Invasive Fungal Disease after Remote Inoculation in Transplant Recipients

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We describe 3 cases of invasive fungal disease in the setting of transplantation-associated immunosuppression, developing months to years after clinically resolved penetrating soft-tissue injuries with wood fragments. Invasive fungal disease resulting from remote inoculation is a distinct syndrome in immunocompromised patients presenting with soft-tissue abnormalities in areas of prior trauma.

Invasive fungal disease (IFD) is associated with significant morbidity and mortality in immunocompromised patients, especially those undergoing transplantation. Some patients with IFD present with cutaneous manifestations with incidence ranging from <10% in patients with aspergillosis or zygomycosis to 65% in patients with fusariosis [1–3].

Cutaneous IFD may result from primary inoculation of fungal organisms into sites of tissue injury after trauma, burns, surgery or intravenous catheter placement [4]. Alternatively, secondary cutaneous IFD may occur in the setting of hematogenous dissemination, usually from a pulmonary source [4].

Traumatic inoculation with fungi rarely causes infection in normal hosts due to immunocompetence [5]. However, in the presence of attenuated phagocytic host responses in an immunocompromised individual, angiinvasive molds may cause infection with tissue infarction and necrosis [5]. Infections reported in this setting usually occur shortly after the inoculation event [1–5].

We have observed several cases of primary cutaneous and soft-tissue IFD in which mechanical injury and immunologic impairment were separated by a long time interval. These patients sustained traumatic injuries from tree branches while immunocompetent with no evidence of IFD following trauma. Interestingly, primary soft-tissue IFD developed months to years later after transplantation at the healed sites of remote injury, which suggests persistence of fungal organisms in a latent state.

This report summarizes our experience and defines IFD arising at sites of remote inoculation with plant matter to be a distinct syndrome with particular relevance for the immunocompromised host.

Case Reports

A 44-year-old male (patient A) with chronic myelogenous leukemia who underwent allogeneic stem-cell-transplantation (SCT) complicated by acute graft-versus-host-disease (GVHD), Clostridium difficile colitis, and methicillin-resistant Staphylococcus aureus bacteremia (MRSA) presented with progressive swelling of his left shin. Thirty years prior to transplantation, he pierced his left shin with a tree branch while vacationing in Martinique. The tibia was exposed, and he was treated empirically for acute osteomyelitis with intravenous antibacterials. Four months after transplantation, the patient presented with swelling and discomfort at the site of previous injury (Table 1 and Figure 1). A fluid collection measuring 9×2×2 cm was identified on ultrasound. Magnetic resonance imaging (MRI) revealed an abnormal signal suggestive for abscess formation in the tibialis anterior muscle and possible osteomyelitis of the tibia. A bone scan performed 2 months prior for the evaluation of MRSA bacteremia had shown no abnormalities in that area. Fine needle aspiration (FNA) demonstrated hyphae on Gram stain; culture grew a mold identified as Phaeoacremonium parastitcum. The abscess was surgically debrided. No osteomyelitis or foreign body was identified during surgical exploration. There was no evidence of IFD elsewhere. The patient was successfully treated with voriconazole for 8 months. Unfortunately, he died of severe hepatic GVHD 3 months after completion of treatment without evidence of recurrent IFD.

A 22-year-old male (patient B) underwent autologous SCT for relapsed metastatic testicular cancer. Four days after transplantation, during profound neutropenia, he developed a solitary tender violaceous papule with a necrotic center on the medial side of his left knee, adjacent to the scar from a...
Table 1. Clinical Characteristics of Transplant Recipients with Invasive Fungal Disease Following Remote Inoculation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of diagnosis</td>
<td>2004</td>
<td>2004</td>
<td>2007</td>
</tr>
<tr>
<td>Age, years</td>
<td>44</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>Chronic myelogenous leukemia</td>
<td>Relapsed metastatic testicular cancer</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>Type of transplantation</td>
<td>Allogeneic SCT</td>
<td>Autologous SCT</td>
<td>Deceased-donor renal transplantation</td>
</tr>
<tr>
<td>WBC at diagnosis, K/µL</td>
<td>3.7</td>
<td>0.05</td>
<td>5.9</td>
</tr>
<tr>
<td>Daily immunosuppression at diagnosis</td>
<td>Prednisone, 20 mg, Sirolimus, 2 mg Tacrolimus, 2 mg</td>
<td>Conditioning with carboplatin, etoposide and cyclophosphamide*</td>
<td>Tacrolimus, 6 mg, Prednisone, 5 mg, Leflunomide, 60 mg</td>
</tr>
<tr>
<td>Onset of symptoms after transplantation, days</td>
<td>116</td>
<td>4</td>
<td>741</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Soft-tissue swelling</td>
<td>Violaceous papule with necrosis</td>
<td>Non-erythematous soft-tissue mass</td>
</tr>
<tr>
<td>Location</td>
<td>Shin</td>
<td>Knee</td>
<td>Thigh</td>
</tr>
<tr>
<td>Fungal species</td>
<td>Phaeoacremonium parasiticum</td>
<td>Zygomycete sp.</td>
<td>Phaeoacremonium sp.</td>
</tr>
<tr>
<td>Antifungal susceptibilities, MIC in µg/mL at 48 h</td>
<td>Amphotericin, 2, Posaconazole, 0.25 Voriconazole, 0.25</td>
<td>No growth in culture</td>
<td>Itraconazole, &gt;8, Posaconazole, 0.25, Terbinafine, 0.25, Voriconazole, 1</td>
</tr>
<tr>
<td>Initial mechanism of injury</td>
<td>Penetrating injury with tree branch</td>
<td>Penetrating injury with tree branch</td>
<td>Penetrating injury with tree branch</td>
</tr>
<tr>
<td>Latency from injury to onset of symptoms</td>
<td>13 years</td>
<td>10 months</td>
<td>10 years</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgery, Posaconazole (8 months)</td>
<td>Surgery, Posaconazole (3 months)</td>
<td>Surgery x 3, Voriconazole (11 months), Terbinafine ongoing</td>
</tr>
<tr>
<td>Duration of follow-up after diagnosis, months</td>
<td>12</td>
<td>66</td>
<td>37</td>
</tr>
<tr>
<td>Outcome</td>
<td>Complete resolution</td>
<td>Complete resolution</td>
<td>Repeat surgical intervention required; resolving minimal drainage</td>
</tr>
</tbody>
</table>

NOTE. MIC, minimum inhibitory concentration; SCT, stem cell transplantation; WBC, white blood cell count.
* Previous treatment included 6 cycles of ifosfamide, etoposide, and cisplatin, followed by 2 cycles of vinblastine, bleomycin, and cisplatin for relapsed disease.

Figure 1. Clinical appearance of affected sites of patients reported. The arrows point to the scars at the sites of remote injury. Panel letters correspond to patients.
snowboarding accident sustained in Colorado 10 months prior to transplantation (Table 1 and Figure 1). The patient had collided with a tree incurring a deep penetrating injury with a branch to his left leg and a left fibular fracture requiring surgical treatment. This area had completely healed and had not changed during previous cycles of chemotherapy for relapsed testicular cancer. Skin biopsy demonstrated angioinvasive hyphae consistent with Zygomycete species on histopathology. There was no growth on fungal cultures. There was no evidence of IFD elsewhere, including unremarkable head and chest imaging. He underwent surgical excision of the affected skin and subcutaneous tissue and was treated with posaconazole for 3 months with complete resolution. He remains well 5 years after transplantation.

A 73-year-old male recipient (patient C) of a deceased-donor renal transplant presented with progressive swelling of his right medial thigh. His post-transplant course had been complicated by BK nephropathy and one episode of rejection 19 months post-transplantation (Banff class 1B); he was treated with a prednisone pulse and increase in tacrolimus target levels. Ten years prior to transplantation, he sustained a penetrating injury to his right thigh from a falling tree branch while gardening in Bermuda. The area became infected, and a 2-inch wood splinter was removed surgically, leading to complete resolution.

Twenty-four months after transplantation, the patient developed a non-tender, non-erythematous right thigh swelling at the site of the previous injury, which increased to the size of a baseball over 3 months (Table 1 and Figure 1). MRI demonstrated a multilobulated cystic mass involving the sartorius and vastus intermedius muscles, concerning for a soft-tissue sarcoma. Cytological analysis of fluid obtained by FNA revealed hyphae, and Phaeoacremonium species grew in culture. The patient underwent surgical debridement, including removal of the sartorius muscle and began treatment with voriconazole. Pathology showed fungal organisms, abscess cavity formation, and granulomatous inflammation. There was no evidence of IFD elsewhere. After 6 months of voriconazole therapy, the patient was switched to terbinafine for 10 additional months because of voriconazole’s cost to the patient. Six weeks after discontinuation of terbinafine, recurrence of the abscess at the distal end of the original scar required repeat surgical debridement. The patient resumed voriconazole for 5 months, followed by terbinafine. He is doing well clinically and remains on antifungal treatment.

Discussion

We propose that soft-tissue IFD following remote inoculation injury is a distinct syndrome associated with a history of significant penetrating soft-tissue trauma with plant matter, followed by immunosuppression.

The cases presented here are unique, because inoculation preceded the onset of IFD by an interval ranging from 10 months to 13 years. These patients were asymptomatic, with complete healing of the injured sites before transplantation.

Traumatic penetrating injuries with introduction of organic matter into subcutaneous tissues was a distinctive feature of all 3 cases and suggests that plant debris may have played a causative role—allowing persistence of fungi in a subclinical or latent form.

There is a single case reported where initial trauma involving plant matter and an equally prolonged latency prior to development of infection was observed. A 32-year-old American woman sustained splinter injuries during a tornado at the age of 10. Twenty-two years later, she developed a cutaneous infection with Cladiophialophora bantiana at the site of injury when she began oral treatment with prednisone for systemic lupus erythematosus [6]. Two other cases have been described after corticosteroid injections into areas of previous trauma [7, 8], but contamination of the administered product was not excluded [9].

A potential explanation for this phenomenon is that the introduction of plant debris at the time of inoculation prevented complete eradication of fungal organisms despite the host’s immunocompetence. Instead, fungi remained latent until neutropenia and immunosuppressive medications impaired immune defenses sufficiently to allow reactivation of organisms, with subsequent fungal proliferation and progression to overt local disease.

Pathogens may establish latency by obtaining access to protected sites such as infected bone or prosthetic devices [10, 11]. However, no evidence of osteomyelitis was found in our cases. Similarly, plant matter or other foreign bodies introduced by traumatic inoculation are inherently avascular and impair access of inflammatory cells, thereby allowing microorganisms to escape from immune responses [10]. Even though no plant debris was identified during surgery, the magnitude and mechanism of trauma suggest that a significant amount of vegetable matter was introduced. Although it is possible that these cases represent secondary spread of IFD, no other site of infection was identified.

These cases demonstrate that skin disruption and immunosuppression do not necessarily have to occur synchronously [5] but can be separated by a long time period, strongly suggesting persistence of latent organisms post-trauma. The presentation of IFD is dependent on the mechanism of anatomic disruption, the magnitude of the inoculum, and the virulence of the organism, as well as the degree of immunosuppression [12].

In the patient with cutaneous zygomycosis, clinical disease developed during profound neutropenia 4 days after SCT, 10 months after the initial trauma, and manifested as a rapidly progressive necrotic lesion due to hyphal angioinvasion. In contrast, the 2 cases of phaeohyphomycosis developed after prolonged immunosuppression and latency, 4–24 months after transplantation and 10–13 years after the initial inoculation.
Both patients developed indolent, slow-growing, painless soft-tissue masses at the sites of previous trauma. Histologically, abscess cavity formation and granulomatous inflammation were seen.

In summary, patients undergoing transplantation may develop soft-tissue infections at sites of remote inoculation with fungal pathogens. These cases demonstrate that fungi may remain latent after major soft-tissue trauma. Subsequent significant immunosuppression allows productive infections to occur. The time course and presentation of infection may vary dramatically, depending on the inoculated fungus. Beyond assessing occupational and lifestyle risk factors, clinicians should also inquire about a history of remote trauma when evaluating patients for transplantation. Physical examination of the area of injury and repeated questioning about changes to these sites following transplantation is crucial for early identification and appropriate treatment of these infections.

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References