Community-acquired Disseminated *Exophiala dermatitidis* Mycosis with Necrotizing Fasciitis in Chronic Graft-versus-host Disease

Eiichi Sato¹, Atsushi Togawa¹, Michio Masaki¹, Akihiko Shirahashi¹, Midori Kumagawa¹,², Yasumasa Kawano³, Hiroyasu Ishikura³, Yui Yamashiro³, Satoshi Takagi³, Hiromi To³, Katsumi Kobata⁴, Morishige Takeshita⁴, Koji Kusaba⁵, Eisaburo Sueoka⁵, Kazuo Tamura¹, Yasushi Takamatsu¹ and Tohru Takata¹,⁸

Abstract:
We herein report a case of systemic phaeohyphomycosis by *Exophiala dermatitidis* (*E. dermatitidis*) with chronic graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). The patient had been taking oral corticosteroids for years to control the GVHD. Yeast-like fungi were identified in a blood culture, so treatment with micafungin (150 mg/day) was begun, with no improvement. The patient passed away on hospital Day 12. A sequence analysis of rRNA revealed the isolate to be *E. dermatitidis*. This report brings attention to an emerging mycosis of community-acquired *Exophiala* species infection in the very-late phase after allogeneic HSCT in patients with chronic GVHD.

Key words: *Exophiala dermatitidis*, chronic graft versus host disease (GVHD), phaeohyphomycosis, immunosuppressive drug, acute myeloid leukemia, necrotizing fasciitis

(Intern Med 58: 877-882, 2019)  
(DOI: 10.2169/internalmedicine.1706-18)

Introduction

Phaeohyphomycosis is an infection caused by pigmented dematiaceous fungi, such as black fungi (1), and is a clinical challenge, especially in hematologic and hematopoietic stem cell transplant (HSCT) recipients, causing significant morbidity and mortality (2). The disease spectrum is vast, varying from localized cutaneous infection to lethal disseminated phaeohyphomycosis with multiorgan involvement (1). Among the melanized fungi, *Exophiala species* (*E. species*) comprise the most clinically relevant black yeasts, often isolated from environmental substrates, including soil, wood and other plant material (3). In particular, *E. dermatitidis* appears to be associated most commonly with systemic infection as well as with poorer outcomes than other *E. species* (4). However, there are few published reports dedicated to studying the infection in transplant recipients.

We herein report a case of community-acquired disseminated *E. dermatitidis* mycosis in the very-late phase (over 7 years) after allogeneic HSCT in a patient with chronic graft-versus-host disease (GVHD).

Case Report

A 21-year-old Japanese woman with acute myeloid leukemia in second remission underwent allogeneic peripheral blood stem cell transplantation from her HLA-identical
brother. She was treated with busulfan and cyclophosphamide as a conditioning therapy and received cyclosporine in combination with methotrexate for the prophylaxis of GVHD. After the transplant, she developed Coombs-negative hemolytic anemia with increased schistocytes in the peripheral blood and an elevated lactate dehydrogenase (LDH) level in serum, in addition to renal dysfunction. She was diagnosed with transplant-associated microangiopathy (TMA).

Although cyclosporine was replaced with tacrolimus, the symptoms became worse. Glucocorticoid was then started. She developed acute GVHD of grade 3 consisting of generalized erythema and liver dysfunction with hyperbilirubinemia and was treated with high-dose glucocorticoid and mycophenolate mofetil. Since she subsequently developed extensive chronic GVHD, including skin lesions, and her liver function fluctuated, she continued oral prednisolone (PSL) at a dose of 8 to 40 mg/day. Accordingly, she suffered from decubitus formation at the left gluteal region, which repeatedly improved and relapsed.

At seven years after the transplant, she was emergently admitted to Fukuoka University Hospital because of exacerbating left buttock pain for two weeks with swelling of the gluteal region and a low-grade fever despite the administration of oral amoxicillin/ clavulanate (750 mg/day) for 3 days. The daily dose of PSL had been increased to 40 mg for 4 months due to the exacerbation of her liver dysfunction. On an examination, her temperature was 36.6°C, blood pressure 142/115 mmHg, pulse rate 95 beats per minute, respiratory rate 16 breaths per minute and oxygen saturation 100% while she was breathing room air. She had an injury (1×1 cm) at the left hip and extensive skin color change at the left knee joint with localized warmth and tenderness (Fig. 1). Otherwise, her physical signs were normal, including her vital signs, and her weight was 60 kg. Laboratory blood tests showed a decreased lymphocyte count (580 cells/μL) and IgG (326 mg/dL) with elevated hepatobiliary enzymes (ALT, ALP, γ-GTP), LDH and C-reactive protein (CRP) (Table 1). Creatine phosphokinase (CPK) was within the normal range.

The administration of ampicillin/sulbactam (12 g/day) and clindamycin (1,800 mg/day) was begun. However, the buttocks and leg lesions were exacerbated, so the antimicrobials were changed to meropenem (3 g/day) and linezolid (2 g/day) from hospital Day 3 (Fig. 2). The blood cultures that had been drawn on admission grew yeast-like fungus (Fig. 3a) on Day 6, and serum (1-3)-β-D-glucan showed a very high titer (>600 pg/mL) with elevated serum lactate and CRP. Micafungin (MCFG) (150 mg/day) was begun, since candidemia was suspected. However, the skin lesions expanded from the waist to the left lower extremities, so relaxation incision surgery was performed from the left buttocks to the left lower leg. Amputation of the left leg was considered, but it was abandoned because the necrotic lesions spread to the hip and leg on the right side just after the incision surgery. On hospital Day 10, the blood culture

---

**Table 1. Laboratory Examination Findings Obtained on Admission.**

| Hematology | Biochemistry |
|------------|--------------|
| WBC 2.900 μL | TP 5.9 mg/dL |
| myelo 1.5 % | Alb 3.6 mg/dL |
| meta 4.0 % | BUN 13.0 mg/dL |
| stab 13 % | Cre 0.39 mg/dL |
| seg 79.5 % | Na 139 mEq/L |
| lymph 2.0 % | K 4.3 mEq/L |
| RBC 376×10⁴ /μL | Cl 101 mEq/L |
| Hb 12.0 g/dL | AST 33 IU/L |
| Hct 37.3 % | ALT 89 IU/L |
| Plt 15.1×10⁴ /μL | Amylase 54 IU/L |
| T-Bil 0.8 mg/dL | LDH 475 IU/L |
| LDH 495 IU/L | ALP 949 IU/L |
| γ-GTP 22 IU/L | CPK 3.53 mg/dL |
| CRP 326 mg/dL | IgG 326 mg/dL |

---
sample was found to be positive for yeast-like fungus, growing black colonies on potato dextrose agar (Fig. 3b), the antifungal agents were thus switched from MCFG to liposomal amphotericin B (L-AMB) (5 mg/kg). However, the disseminated lesions spread to the upper limbs, upper body and face. On hospital Day 10, the patient became complicated with hemoptysis, and her respiratory failure worsened; she ultimately passed away on hospital Day 12.

A sequence analysis of the internal transcribed spacer region of the rRNA gene revealed the isolate to be *E. dermatitidis*. Postmortem needle biopsies showed disseminated invasion to multiple organs, including the muscle, lung, liver, and intestinal mucosa with massive necrosis, so the final diagnosis was disseminated phaeohyphomycosis caused by *E.*
without underlying disease revealed that screening of 2,300 samples of feces from humans with and formation due to skin GVHD or through the disrupted gas-entrance through her hip injury by recurrent gluteal decubitus case, under long-term immunosuppressive therapy with PSL. E. dermatitidis neic HSCT recipient. In the case reported by Chalkias et al., E. dermatitidis seminated though its distribution is worldwide. have been reported mainly from Asia (3), al-
tent individuals after intravenous drug use or, more recently, infection has also been observed in seemingly immunocompe-
tient individuals after intravenous drug use or, more recently, after infection with contaminated corticosteroid com-
ounds (6). Interestingly, the clinical cases caused by E. dermatitidis have been reported mainly from Asia (3), al-
though its distribution is worldwide.

To our knowledge, this is the second case report of dis-
seminated E. dermatitidis infection observed in an allogeneic HSCT recipient. In the case reported by Chalkias et al., E. dermatitidis infection occurred 2 years after transplantation (4). In contrast, it occurred 7 years after HSCT in our case, under long-term immunosuppressive therapy with PSL for chronic GVHD. We were unable to identify the invasive entrance of E. dermatitidis but suspect it occurred via direct entry through her hip injury by recurrent gluteal decubitus formation due to skin GVHD or through the disrupted gastrointestinal lining due to intestinal GVHD. Of note, a screening of 2,300 samples of feces from humans with and without underlying disease revealed that E. dermatitidis is present at a frequency of 5.2 per 1,000 (n=12) (7).

Among 2,191 invasive fungal infections described in the TRANSNET cohort, 56 (2.6%) cases were categorized as phaeohyphomycosis. In the present case, phaeohyphomycosis caused by E. dermatitidis developed 7 years after allogenic HSCT, which was a relatively late onset compared with the TRANSNET data (median time: 100 days) (8). It is therefore important to maintain a clinical suspicion for this mycosis in order to make an accurate diagnosis promptly.

Our report brings attention to the emerging opportunistic mycosis of community-acquired E. species infection, which should be considered in allogeneic HSCT patients with chronic GVHD.

The diagnostic tools and optimization of treatment for E. dermatitidis are still being developed. (1→3)-β-D-glucan, which is a representative surrogate marker for the rapid diagnosis of invasive fungal infections (9), showed a very high titer (>600 pg/mL) in this case at the time of the growth of yeast in blood culture on Day 6. The association between invasive Exophiala infections and the (1→3)-β-D-glucan level has rarely been described in clinical cases, and we found only 4 previous reports (Table 2) (10-13). Among them (1→3)-β-D-glucan was reported to be elevated in 3 cases. In the present case, whether or not the (1→3)-β-D-glucan level was elevated in earlier stages of the clinical course is unknown; however, further studies to validate (1→3)-β-D-glucan as the modality of invasive Exophiala infections may be warranted.

For the treatment of E. species systemic infections, a combination of antifungal therapy and surgical intervention is often necessary, in contrast to localized cutaneous disease (4). Regarding antifungal therapy, there are no comparative studies of the efficacy of antifungal agents against phaeohyphomycosis. An evaluation of 66 clinical isolates of E. dermatitidis demonstrated good in vitro activity of posaconazole (PSZ), ITCZ, VRCZ and AMPH-B (14). Regarding E. dermatitidis, there are no established minimum inhibitory concentration (MIC) breakpoints to interpret susceptibility results in a standardized fashion. As antifungal agents, ITCZ, PSZ, VRCZ and AMPH-B are known to exhibit a combination of antifungal therapy and surgical intervention. In animal models of disseminated infection by E. dermatitidis, PSZ was more effective than AMPH-B and ITCZ (15). The species appears to be non-susceptible to echinocandins, probably due to the reduced presence of (1→3)-β-D-glucan in the fungal cell walls (14, 16). Breakthrough fungemia was observed while the patient was being treated with MCFG in the present case.

E. dermatitidis can have a yeast-like appearance with conventional staining, and thus its misidentification as Candida or Cryptococcus species has been reported. In addition, E. dermatitidis takes a long time (typically three days) to develop a black color in Sabouraud dextrose agar, making it

Table 2. (1→3)β-D-glucan Levels in Previous Case Reports of Invasive Exophiala Spp. Infections.

| Age/gender | Underlying diseases | Neutropenia | Primary site of infection | Site of detection culture | (1→3)β-D-glucan | Prognosis | Reference |
|------------|---------------------|-------------|---------------------------|--------------------------|-----------------|----------|-----------|
| 47/F       | Recurrent tongue carcinoma | 600/μL | Oral | Blood | 108pg/mL | Cured | 10 |
| 54/F       | Right middle lobe bronchiectasis | - | Lung | Lung | 41pg/mL | Cured | 11 |
| 53/F       | Bronchiectasis | - | Lung | Lung | 40.0pg/mL | Cured | 12 |
| 65/M       | Multiple Myeloma | - | Lung | Lung | <3.7pg/mL | Cured | 13 |

**Discussion**

This case was diagnosed as disseminated phaeohyphomyco-
cosis caused by E. dermatitidis complicating necrotizing fasciitis (NF) because the patient showed multi-system involve-
ment, including the skin and lungs. E. dermatitidis infection has been reported in immunocompromised hosts, such as patients with hematologic malignances or allogenic HSCT or patients requiring renal replacement therapy by peritoneal dialysis. Compared to other species, E. dermatitidis is more frequently associated with disseminated infection in many organs, including the brain, heart valves, lungs and gastrointestinal tract (4). In these cases of disseminated phaeohyphomyco-

---

**Table 2. (1→3)β-D-glucan Levels in Previous Case Reports of Invasive Exophiala Spp. Infections.**

| Age/gender | Underlying diseases | Neutropenia | Primary site of infection | Site of detection culture | (1→3)β-D-glucan | Prognosis | Reference |
|------------|---------------------|-------------|---------------------------|--------------------------|-----------------|----------|-----------|
| 47/F       | Recurrent tongue carcinoma | 600/μL | Oral | Blood | 108pg/mL | Cured | 10 |
| 54/F       | Right middle lobe bronchiectasis | - | Lung | Lung | 41pg/mL | Cured | 11 |
| 53/F       | Bronchiectasis | - | Lung | Lung | 40.0pg/mL | Cured | 12 |
| 65/M       | Multiple Myeloma | - | Lung | Lung | <3.7pg/mL | Cured | 13 |

**Discussion**

This case was diagnosed as disseminated phaeohyphomyco-
cosis caused by E. dermatitidis complicating necrotizing fasciitis (NF) because the patient showed multi-system involve-
ment, including the skin and lungs. E. dermatitidis infection has been reported in immunocompromised hosts, such as patients with hematologic malignances or allogenic HSCT or patients requiring renal replacement therapy by peritoneal dialysis. Compared to other species, E. dermatitidis is more frequently associated with disseminated infection in many organs, including the brain, heart valves, lungs and gastrointestinal tract (4). In these cases of disseminated phaeohyphomyco-

---

**Table 2. (1→3)β-D-glucan Levels in Previous Case Reports of Invasive Exophiala Spp. Infections.**

| Age/gender | Underlying diseases | Neutropenia | Primary site of infection | Site of detection culture | (1→3)β-D-glucan | Prognosis | Reference |
|------------|---------------------|-------------|---------------------------|--------------------------|-----------------|----------|-----------|
| 47/F       | Recurrent tongue carcinoma | 600/μL | Oral | Blood | 108pg/mL | Cured | 10 |
| 54/F       | Right middle lobe bronchiectasis | - | Lung | Lung | 41pg/mL | Cured | 11 |
| 53/F       | Bronchiectasis | - | Lung | Lung | 40.0pg/mL | Cured | 12 |
| 65/M       | Multiple Myeloma | - | Lung | Lung | <3.7pg/mL | Cured | 13 |

**Discussion**

This case was diagnosed as disseminated phaeohyphomyco-
cosis caused by E. dermatitidis complicating necrotizing fasciitis (NF) because the patient showed multi-system involve-
ment, including the skin and lungs. E. dermatitidis infection has been reported in immunocompromised hosts, such as patients with hematologic malignances or allogenic HSCT or patients requiring renal replacement therapy by peritoneal dialysis. Compared to other species, E. dermatitidis is more frequently associated with disseminated infection in many organs, including the brain, heart valves, lungs and gastrointestinal tract (4). In these cases of disseminated phaeohyphomyco-

---

**Table 2. (1→3)β-D-glucan Levels in Previous Case Reports of Invasive Exophiala Spp. Infections.**

| Age/gender | Underlying diseases | Neutropenia | Primary site of infection | Site of detection culture | (1→3)β-D-glucan | Prognosis | Reference |
|------------|---------------------|-------------|---------------------------|--------------------------|-----------------|----------|-----------|
| 47/F       | Recurrent tongue carcinoma | 600/μL | Oral | Blood | 108pg/mL | Cured | 10 |
| 54/F       | Right middle lobe bronchiectasis | - | Lung | Lung | 41pg/mL | Cured | 11 |
| 53/F       | Bronchiectasis | - | Lung | Lung | 40.0pg/mL | Cured | 12 |
| 65/M       | Multiple Myeloma | - | Lung | Lung | <3.7pg/mL | Cured | 13 |
difficult to diagnose the fungus in the early stage of infections. It is therefore important to maintain a clinical suspicion for this mycosis in order to make an accurate diagnosis promptly, and isolation of the yeast under cGVHD should not be dismissed lightly. A recent study showed that matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) allows for the rapid and accurate identification of a wide range of clinically relevant Exophiala species; therefore, the introduction of MALDI-TOF MS to laboratory testing may dramatically aid in the early identification of an unknown colony (17).

A number of fungal species can manifest skin lesions as the presentation of their systemic fungal infections in immunocompromised patients with onco-hematological diseases and/or a history of HSCT. These fungi include yeasts, such as Trichosporon (18) or Cryptococcus (19); molds, such as Fusarium (20), Mucor (21) or Pseudallescheria (Pseudallescheria/Scedosporium complex) (22); and other black fungi, such as Fonsecaea (23). Importantly, all of these fungi, including Exophiala, are non-susceptible to echinocandins, which are one of the most empirically used antifungal drugs for deep-seated mycoses.

In a recently published Japanese guideline (24), prophylaxis with antifungal agents mainly targeting Aspergillus (ITCZ, VRCZ, MCFG) is recommended for chronic GVHD after allogenic HSCT. Given the rarity of the disease and the difficulty of effective treatment, in addition to daily life advice, prophylaxis with oral triazoles should be considered in order to prevent this infection among chronic GVHD patients with immunosuppression.

In summary, E. dermatitidis should be kept in mind as a cause of opportunistic invasive mycosis, especially in patients with long immunosuppression after allogeneic HSCT with chronic GVHD. When suspected, the early implementation of debridement and appropriate antifungal therapy should be considered.

Author’s disclosure of potential Conflicts of Interest (COI). Kazuo Tamura: Honoraria, Ono Pharmaceutical, Kyowa Hakko Kirin Pharma and Eli Lilly Japan; Fees for promotional materials, Celgene, Ono Pharmaceutical, Kyowa Hakko Kirin Pharma and Eli Lilly Japan. Tohru Takata: Honoraria, Taisho Toyama Pharmaceutical.

References
1. Matsumoto T, Padhye AA, Ajello L. Medical significance of the so-called black yeasts. Eur J Epidemiol 31: 87-95, 1987.
2. Ben-Ami R, Lewis RE, Raad II, Kontoyiannis DP. Phaeohyphomycosis in a tertiary care cancer center. Clin Infect Dis 48: 1033-1041, 2009.
3. Chowdhary A, Meis JF, Guarro J, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect 20: 47-73, 2014.
4. Chalkias S, Alonso CD, Levine JD, Wong MT. Emerging pathogen in immunocompromised hosts: Exophiala dermatisidiotic mycosis in graft-versus-host disease. Transpl Infect Dis 16: 616-620, 2014.
5. Revankar SG, Sutton DA. Melanized fungi in human disease. Clin Microbiol Rev 23: 884-928, 2010.
6. Centers for Disease Control and Prevention (CDC) MMWR Mortal Wkly Rep 51: 1109-1112, 2002.
7. de Hoog GS, Matos T, Sudhadham M, Luijsterburg KF, Haase G. Intestinal prevalence of the neurotropic black yeast Exophiala (Wangiella) dermatisiditidis in healthy and impaired individuals. Mycoses 48: 142-145, 2005.
8. McCarty TP, Baddley JW, Walsh TJ, et al. Phaeohyphomycosis in transplant recipients: results from the Transplant Associated Infection Surveillance Network (TRANSNET). Med Mycol 53: 440-446, 2015.
9. Theel ES, Doern CD. β-D-Glucan testing is important for diagnosis of invasive fungal infections. J Clin Microbiol 51: 3478-3483, 2013.
10. Kakuya T, Yoshida S, Saito S, Ichikawa H, Ito A, Tanaka J. A case of fungemia caused by Exophiala dermatisiditidis after chemotherapy for recurrent tongue carcinoma. Jpn J Oral Maxillofacial Surg 60: 441-445, 2014 (in Japanese, Abstract in English).
11. Mukaino T, Koga KT, Oshita Y, et al. Exophiala dermatisiditidis infection in non-cystic fibrosis bronchiectasis. Respir Med 100: 2069-2071, 2006.
12. Tanamachi C, Hashimoto K, Nakata K, Sagawa. A case of pulmonary chromomycosis caused by Exophiala dermatisiditis. J Jpn Soc Clin Microbiol 18: 25-30, 2008 (in Japanese, Abstract in English).
13. Suzuki K, Nakamura A, Fujieda A, Nakase K, Katayama N. Pulmonary infection caused by Exophiala dermatisiditis in a patient with multiple myeloma: a case report and a review of the literature. Med Mycol Case Rep 17: 95-98, 2012.
14. Badali H, de Hoog GS, Sudhadham M, Meis JF. Microdilution in vitro antifungal susceptibility of Exophiala dermatisiditidis, a systemic opportunist. Med Mycol 49: 819-824, 2011.
15. Calvo E, Pastor FJ, Guarro J. Antifungal therapies in murine disseminated phaeohyphomycoses caused by Exophiala species. J Antimicrob Chemother 65: 1455-1459, 2010.
16. Odabasi Z, Paetznick VL, Rodriguez JR, Chen E, Ostrosky-Zeichner L. In vitro activity of anidulafungin against selected clinically important mold isolates. Antimicrob Agents Chemother 48: 1912-1915, 2004.
17. Borman AM, Fraser M, Szekely A, Larcombe DE, Johnson EM. Rapid identification of clinically relevant members of the genus Exophiala by matrix-assisted laser desorption ionization-time of flight mass spectrometry and description of two novel species, Exophiala campbellii and Exophiala lavatrina. J Clin Microbiol 55: 1162-1176, 2017.
18. Mariné M, Brown NA, Riaño-Pachón DM, Goldman GH. On and under the skin: emerging Basidiomycetous yeast infections caused by Trichosporon species. PLoS Pathog 11: e1004982, 2015.
19. Park SS, Lee H, Park WS, et al. A case of disseminated infection with skin manifestation due to non-neoformans and non-gattii Cryptococcus in a patient with refractory acute myeloid leukemia. Infect Chemother 49: 142-145, 2017.
20. Varon AG, N OUTER SA, Barreiros G, et al. Superficial skin lesions positive for Fusarium are associated with subsequent development of invasive fusariosis. J Infect 68: 85-89, 2014.
21. Kanemaru M, Tashima S, Yamazaki A, et al. Disseminated chromomycosis due to Rhizopus oryzae diagnosed by skin biopsy. J Dermatol 42: 100-101, 2015.
22. Tsuchi G, Takei K, Takahara M, et al. Cutaneous Pseudallescheria boydii/Scedosporium apiospermum complex infection in immunocompromised patients: a report of two cases. J Dermatol 44: 1067-1068, 2017.
23. Tsai WC, Lee CH, Wu WM, et al. Cutaneous manifestations of subcutaneous and systemic fungal infections in tropical regions: a retrospective study from a referral center in southern Taiwan. Int J Dermatol 56: 623-629, 2017.
24. Kohno S, Tamura K, Niki Y, et al. Executive summary of Japanese domestic guidelines for management of deep-seated mycosis 2014. Med Mycol J 57: 117-163, 2016.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).