis, or other) and skin lesions that imply presence of fungal infection</td>
</tr>
<tr>
<td>Preventive measures (before immunosuppression) for patients with skin breakdown include the following:</td>
</tr>
<tr>
<td>Perform local debridement with biopsy and culture of areas with skin breakdown</td>
</tr>
<tr>
<td>Apply topical antifungal agents active against <em>Fusarium</em> species and other pathogenic molds (terbinafine, natamycin, or other) at site of skin breakdown before and throughout immunosuppression</td>
</tr>
<tr>
<td>Consider delaying severely immunosuppressive therapies (when possible) until areas of skin breakdown have healed</td>
</tr>
<tr>
<td>Maintain lowest immunosuppression possible throughout therapy</td>
</tr>
<tr>
<td>Select donors very carefully in settings of organ or stem cell transplantation (to avoid immunosuppressive effects of GVHD and organ rejection and their therapies)</td>
</tr>
<tr>
<td>Consider in vitro susceptibility testing of <em>Fusarium</em> species isolated from skin breakdown areas and incorporation of active agents in antifungal prophylactic regimen</td>
</tr>
</tbody>
</table>

**NOTE.** GVHD, graft-versus-host disease.
patients should prompt considerations for such approaches in patients with fusariosis and may improve the otherwise dismal prognosis of these patients.

References


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