Published in final edited form as:

Transpl Infect Dis. 2019 October ; 21(5): e13153. doi:10.1111/tid.13153.

Angioinvasive, cutaneous infection due to *Colletotrichum siamense* in a stem cell transplant recipient: Report and review of prior cases

William A. Werbel¹, Riccardo Baroncelli², Shmuel Shoham¹, Sean X. Zhang³

¹Division of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, MD, USA

²Instituto Hispano-Luso de Investigaciones Agrarias (CIALE), University of Salamanca, Salamanca, Spain

³Division of Microbiology, Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD, USA

Abstract

Colletotrichum is an important fungal plant pathogen, yet an uncommon cause of human disease. Herein we report a case of invasive, cutaneous infection in a stem cell transplant recipient due to *Colletotrichum* species, with accompanying review of the literature. The infection was successfully treated with a combination of liposomal amphotericin B and voriconazole. Multilocus phylogenetic analysis revealed that the distinct isolate belongs to *Colletotrichum siamense*, a member of the *Colletotrichum gloeosporioides* species complex not previously described as a human pathogen. *Colletotrichum* infection remains in the differential for skin lesions in the immune compromised host.

Keywords

Colletotrichum; *Colletotrichum gloeosporioides*; *Colletotrichum siamense*; *Glomerella*; phaeohyphomycosis; stem cell transplant

1 | INTRODUCTION

Colletotrichum species are filamentous fungi that infect a diversity of economically important crops worldwide, causing “anthracnose” disease, and are extensively studied as a model pathosystem in plant pathology.^{1,2} This plant pathogen is increasingly recognized in human infections, with disease primarily related to inoculation of organic or woody material into ocular or cutaneous surfaces.^{3,4} Keratitis and/or endophthalmitis are typical in non-

Correspondence: William A. Werbel, Johns Hopkins University School of Medicine, Pre-Clinical Teaching Building, Suite 211, 725 North Wolfe Street, Baltimore, MD 21205, USA. wwerbel1@jhmi.edu.

AUTHOR CONTRIBUTIONS

Dr Werbel wrote the manuscript and performed the literature review. Dr Baroncelli performed the phylogenetic and sequence analyses in addition to editing the manuscript. Dr Shoham edited the manuscript and assisted with the literature review. Dr Zhang performed initial pathogen culture, microscopy, and sequencing, in addition to editing the manuscript.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

immunocompromised patients,⁴ while skin and soft tissue infections are rarely described and predominantly seen in immunocompromised patients.⁵ Deeper infection beyond the immediately surrounding structures (eg, pneumonia) has been speculated, but not definitively proven.⁶ Described treatment modalities include local debridement $\pm$ a triazole or amphotericin, though ideal therapy has not been established.

Complicating matters of identification and treatment selection, the genus *Colletotrichum* has undertaken many taxonomic changes in the last two decades, with 14 currently accepted monophyletic clades (ie, “species complexes”) encompassing >200 species.⁷ Of these, primarily *Colletotrichum gloeosporioides*^{3,5,8–12} and *Colletotrichum coccodes*,^{6,13} as well as *Colletotrichum crassipes*,¹⁴ *Colletotrichum truncatum*,¹⁵ *Colletotrichum graminicola*,¹⁶ and *Colletotrichum dematium*,⁴ have been identified as causes of human infections. *C. gloeosporioides*, however, is now considered a species complex comprised of multiple species including *Colletotrichum siamense*.¹⁷

We present here an unusual case of angioinvasive, extraocular *Colletotrichum* infection, identified as a novel isolate via contemporary phylogenetic analysis.

2 | CASE REPORT

The patient was a 66-year-old woman with relapsed diffuse large B-cell lymphoma for which she underwent non-myeloablative peripheral blood stem cell transplant complicated by profound neutropenia. Her conditioning regimen included rituximab, ifosfamide, carboplatin, etoposide, and total body irradiation, in addition to cyclophosphamide and intravenous cefepime for transient peri-transplant fever consistent with cytokine release syndrome. Her post transplant maintenance immune suppression included mycophenolate mofetil and tacrolimus, and she received anti-infective prophylaxis with acyclovir and fluconazole.

At 24 days post transplant, she developed *Enterococcus faecium* bloodstream infection and septic shock, characterized by hypotension, renal failure, and altered mentation. Absolute neutrophil count was <50 cells/ μ L. During evaluation, a single cutaneous ulcer was discovered on the right fourth finger, at a site underneath mitten hand restraints (Figure 1A). The ulceration had a dusky, crusted, necrotic center, as well as surrounding violaceous induration. There was no evident proximal interphalangeal joint involvement by examination or radiograph; computed tomography of the chest did not reveal nodules or cavitation.

A shave biopsy of the lesion was performed, removing the majority of affected tissue. Cultures grew vancomycin-resistant *Enterococcus faecium*, coagulase-negative *Staphylococcus* species, and a filamentous fungus in three of three slants. Tissue histology examination showed numerous fungal hyphae invading blood vessels and dermis (Figure 1B). Serum galactomannan index (GM) was 0.06, and serum beta-D-glucan (BDG) was elevated to 136 pg/mL (vs <31 pg/mL three weeks earlier).

The fungus was initially identified as a member of the *C. gloeosporioides* species complex based on colony morphologies and microscopic features (Figure 1C, 1D) as well as ITS/D1-D2 sequencing identification. To further determine species designation of this unusual

isolate, a multilocus phylogenetic analysis was performed using nine genomic loci^{18,19}: the internal transcribed spacer (ITS) region, partial sequence of the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, beta-tubulin 2 gene (TUB2), chitin synthase 1 gene (CHS-1), actin gene (ACT), glutamine synthetase (GS), superoxide dismutase (SOD2), calmodulin (CAL), and the Apn2/Mat1-2-1 intergenic spacer (ApMAT). Sequences of 48 reference strains within the *C. gloeosporioides* species complex were selected for phylogenetic analysis. Amplification/sequencing reactions and products as well as sequence alignments and phylogenetic analysis are provided in Appendix S1. Results of the multilocus sequence alignment revealed a distinct isolate, most closely related to *C. siamense* (Figure 2).

In addition to antibacterial therapy for enterococcal infection (daptomycin), the patient was initially treated with liposomal amphotericin B (L-AmB) 5 mg/kg/d and voriconazole 6 mg/kg twice-daily load, followed by 4 mg/kg twice-daily maintenance. L-AmB and voriconazole were continued together for two weeks during which her neutropenia resolved. Antifungal susceptibility testing by broth dilution in accordance with Clinical and Laboratory Standards Institute document M38-A3 standards for molds returned during follow-up, revealing minimum inhibitory concentrations (MICs) for the following antifungal drugs: amphotericin B 0.5 µg/mL; voriconazole 2 µg/mL; posaconazole 1 µg/mL; and isavuconazole 0.5 µg/mL (University of Texas Health Science Center). Voriconazole monotherapy was continued for a total of 2 months given the patient's ongoing clinical improvement, with serum levels ranging 0.8-2.1 µg/mL during follow-up. Serial blood BDG levels normalized from 99-41 pg/mL to < 31 pg/mL over a 3-month period. The finger lesion healed completely, and she remained free of evident local or systemic fungal disease until her death 5 months later due to an unrelated *Pseudomonas aeruginosa* bloodstream infection.

3 | DISCUSSION

With advances in antifungal prophylaxis drugs as well as technologies for fungal identification, the spectrum of invasive mold infection is expanding among immune compromised hosts.^{20,21} *Colletotrichum* (sexual state: *Glomerella*) is one such emerging pathogen, for which we present the 14th described angioinvasive, extraocular infection in the known literature (see Table 1).^{3,5,6,8-15} Through phylogenetic analysis, we have also identified a *Colletotrichum* strain closely related to prior isolates designated as *C. siamense*, which should now be considered a potential human pathogen. It is notable, however, that prior reports of human *Colletotrichum* infection rarely incorporated species-level analysis.

The majority of reported *Colletotrichum* cases have occurred in solid organ or stem cell transplant recipients after exposure to plant material, typically producing cutaneous nodules, ulcers, and cysts consistent with phaeohyphomycosis (Table 1). In this present case, although no clear plant exposure was ascertained, opportunistic infection occurred in the setting of prolonged neutropenia post stem cell transplant, during fluconazole prophylaxis. There was no evidence of local trauma related to the temporary soft mitten restraint, which was secured at the wrist and evaluated daily per ward protocol.

Other clinically relevant findings include first documentation of elevated BDG during infection, normalizing during treatment, with normal serum GM index. One other case has reported normal serum BDG and GM during *Colletotrichum* infection,¹⁵ whereas another documented elevated GM index in the setting of concurrent *Cunninghamella* infection and probable aspergillosis.¹³ Broad in vitro antifungal MIC data are reported here, consistent with prior studies, and suggesting potential clinical activity of the newer triazoles. Treatment success was obtained with excisional shave biopsy and dual antifungal induction with eventual voriconazole monotherapy, in the context of immune reconstitution.

4 | CONCLUSIONS

Cutaneous infection with the environmental mold *Colletotrichum* is uncommon, but does occur in heavily immunocompromised patients, including those post solid organ or stem cell transplant. This fungus should remain in the differential of cutaneous lesions in at-risk patients not receiving mold-active triazole prophylaxis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors would like to thank the staff members in the Mycology Laboratory at the Johns Hopkins Hospital for their excellent technical support.

Funding information

National Institute of Allergy and Infectious Diseases, Grant/Award Number: T32AI007291

REFERENCES

1. Baroncelli R, Talhinas P, Pensec F, Sukno SA, Le Floch G, Thon MR. The *Colletotrichum* acutatum species complex as a model system to study evolution and host specialization in plant pathogens. *Front Microbiol* 2017;8:2001. [PubMed: 29075253]
2. Dean R, Van kan JAL, Pretorius ZA, et al. The Top 10 fungal pathogens in molecular plant pathology. *Mol Plant Pathol* 2012;13(4):414–430. [PubMed: 22471698]
3. Severo CB, Oliveira Fde M, Pilar EF, Severo LC. Phaeohyphomycosis: a clinical-epidemiological and diagnostic study of eighteen cases in Rio Grande do Sul, Brazil. *Mem Inst Oswaldo Cruz* 2012;107(7):854–858. [PubMed: 23147139]
4. Squizzato V, Yucel YH, Richardson SE, et al. *Colletotrichum truncatum* species complex: treatment considerations and review of the literature for an unusual pathogen causing fungal keratitis and endophthalmitis. *Med Mycol Case Rep* 2015;9:1–6. [PubMed: 26137437]
5. Lin LY, Yang CC, Wan JY, Chang TC, Lee JY. Cutaneous infection caused by plant pathogen *Colletotrichum gloeosporioides*. *JAMA Dermatol* 2015;151(12):1383–1384. [PubMed: 26287364]
6. O'Quinn RP, Hoffmann JL, Boyd AS. *Colletotrichum* species as emerging opportunistic fungal pathogens: a report of 3 cases of phaeohyphomycosis and review. *J Am Acad Dermatol* 2001;45(1):56–61. [PubMed: 11423835]
7. Cannon PF, Damm U, Johnston PR, Weir BS. *Colletotrichum* - current status and future directions. *Stud Mycol* 2012;73(1):181–213. [PubMed: 23136460]
8. Figtree M, Weeks K, Chan L, et al. *Colletotrichum gloeosporioides* sensu lato causing deep soft tissue mycosis following a penetrating injury. *Med Mycol Case Rep* 2013;2:40–43. [PubMed: 24432213]

9. Ogawa M, Reis V, Godoy P, Gatti de Menezes F, Enokihara M, Tomimori J. [Phaeohyphomycosis caused by *Colletotrichum gloeosporioides* and *Alternaria infectoria* in renal transplant recipient]. *Rev Chilena Infectol* 2014;31(4):468–472. [PubMed: 25327202]
10. Guarro J, Svidzinski TE, Zaror L, Forjaz MH, Gene J, Fischman O. Subcutaneous hyalohyphomycosis caused by *Colletotrichum gloeosporioides*. *J Clin Microbiol* 1998;36(10):3060–3065. [PubMed: 9738070]
11. Allton DR, Parvez N, Ranganath S, Jinadatha C. Surgical management of subcutaneous *Colletotrichum gloeosporioides*. *BMJ Case Rep* 2015;2015:pil bcr2014207540
12. Kammeyer PL, Mondo DM, Wadhwani N, Mandrell J. Orthotopic heart transplant recipient with *Glomerella cingulata* and *Alternaria* cutaneous infections after deer hunting excursion. *Mycoses* 2012;55(S4):212.
13. Lee SH, Sun HY, Ko BS, Chang SC. Breakthrough invasive fungal infection under the use of posaconazole and voriconazole. *J Formos Med Assoc* 2016;115(5):384–385. [PubMed: 25891760]
14. Castro LG, da Silva LC, Guarro J, et al. Phaeohyphomycotic cyst caused by *Colletotrichum crassipes*. *J Clin Microbiol* 2001;39(6):2321–2324. [PubMed: 11376082]
15. Howard LM, Gilbert L, Zwerner JP, Snyder KM, Di Pentima MC. Subcutaneous *Colletotrichum truncatum* infection in a child. *Pediatr Infect Dis J* 2016;35(4):455–457. [PubMed: 26673980]
16. Yegneswaran PP, Pai V, Bairy I, Bhandary S. *Colletotrichum graminicola* keratitis: first case report from India. *Indian J Ophthalmol* 2010;58(5):415–417. [PubMed: 20689197]
17. Damm U, Sato T, Alizadeh A, Groenewald JZ, Crous PW. The *Colletotrichum dracaenophilum*, *C. magnum* and *C. orchidearum* species complexes. *Stud Mycol* 2019;92:1–46. [PubMed: 29997400]
18. Weir BS, Johnston PR, Damm U. The *Colletotrichum gloeosporioides* species complex. *Stud Mycol* 2012;73(1):115–180. [PubMed: 23136459]
19. Marin-Felix Y, Groenewald JZ, Cai L, et al. Genera of phytopathogenic fungi: GOPHY 1. *Stud Mycol* 2017;86:99–216. [PubMed: 28663602]
20. Douglas AP, Chen SC, Slavin MA. Emerging infections caused by non-*Aspergillus* filamentous fungi. *Clin Microbiol Infect* 2016;22(8):670–680. [PubMed: 26812445]
21. Lionakis MS, Lewis RE, Kontoyiannis DP. Breakthrough invasive mold infections in the hematology patient: current concepts and future directions. *Clin Infect Dis* 2018;67(10):1621–1630. [PubMed: 29860307]

FIGURE 1.

Gross and microscopic evidence of invasive fungal infection. A, Lesion on the fourth finger, distal to the proximal interphalangeal joint, of approximately 0.75×1.0 cm in size. This consisted of a central crusted ulcer with surrounding violaceous changes and thin base of erythema. B, Hematoxylin and eosin staining. Presence of fungal hyphae inside the blood vessel and in the surrounding necrotic tissue, demonstrating angio- and tissue-invasive fungal infection. Scale bar 20 µm. C, Fungal colonies effuse, gray to brown. D, Conidia are straight, cylindrical, and obtuse at the apex; appressoria are clavate or irregular. Image captured at $\times 40$ magnification

FIGURE 2.

Phylogenetic tree of *Colletotrichum* species demonstrating the strain isolated in this study (in bold) belongs to *C siamense*. The Bayesian inference phylogenetic tree shown was reconstructed from a combined ITS, GAPDH, CHS-1, ACT, TUB2, GS, SOD2, ApMAT, and CAL sequence alignment of 49 isolates including the out-group. Bayesian posterior probability (BPP) values (above 0.50) are represented by thickness of the node. Maximum parsimony bootstrap (MPB) values obtained by 1,000 replicates are reported as numbers next to the node. *C boninense* CBS: 123755 is used as out-group. The scale bar represents the number of expected substitutions per site. Sequence information as well as detailed methods used can be found in supplementary files

TABLE 1

Cases of invasive *Colletotrichum* infection: features, risk factors, and therapy

Age, sex (ref)	Comorbidity	Immune suppression	Lesions	Risk	Species	Therapy	Outcome
56, M ⁽¹⁰⁾	DM	Prednisone 20 mg/d (self-prescribed)	Multiple nodules	Agriculture worker	<i>C gloeosporioides</i>	None	Death (Accident)
58, M ⁽⁶⁾	NHL + allo-SCT	Chemotherapy, radiation	Cutaneous macular lesion, possibly lung	Unknown	<i>C coccodes</i>	d-AmB, + 5-FC + ITZ	Death (Cavitary pneumonia)
47, M ⁽⁶⁾	NHL + allo-SCT	Chemotherapy	Cutaneous nodule	Unknown	<i>C coccodes</i>	d-AmB, followed by ITZ	Response
34, M ⁽⁶⁾	ALL	Chemotherapy, prednisone	Cutaneous nodule	Cactus thorn injury	<i>C gloeosporioides</i>	d-AmB, followed by ITZ	Response
34, M ⁽¹⁴⁾	Renal transplant	CNI, AZA, prednisone	Subcutaneous nodule	Work as a gardener	<i>C crassipes</i>	Surgery	Resolution
57, M ⁽⁸⁾	None	None	Skin and soft tissue infection	Lemon tree thorn injury	<i>C gloeosporioides</i>	Surgery	Resolution
53, M ⁽³⁾	Lung transplant	CNI, AZA, prednisone	Subcutaneous cyst	Unknown	<i>C gloeosporioides</i>	Surgery	Death (CMV)
62, M ⁽¹²⁾	Heart transplant	Not reported	Cutaneous papules, nodules	Deer hunting	<i>C gloeosporioides</i>	Not reported	Not reported
68, M ⁽⁹⁾	Renal transplant	CNI, AZA, prednisone	Cutaneous nodule	Work as a gardener	<i>C gloeosporioides</i>	Surgery	Resolution
52, M ⁽¹¹⁾	Cirrhosis, DM, sarcoidosis	Prednisone 10	Cutaneous nodules	Thorn injury	<i>C gloeosporioides</i>	Surgery	Resolution
70, F ⁽⁵⁾	Stasis dermatitis	Steroid	Ulcers	Local traumatic plant injury	<i>C gloeosporioides</i>	ITZ	Resolution
4, M ⁽¹⁵⁾	Neuroblastoma	Chemotherapy	Multiple cutaneous plaques/ulcers	Unknown	<i>C truncatum</i>	L-AmB + VCZ + surgery followed by VCZ	Resolution
60, M ⁽¹³⁾	NHL + allo-SCT	Methyl prednisolone, etanercept (for GVHD)	Septic arthritis of MTP joint	Unknown	<i>C coccodes</i>	d-AmB followed by VCZ	Death (Cunninghamella)
66, F (case)	NHL + SCT	CNI, mycophenolate	Cutaneous ulcer	Unknown	Novel species	L-AmB, VCZ	Resolution

Abbreviations: 5-FC, flucytosine; ALL, acute lymphoblastic leukemia; allo-SCT, allogeneic stem cell transplant; AZA, azathioprine; CNI, calcineurin inhibitor (ie, tacrolimus or cyclosporine); d-AmB, deoxycholate amphotericin B; DM, diabetes mellitus; GVHD, graft-versus-host disease; ITZ, itraconazole; L-AmB, liposomal amphotericin B; MTP, metatarsophalangeal joint; NHL, non-Hodgkin's lymphoma; VCZ, voriconazole.