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Fusarium solani Skin and Soft Tissue Infection in a Patient With Chronic Sclerosing Skin Graft-vs-Host Disease: A Case Report

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Manuscript Preparation E
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Patient: Female, 64-year-old
Final Diagnosis: Fusarium infection
Symptoms: Hand wound cellulitis
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease

Background: Fusariosis is an exceedingly rare infection most often attributable to the fungus *Fusarium solani*. It is a rare but known cause of invasive mold infections in immunocompromised patients post-hematopoietic cell transplant (post-HCT). Fusariosis can be extremely difficult to treat due to its tendency to disseminate in the context of underlying immunosuppression, and its high in vitro resistance to mainline antifungal agents.

Case Report: Here we present a post-HCT patient undergoing immunosuppressive therapy for diagnosed chronic graft-versus-host disease (GVHD) of the skin who presented with subacute skin and soft tissue infection of the right hand and arm with multi-drug-resistant *F. solani*. She initially presented with complaints of erythema and worsening wound exudation at her GVHD site, which had worsened over the course of days. The diagnosis was delayed due to chronic and diffuse scleroderma-like changes due to the underlying GVHD. Following fungal cultures demonstrating multi-drug resistance, the patient was successfully treated with an investigational antifungal drug, fosmanogepix.

Conclusions: This case demonstrates the importance of including fusariosis as a differential diagnosis in patients post-HCT, even long into the post-transplant period. Contrary to disseminated fusariosis, which arises most commonly in neutropenic patients, isolated skin and soft tissue fusariosis can occur in non-neutropenic post-transplant patients with chronic GVHD receiving immunosuppression. In addition, this case outlines the high complexity of fusariosis treatment due to the capacity of this organism to develop multi-drug-resistance to mainline antifungals. This report illustrates clinical and radiographic improvement following implementation of fosmanogepix therapy in a severely immunocompromised patient with GVHD and complex multi-drug-resistant *Fusarium* infection.

Keywords: Fusarium • Multi-Drug Resistance • Antifungal Agents • Hematopoietic Stem Cell Transplantation

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Introduction

Skin and soft tissue infections are common in transplant patients receiving chronic immunosuppression, and this population demonstrates a significantly higher risk of deep-space soft tissue infections and osteomyelitis [1,2]. In patients undergoing immunosuppression for the treatment of hematologic malignancies or after hematopoietic cell transplantation (HCT), *Staphylococcus aureus,* including methicillin-resistant *Staphylococcus aureus* (MRSA), is the most common causative agent of deep soft tissue infections, followed by other streptococcal species. However, *Nocardia*, *Actinomyces*, mycobacteria, and fungi cannot be ignored in this population [3,4]. With respect to fungal etiologies, yeasts, molds and endemic dimorphic fungi are all known to cause invasive infections in non-HIV immunocompromised patients, with *Candida* representing the most common yeast and *Aspergillus* representing the most common mold [4]. Less commonly, *Fusarium*, dematiaceous molds, and Mucorales genera such as *Rhizopus*, *Absidia*, *Mucor*, and *Cunninghamella* are also known to cause invasive mold disease in this population [4]. Patients with chronic skin GVHD, particularly sclerosing type, are prone to skin erosions and ulcerations that subsequently increase the risk of skin and soft tissue infections. In chronic GVHD patients treated for skin and soft tissue infections, and in the absence of response to antimicrobial therapies, atypical infectious pathogens need to be considered. Here, we present a case-based illustration of delayed recognition of multi-drug-resistant *Fusarium* soft tissue infection complicated by chronic sclerosing skin GVHD. We then present a description of our successful salvage use of the investigational antifungal compound fosmanogepix.

Case Report

A 64-year-old woman with myelodysplastic syndrome underwent matched unrelated donor allogeneic HCT prior to presentation (over 4.5 years earlier) and remained in remission (**Figure 1**). Her post-transplant course was complicated by chronic GVHD of multiple sites with ongoing ocular and sclerosing skin involvement. She therefore remained on immunosuppression with ruxolitinib (10 mg daily, oral) belumosudil (200 mg daily, oral), prednisone (5 mg daily, oral), and extracorporeal photopheresis (2 treatments every other week). In terms of chronic sclerosing skin GVHD, the patient experienced tightness of both hands, forearms, and posterior upper arms as well as scleroderma-like changes to her mid-torso area. Her hand mobility on both sides was limited due to skin tightness.

Several months prior to the current presentation, she developed swelling and erythema of the dorsum of her right hand and wrist and was diagnosed with cellulitis. Over the course of the next 3-4 months, she was diagnosed with multiple recurrences of cellulitis, which were treated with several courses of intravenous and oral antibiotics. She reported formation of blisters that would collapse and open up during several cellulitis episodes.

The patient presented to the extracorporeal photopheresis center at our institution for a scheduled treatment and was noted to have erythema and a draining wound on her right forearm. She was subsequently admitted to the hospital. She denied recent trauma, soil or plant exposure, exposure to fresh or salt water, or animal bites. The patient had previously worked in meat processing but had not worked for an extended period. From an infectious disease perspective, the patient was taking acyclovir (800 mg twice a day, oral), isavuconazole (372 mg daily, oral), trimethoprim-sulfamethoxazole (80 mg – 400 mg daily, oral), and letermovir (480 mg daily, oral) for prophylaxis.

On initial evaluation, the patient was afebrile and non-toxic appearing. She was noted to have a draining wound on the right forearm, with associated erythema, tenderness, and decreased range of motion over the volar aspect of the right wrist (**Figure 2**). The rest of the physical examination was unremarkable. Laboratory evaluation on admission revealed a white blood cell count of 13.51 k/µl (normal range 4.00-10.90) and a neutrophil count of 10.07 kµul (normal range 1.80-7.80). X-ray of the hand and arm demonstrated evidence of soft tissue edema over the volar aspect of the distal forearm, wrist, and hand, with no evidence of soft tissue mineralization. Blood cultures and superficial wound cultures were obtained on admission. Magnetic resonance imaging (MRI) demonstrated evidence of cellulitis with multifocal abscesses surrounding the extensor tendons and within the deep flexor compartment of the forearm, wrist, and hand (**Figure 3A**). Empiric treatment for cellulitis was initiated with intravenous vancomycin (1250 mg daily) and ceftriaxone (2 g daily). All antimicrobial prophylaxis medications listed above were continued on admission.

The superficial wound culture was positive for gram-positive skin flora and *Fusarium solani* complex. When cultures were found to be positive for *Fusarium* spp., computed tomography of the chest was conducted to rule out disseminated fusariosis and did not reveal acute pathology.

On identification of *Fusarium* spp. in the cultures, isavuconazole was rapidly changed to oral voriconazole (400 mg twice a day) treatment. Aspiration of the hand fluid collections was conducted by interventional radiology, with deep cultures again growing *F. solani* complex. As the patient's condition improved, she was then discharged home with a plan to complete a 4-week course of ceftriaxone; in addition, a single 1500-mg dose of intravenous dalbavancin was administered the day after discharge, after the patient had received 13 days of vancomycin in total. Voriconazole was continued on discharge.

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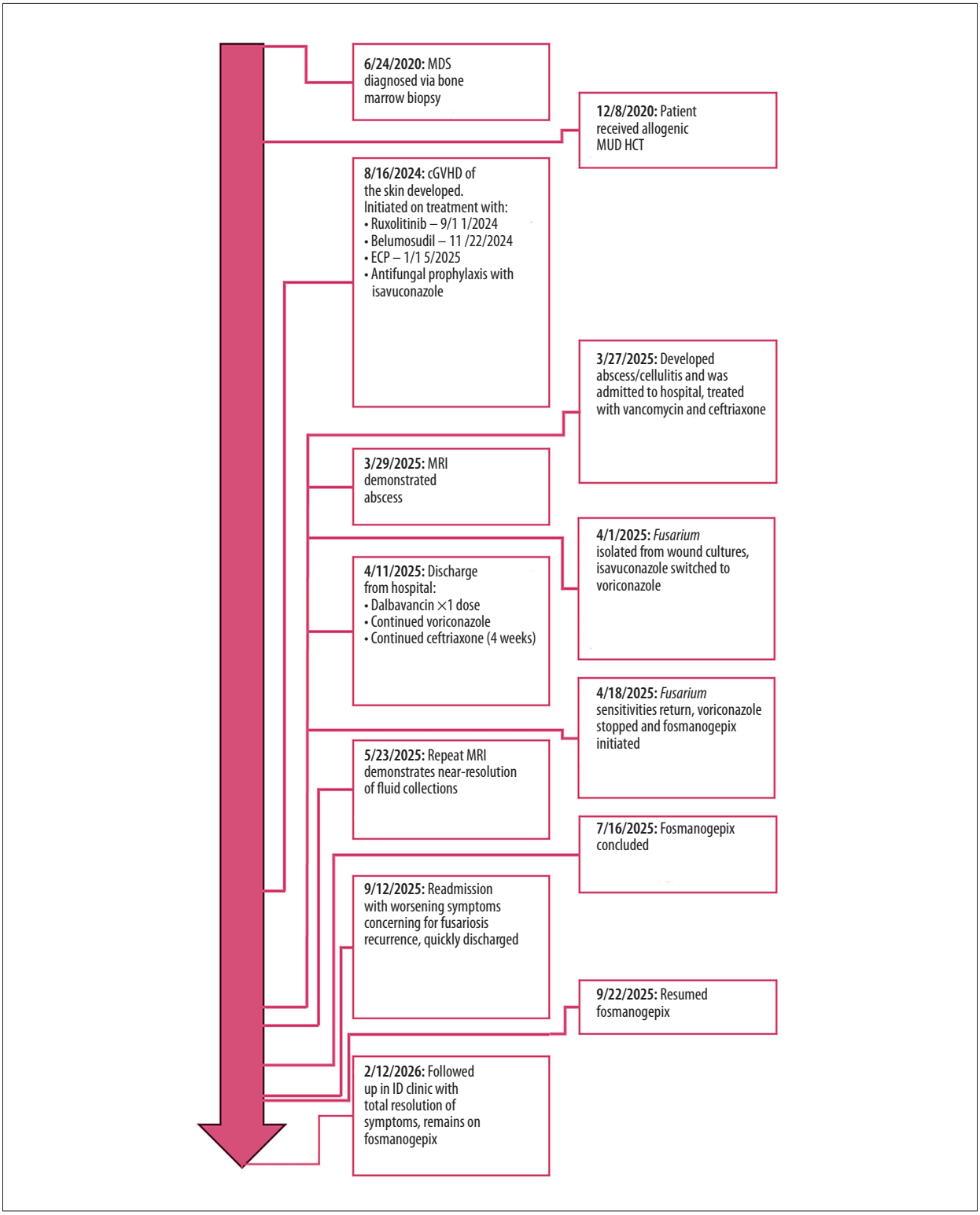

Figure 1. Timeline demonstrating the patient's clinical course from original MDS diagnosis to final follow-up at an outpatient infectious disease clinic while receiving fosmanogepix therapy. MDS, myelodysplastic syndrome; MUD HCT, matched unrelated donor hematopoietic cell transplant; cGVHD, chronic graft-vs-host disease; ECP, extracorporeal photopheresis; MRI, magnetic resonance imaging.

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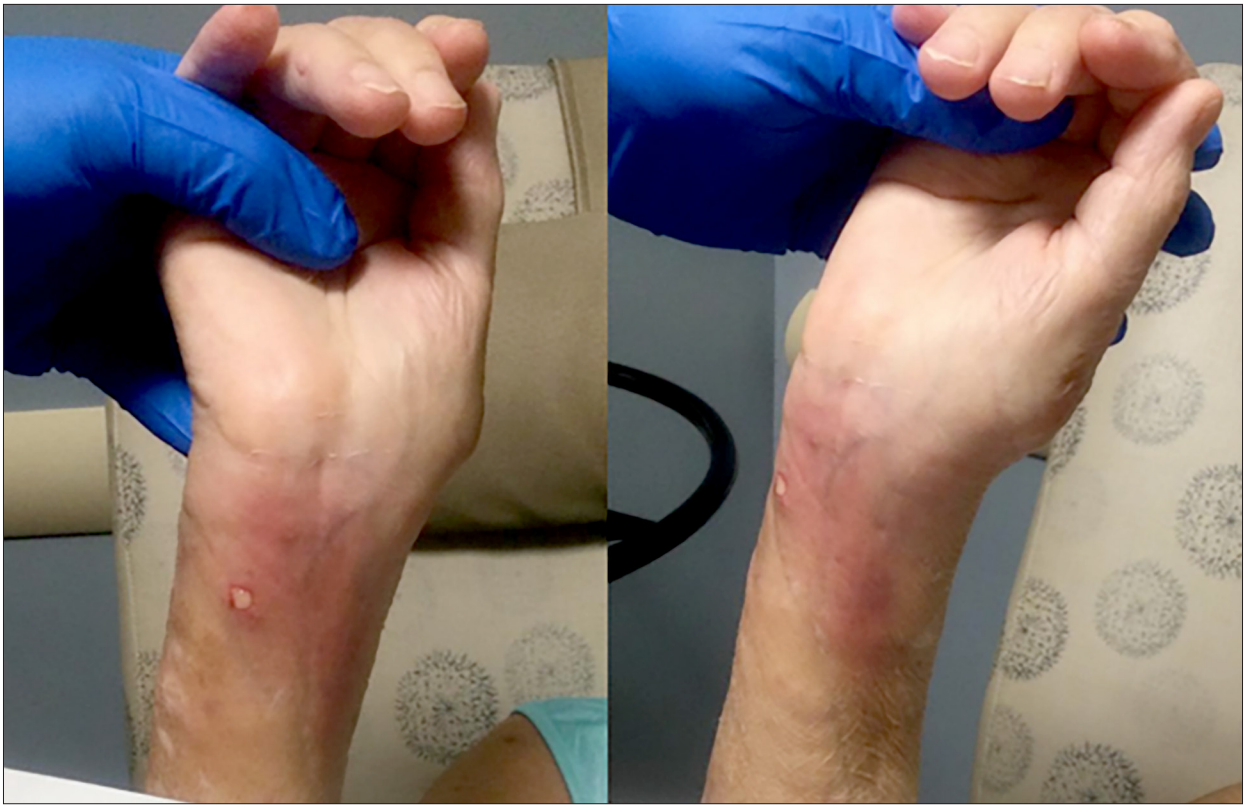

Figure 2. External appearance of affected forearm and wrist. Notable are the open draining wound site on the volar forearm and associated erythema radiating out into the rest of the forearm proximally and the wrist distally.

Fungal susceptibilities were completed (ARUP Laboratories, USA) and demonstrated high minimal inhibitory concentration (MIC) to voriconazole (MIC ≥8 µg/ml), isavuconazole (MIC ≥8 µg/ml), itraconazole (MIC ≥8 µg/ml), posaconazole (MIC ≥8 µg/ml), and terbinafine (MIC ≥2 µg/ml). Furthermore, the MIC for amphotericin B was 1 µg/ml. Based on the known high incidence of multidrug resistant (MDR) *Fusarium* spp., susceptibility testing to manogepix, a novel investigational antifungal agent, was completed, and indicated a MIC of 0.015 µg/ml (Fungal Testing Laboratory at University of Texas Health Sciences Center—San Antonio, TX). Permission from the drug manufacturer was obtained (Basilea Pharmaceutica International Ltd, Allschwil, Switzerland) to access fosmanogepix, the prodrug for manogepix, and a single-patient investigational new drug application was submitted and approved allowing initiation of fosmanogepix treatment in this patient.

Once fosmanogepix treatment (800 mg/day in a single oral dose) was initiated, voriconazole was discontinued. She reported nausea and retching associated with fosmanogepix therapy. To alleviate this, she was transitioned from a single oral 800-mg daily dose to 400 mg twice a day, and was prescribed ondansetron (4-8 mg every 8 hours as needed, oral), which she used intermittently for breakthrough symptoms. At 6-week follow-up after fosmanogepix initiation, the patient reported significant improvement in swelling and erythema of the right forearm. Repeat MRI of the right upper extremity at that point demonstrated near-resolution of the previously seen fluid collections (**Figure 3B**). The patient received a 3-month course of fosmanogepix. About 2 months after discontinuation, the patient experienced worsening of erythema and edema of the affected right upper extremity and underwent repeat evaluation and MRI. Repeat imaging revealed evidence of olecranon bursitis, superficial subcutaneous edema, and enhancement along the dorsal aspect of the distal forearm, wrist, and hand. Even though fungal work-up was negative, the patient was restarted on fosmanogepix (oral, 800 mg/day) as recurrent fusariosis could not be ruled out and secondary prophylaxis was recommended while she remains on immunosuppression for chronic GVHD. The patient's symptoms improved, with resolution of the bursitis, and she was able to return back to work 4 months later.

Discussion

Fusarium spp. are ubiquitous fungi that are widely distributed in the environment. In immunocompetent hosts, *Fusarium* infections are generally limited to onychomycosis and keratitis [5]. In immunocompetent patients, invasive skin and soft

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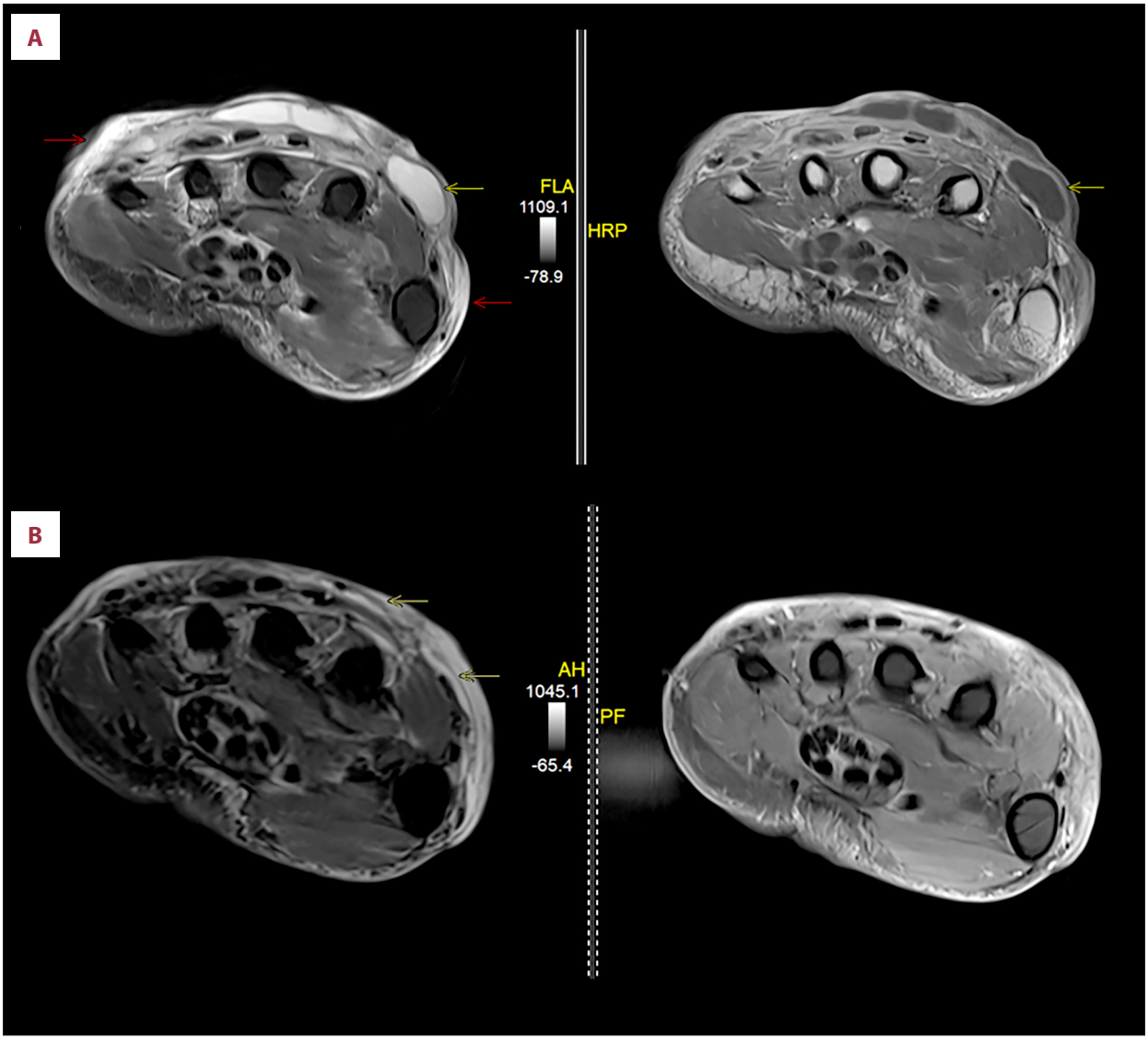

Figure 3. (**A**) Axial fat-suppressed T2-w and axial T1-w contrast-enhanced magnetic resonance images of the right hand at the level of the proximal metacarpals demonstrate extensive ill-defined subcutaneous edema (red arrows) and several rim-enhancing fluid collections (yellow arrows) involving the dorsal hand, suggesting cellulitis with abscesses. (**B**) Axial fat-suppressed T2-w and axial T1-w contrast-enhanced magnetic resonance images at the same level as in (**A**), which were obtained 8 weeks later, demonstrate near complete resolution of fluid collections (yellow arrows) with persistent but decreased subcutaneous edema of the dorsal hand.

tissue infections due to *Fusarium* are extremely rare and almost always secondary to trauma, severe burns, or surgical wound contamination, as this allows for mold inoculation into the deep soft tissues [6,7]. More specifically, invasive fungal infections including *Fusarium* are a known complication of combat wounds and burns associated with military activities due to wound contamination with soil, water, and plant material [8]. On the contrary, in patients with hematologic malignancies and allogeneic HCT recipients, disseminated fusariosis is the most encountered clinical presentation [5,6]. This generally manifests as persistent fever, multiple skin lesions, and pulmonary and sinus involvement in a patient with prolonged neutropenia [5,6]. Isolated skin and soft tissue fusariosis is less common in the immunosuppressed patient population, and, if it does occur, is generally preceded by a skin breakdown that allows inoculation of environmental molds into the sterile tissues [5,6]. We hypothesize that chronic skin GVHD with intermittent skin blistering and breakdown served as an entry site for *Fusarium* in our patient.

This patient demonstrated proven invasive fungal disease, with the growth of mold in cultures of samples obtained by

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sterile interventional radiology aspiration from deep soft tissue, which is usually a sterile site. This demonstrated abnormality was consistent with an infectious process [9].

In terms of treatment, until now, voriconazole has demonstrated the best effectiveness, with posaconazole and liposomal amphotericin B as potential second line therapy strategies in the case of refractory disease [10]. There is also no well-defined timeframe for the length of antifungal therapy against invasive disease in immunocompromised patients. Therefore, the decision for discontinuation is generally guided by many individual considerations, such as immune reconstitution, ongoing immunosuppression, and source control [10,11]. Even with extended duration, there is significant risk of recurrence if the patient remains on immunosuppression [11]. In addition to antifungal therapy, surgical debridement of necrotic wounds is also often necessary [7,8]. *Fusarium* has been known to demonstrate very high rates of antimicrobial resistance, including against both amphotericin B and the azole antifungals, as was seen in this patient's case [12,13]. Cases of MDR fusariosis have been demonstrated to be associated with increased length of hospitalization, increased cost to the patient, and increased mortality [12], as well as longer (sometimes lifelong) antifungal therapy and its associated toxicity to the patient [13].

The emergence of MDR *Fusarium* species, as was seen in this patient, has created a need for novel therapeutic strategies against this rare disease. Recently, the novel antifungal medication fosmanogepix has been used to treat complex MDR *Fusarium* infections in severely immunosuppressed transplant and hematologic malignancy patients [14,15]. Fosmanogepix is a prodrug that is converted in vivo into the active antifungal compound manogepix [14,16]. Manogepix is an inhibitor of Gwt1, a highly conserved fungal enzyme that is an early critical step in the glycosylphosphatidylinositol (GPI)-anchor biosynthesis pathway. This pathway is critical for the trafficking and anchoring of GPI-anchored mannoproteins to the fungal cell wall. Disruption of it leads to broad-spectrum antifungal activity against both yeasts and molds as these mannoproteins play an important role in many aspects of fungal physiology [16].

Gastrointestinal irritation in the form of nausea, vomiting, and diarrhea have been reported to be one of the more common adverse effects of fosmanogepix therapy, with the transition of once daily dosing to twice daily dosing being the current recommended strategy for alleviation of gastrointestinal symptoms [17]. In this case, the implementation of fosmanogepix as therapy for *Fusarium* soft tissue infection was associated with improvement in both the patient's clinical and radiographic findings. However, this was done in the setting of salvage therapy for a patient with multi-drug-resistant disease in conjunction with source control via interventional radiology aspiration and previous antibacterial and antifungal therapy. These findings indicate a potential use for this novel antifungal agent as salvage therapy for patients with highly resistant disease that have not demonstrated clinical improvement through other methods. These results were also seen specifically in an immunocompromised patient with altered skin barrier due to GVHD and localized fusariosis with no evidence of dissemination. However, the association between fosmanogepix therapy and clinical improvement in this case indicates promising potential for further investigation of this novel agent for use against rare and complex fungal diseases in the vulnerable population of transplant and hematologic malignancy patients.

Conclusions

This case demonstrates the importance of considering *Fusarium* infection in patients with non-resolving skin and soft tissue lesions in immunosuppressed post-HCT patients with disrupted skin barrier due to GVHD, even long into the post-transplant period. It also demonstrates the potential use of fosmanogepix as salvage therapy in patients with localized multi-drug-resistant fusariosis.

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Patient Consent and Ethics Approval

Written consent was obtained from the patient. Ethics approval was not needed as per institutional guidelines for single cases.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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