HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
PROGRAMA DE RESIDÊNCIA MÉDICA EM HEMATOLOGIA E HEMOTERAPIA - ÁREA DE ATUAÇÃO: TRANSPLANTE DE MEDULA ÓSSEA

AUTORA: ALINE SINHORELO RIBEIRO
ORIENTADORA: LISANDRA DELLA COSTA RIGONI

SINUSITE FÚNGICA INVASIVA POR *COLLETOTRICHUM SPECIES* EM UM RECEPTOR DE TRANSPLANTE DE MEDULA ÓSSEA ALOGÊNICO: PRIMEIRO RELATO DE CASO E REVISÃO DA LITERATURA

PORTO ALEGRE, FEVEREIRO DE 2022

ALINE SINHORELO RIBEIRO

SINUSITE FÚNGICA INVASIVA POR *COLLETOTRICHUM SPECIES* EM UM RECEPTOR DE TRANSPLANTE DE MEDULA ÓSSEA ALOGÊNICO: PRIMEIRO RELATO DE CASO E REVISÃO DA LITERATURA

Trabalho de Conclusão de Residência Médica, apresentado como requisito para obtenção de grau de especialista em Transplante de Medula Óssea, pelo Hospital de Clínicas de Porto Alegre.

Orientadora: Dra Lisandra Della Costa Rigoni

CIP - Catalogação na Publicação

Ribeiro, Aline Sinhorelo
Sinusite fúngica invasiva por Colletotrichum species em um receptor de transplante de medula óssea alogênico: primeiro relato de caso e revisão da literatura / Aline Sinhorelo Ribeiro. -- 2022.
20 f.
Orientadora: Lisandra Della Costa Rigoni.

Trabalho de conclusão de curso (Especialização) -- Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Hematologia e Hemoterapia - Área de atuação: Transplante de Medula Óssea, Porto Alegre, BR-RS, 2022.

1. Transplante de células-tronco hematopoiéticas. 2. Hemoglobinúria paroxística noturna. 3. Feo-hifomicose. 4. Sinusite. I. Rigoni, Lisandra Della Costa, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

SUMÁRIO

RESUMO 5
1 INTRODUCTION 7
2 CASE REPORT 8
3 LITERATURE REVIEW 9
4 DISCUSSION 10
5 CONCLUSIONS 12
REFERENCES 14
APÊNDICE 20

RESUMO

Introdução: Infecção fúngica invasiva é uma importante causa de morbimortalidade em pacientes imunocomprometidos, como os submetidos à transplante de células-tronco hematopoiéticas (TCTH). Embora *Candida* e *Aspergillus* sejam as espécies fúngicas mais comumente isoladas nestes pacientes, outras espécies menos comuns vem se tornando prevalentes, como os fungos demáceos, caracterizados pela presença de melanina, que causam diversas síndromes clínicas chamadas de feohifomicoses. Distribuídos mundialmente e encontrados no solo, são adquiridos presumivelmente por inalação ou trauma. Sinusite fúngica invasiva (SFI) por fungo demáceo é uma doença rara, com apresentação clínica usual com sintomas crônicos de efeito de massa, incluindo dor e pressão em seios da face. Métodos: objetivamos descrever o primeiro caso de SFI por fungo demáceo do tipo *Colletotrichum* species em uma paciente com hemoglobinúria paroxística noturna (HPN) submetida à TCTH, e realizar uma revisão de literatura sobre SFI por fungos demáceos em pacientes imunocomprometidos que realizaram TCTH. Resultados: paciente do sexo feminino, 21 anos, com diagnóstico de HPN e manifestações abdominais trombóticas. Evoluiu com falência medular e foi submetida à TCTH alogênico não aparentado 11x12, tendo recebido profilaxia antifúngica pós transplante com fluconazol. No D+9 iniciou com cefaleia holocraniana e facial, e tomografia computadorizada de seios da face evidenciou espessamento da mucosa do seio maxilar, compatível com sinusopatia inflamatória. Nasofibroscopia revelou área enegrecida na concha média, coberta por pontos brancos. Realizou extração de corneto médio com septoplastia. Anatomopatológico revelou elementos fúngicos com esporos e hifas septadas e brotamento, com extensa angioinvasão. A pesquisa direta foi positiva para hifas hialinas e a cultura evidenciou um fungo demáceo - Colletotrichum sp. Utilizou complexo lipídico de anfotericina B por 14 dias, seguido de voriconazol com resposta completa. Foram encontrados na literatura 8 casos, incluindo o atual, de SFI por fungo demáceo em pacientes imunocomprometidos que foram submetidos a TCTH em algum momento, sendo que metade dessas infecções ocorrendo após o transplante. Em todos os casos, exceto o nosso, os gêneros encontrados foram os mais comuns de fungos melanizados (*Alternaria* e *Exserohilum*), sendo o nosso o único por *Colletotrichum specie*. Todos os tratamentos incluíram Anfotericina B e apresentaram resposta

completa ao tratamento da infecção fúngica, sem sinais de recaída. Metade dos paciente foi à óbito por outras infecções relacionadas à imunossupressão. Conclusão: este caso inclui a espécie *Colletotrichum* como um dos gêneros de fungos demáceos que causam sinusite invasiva em pacientes imunocomprometidos, como receptores de TCTH. Nossa paciente foi tratada com sucesso, com resposta completa da infecção fúngica com cirurgia mais anfotericina B complexo lipídico por duas semanas, seguido de voriconazol até o desfecho, e sem recidiva até o óbito. É crucial relatar todos os casos de sinusite invasiva causada por fungos melanizados, pois a experiência clínica é determinante nesse tipo de patologia rara.

Palavras-chave: Transplante de células-tronco hematopoiéticas. Hemoglobinúria paroxística noturna. Feo-hifomicose. Sinusite.

1 INTRODUCTION

Invasive fungal infections are an important cause of morbidity and mortality in immunocompromised patients, like those who underwent allogeneic hematopoietic stem cell transplantation (HSCT).[1] The lack of an adequate immune system has made these patients more likely to infections caused by organisms that were previously considered environmental contaminants and not true pathogens.[2] This may be related to several factors, including prolonged granulocytopenia, the utilization of broad-spectrum antibacterial agents, type of conditioning regimen, the disruption of normal mucosa barriers by chemotherapy, radiation therapy, patient age, donor match, occurrence of graft-versus-host disease (GVHD), and the increasing use of central venous access devices.[3]

Although *Candida* and *Aspergillus* species have been the most common fungi isolated from bone marrow transplant patients, other less common microorganisms are becoming prevalent with the use of antifungal prophylaxis, like mucorales, dematiaceous molds, and plant pathogens such as *Fusarium*. These emerging fungi are associated with high mortality, and our understanding regarding their pathogenesis and treatment is limited.[1,2,3]

“Dematiaceous” or “melanized” molds, as often described in literature, is a large and heterogeneous group of darkly pigmented fungi who cause phaeohyphomycosis, which indicates a variety of infectious syndromes.[2,4] More than 150 species and 70 genera of dematiaceous fungi have been implicated in human diseases.[5] They are commonly found in the soil and are worldwide distributed, which suggests that most individuals are exposed to them, presumably from inhalation or trauma.[6] The clinical syndromes include allergic disease, keratitis, superficial cutaneous or subcutaneous disease, deep local infections (like invasive sinusitis), pulmonary infections, central nervous system infections, and disseminated disease.[7]

Invasive dematiaceous fungal sinusitis (IDFS) is a rare disorder, mainly associated with *Curvularia*, *Alternaria* e *Exserohilum* genera.[4] The usual clinical presentation is chronic symptoms of mass effect, including sinus pain and facial pressure, with endoscopic examination commonly revealing polyps and, rarely, eschars.[8] If invasion of the mucosa is demonstrated on histological examination, in

addition to surgical debridement and washout, systemic antifungal therapy is indicated to prevent relapse, orbital complications and intracranial extension.[9]

We report the first case of IDFS by *Colletotrichum* specie, a rare melanized fungus, in a woman with paroxysmal nocturnal haemoglobinuria (PNH) post-allogeneic HSCT, and provide a literature review of IDFS in immunocompromised patients who underwent allogeneic HSCT at some point.

2 CASE REPORT

A 21-year-old caucasian female with a history of marrow failure diagnosis in 2013 was treated with cyclosporine (withdrawn due to encephalopathy) and thymoglobulin, without response. In 2014 she was diagnosed with PNH, with thrombotic abdominal manifestations. She started intermittent anticoagulation, due to thrombocytopenia. PNH initial clones were present in 45% of neutrophils, 50,9% of monocytes and 8,3% of erythrocytes. She had multiple new abdominal thrombosis. Eculizumab was not available, despite a court order, which was denied. She progressed with worsening of the bone marrow failure and HSCT was then indicated.

The patient was submitted to a matched unrelated allogeneic HSCT 11x12 with non-permissive DPB1 mismatch, female donor, 40 years old, ABO isogroup, both donor and patient CMV seropositive. Reduced-intensity conditioning was adopted using fludarabine, cyclophosphamide, and total body irradiation (2 Gy), and GVHD prophylaxis consisted of thymoglobulin, methotrexate and tacrolimus. The graft source was cryopreserved bone marrow with 5x10ˆ6/kg of CD34 cells and 5x10ˆ8/kg of total nucleated cell. Neutrophil engraftment occurred on post-transplant D+13 and platelet on D+33.

On D+9 she started with a holocranial headache and facial pressure. Sinuses CT (computerized tomography) showed mucosal thickening of the maxillary sinus, compatible with inflammatory sinusopahty. Nasofibroscopy revealed a blackish area on medium turbinate, covered with white dots. She did a middle turbinate extraction with septoplasty. Anatomopathological revealed fungal elements with spore and septate hyphae and sprouting, with extensive angioinvasion. Direct search was positive for hyaline hyphae and culture displayed a dematiaceous fungus, *Colletotrichum* species, confirming the invasive dematiaceous fungal sinusitis (IDFS).

She used amphotericin B lipid complex for 14 days, followed by voriconazole as secondary prophylaxis until the outcome of this case, with complete response.

On D+31 she had a diagnosis of acute skin GVHD stage II Grade 2, starting prednisone 1mg/kg/day and posteriorly progressing for methylprednisolone 2mg/kg/day, with complete response in 14 days. She had the necessity of tacrolimus suspension because of microangiopathy, exchanged for sirolimus. On D+51 she was diagnosed with volcano-like gastric erosions, and immunohistochemistry was compatible with cytomegalovirus infection. She used ganciclovir for 15 days, with severe hematological toxicity, and changed to foscarnet until 21 days of treatment, with complete response. She had a 100% donor chimerism and no detectable PNH clone on D+60.

Despite the excellent initial evolution after HSCT, she persisted with poor graft function, with frequent transfusion requirements and also diffuse gastric bleeding secondary to plaquetopenia, with no new lesion or evidence of GVHD identified on endoscopy. The patient also had ascites due to portal hypertension requiring multiple paracentesis for relief. Then, she was diagnosed with a bloodstream infection by a metallocabapenemase-producing *Proteus sp.* isolated in blood cultures, sensitive to amikacin, which was initiated. However, the patient progressed to refractory hypoxemia and septic shock, and died on post-transplant D+170, after seven months of hospitalization. There was no relapse of the IDFS until her death.

3 LITERATURE REVIEW

An extensive literature review of IDFS in immunocompromised patients, who had allogeneic HSCT at some point, was performed using PubMed database, applying different search terms, limited to english language articles only.

The search identified nineteen reported cases of phaeohyphomycosis in patients recipients of allogeneic HSCT, causing different clinical syndromes. Of these, only seven were about invasive fungal sinusitis due to melanized fungi. All these articles were published between 1993 and 2017. Cases with invasive nasal septum disease in the absence of concomitant sinusitis were omitted.

This seven cases were analyzed and classified in proven or probable invasive fungal sinusitis according to the revised and updated consensus definitions

established by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) published in 2020.[10]

4 DISCUSSION

Our case was the eighth published case of IDFS related to HSCT, and the first IDFS, until now, due to *Colletotrichum* species, a very rare melanized fungal, in a patient with PNH post-allogeneic HSCT. Table 1 summarizes the characteristics of the eight cases.

In all cases except ours, the genera associated with IDFS were the most common melanized fungi (*Alternaria* and *Exserohilum*). The clinical presentation was diverse, and included purulent nasal discharge, olfactory impairment, headache and facial pressure; fever occurred in two patients with no other symptoms associated; in another two, skin lesions led to further investigation and discovery of invasive sinusitis; and in one case, information about clinic was not informed. As the manifestations are highly variable, clinical suspicion should always be made in this population. CT is commonly performed for searching the diagnosis, although it is nonspecific in patients with invasive fungal rhinosinusitis and does not correlate with surgical and pathological findings. In this sense, a team of otolaryngologists with experience in this field is essential in the management of these subjects. In addition, it seems advisable to screen all patients undergoing allogeneic hematopoietic HSCT with CT prior to the procedure, to identify a possible sinus focus, and treat properly.[18]

Except for two cases (cases 6 and 7), the invasive fungal sinusitis (IFS) were classified as proven according to the EORTC/MSG criteria. Case 6 was considered probable IFS based on host and clinical factors in the presence of sinusitis on imaging, but no tissue or vessel invasion was described. By the other hand, in case 7, microbiological analysis was performed by culture of a sinus mucosal swab containing purulent discharge, and since sinus swab or discharge is not sterile, colonization could not be excluded, resulting in also probable IFS.

In four cases including ours (case 1, 6, 7 and 8), the invasive fungal sinusitis occurred post-HSCT. In case 1 the onset was on D+15 post-allogeneic HSCT and there were no more described details about the transplant. Case 6 described sinusitis right after D+78, in a non-myeloablative (FluCy) allogeneic peripheral blood stem cell

transplantation, using cells from a HLA-matched sister. The patient in case 7 underwent allogeneic cord blood transplantation (CBT) with reduced-intensity conditioning, which resulted in graft rejection and he urgently received a second CBT, and was affected by IFS on D+83. The occurrence of sinusitis post-HSCT is usually related to the first 120 days after the procedure.[19] In one article (case 3), the patient was submitted to myeloablative conditioning and haploidentical transplantation, with fungal infection diagnosis prior to HSCT and still active on admission to transplant (based on clinical and radiological evidence of progression).

Low neutrophil count is a well-described risk factor for sinusitis after HSCT, and a white blood cell count of less than 2.0 G/L is associated with poor prognosis. This is even more remarkable in patients with marrow failure syndromes, who have prolonged neutropenia, as our described case. In regard to other risk factors related to the transplant, higher TBI dose (1440 or 1320 cGy vs. 1200 cGy) was associated with sinusitis development, while matched unrelated donor transplant or donor CMV seropositivity reached a borderline significance.[20,21,22]

In relation to treatment, all cases included amphotericin B, which has been useful as alternative therapy in some cases, because it is a rapidly fungicidal broad-spectrum agent active against many species in vitro, and generally has good activity against most clinically important dematiaceous fungi.[4,5,23,24] In three cases, including ours, surgery was also performed. Except for our case, the other reports did not mention time of treatment; case 5 reported treatment duration for lung fungal infection, who persisted with initial therapy, without specification of time to improvement of sinusitis, but informing that therapy was discontinued three months after discontinuing all immunosuppressive agents. All cases had a complete response to antifungal treatment, with no signs of relapse of IFDS. Despite this, half of the patients died, none from causes directly related to the dematiaceous fungi infection, but from other infections related to their underlying immunosuppression. Two of four patients who survived were treated with a combination of surgical debridement and systemic antifungals.

There is no standard approach for the treatment of the IDFS; therefore, the optimal duration of therapy and choice of intervention are primarily based on clinical presentation, underlying condition of the host, and initial response to treatment.[23]

Fluconazole does not have reliable activity against this group of organisms. Voriconazole, posaconazole and itraconazole demonstrate the most consistent in

vitro activity against this group of fungi. Oral itraconazole had been considered the drug of choice for most situations, given the extensive clinical experience; however, it has fallen out of favor due to side effects and the lack of an intravenous formulation. Voriconazole is likely the empiric drug of choice due to its very broad activity, clinical experience, preferable side effect profile and availability of an intravenous formulation; in addition, may presumably be superior for central nervous system infections, and can be used in case of complication of invasive sinusitis with intracranial extension. Posaconazole is a broad-spectrum alternative that is well-tolerated, though backed by less clinical experience, but with excellent salvage treatment results after failure of other antifungals, and is available in oral and intravenous formulation.[4,5,23,24] Isavuconazole is the newest azole, that can be used against these fungi as suggested by in vitro data, with a tolerability profile comparable to fluconazole and less drug interactions than voriconazole and itraconazole, but still no clinical experience in treating phaeohyphomycosis.[2,4,24]

Arcobello et al[4] suggests that therapy for invasive dematiaceous sinusitis is surgery associated with two weeks of liposomal amphotericin B followed by voriconazole. Neutrophil recovery appears crucial for a successful outcome. The ESCMID and ECMM joint clinical guideline for the diagnosis and management of systemic phaeohyphomycosis[23] have a similar antifungal therapy recommendation, liposomal amphotericin B for two weeks followed by voriconazole for three months.

We consider a suitable approach, in these cases, maintaining secondary prophylaxis during immunosuppressive agents use, considering the high risk of recurrence of IDFS. Voriconazole appears to be safe and effective for secondary prophylaxis of invasive fungal infections after allogeneic stem cell transplantation.[25]

5 CONCLUSIONS

This case includes *Colletotrichum* specie as one of the genera of dematiaceous fungi that causes invasive sinusitis in immunocompromised patients such as HSCT recipients. Our patient was successfully treated with surgery plus amphotericin B lipid complex for two weeks, followed by voriconazole until the outcome, with complete response of fungal infection and no relapse until the outcome of this case.

These infections have not been studied in clinical trials and probably will not, given their rarity.[26] So it is crucial to report every case of invasive sinusitis caused by melanized fungi, because overall clinical experience will ultimately determine which agent or combination of agents is most effective, as well as the length of therapy.

REFERENCES

1. Meyers JD. Infection in bone marrow transplant recipients. Am J Med. 1986 Jul 28;81(1A):27-38. doi: 10.1016/0002-9343(86)90511-5. PMID: 3090877.

2. Arif S, Perfect JR. Emergence of the Molds Other than Aspergillus in Immunocompromised Patients. Clin Chest Med. 2017 Sep;38(3):555-573. doi: 10.1016/j.ccm.2017.04.014. Epub 2017 Jun 2. PMID: 28797495.

3. Meyers JD. Fungal infections in bone marrow transplant patients. Semin Oncol. 1990 Jun;17(3 Suppl 6):10-3. PMID: 2353204.

4. Arcobello JT, Revankar SG. Phaeohyphomycosis. Semin Respir Crit Care Med. 2020 Feb;41(1):131-140. doi: 10.1055/s-0039-3400957. Epub 2020 Jan 30. PMID: 32000289.

5. Revankar SG, Sutton DA. Melanized fungi in human disease. Clin Microbiol Rev. 2010 Oct;23(4):884-928. doi: 10.1128/CMR.00019-10. Erratum in: Clin Microbiol Rev. 2012 Oct;25(4):720. PMID: 20930077; PMCID: PMC2952981.

6. Wong EH, Revankar SG. Dematiaceous Molds. Infect Dis Clin North Am. 2016 Mar;30(1):165-78. doi: 10.1016/j.idc.2015.10.007. PMID: 26897066.

7. Thomas E, Bertolotti A, Barreau A, Klisnick J, Tournebize P, Borgherini G, Zemali N, Jaubert J, Jouvion G, Bretagne S, Picot S. From phaeohyphomycosis to disseminated chromoblastomycosis: A retrospective study of infections caused by dematiaceous fungi. Med Mal Infect. 2018 Jun;48(4):278-285. doi: 10.1016/j.medmal.2017.09.011. Epub 2018 Apr 12. PMID: 29656841.

8. Revankar SG, Baddley JW, Chen SC, Kauffman CA, Slavin M, Vazquez JA, Seas C, Morris MI, Nguyen MH, Shoham S, Thompson GR 3rd, Alexander BD, Simkins J, Ostrosky-Zeichner L, Mullane K, Alangaden G, Andes DR, Cornely OA, Wahlers K, Lockhart SR, Pappas PG. A Mycoses Study Group International Prospective Study of Phaeohyphomycosis: An Analysis of 99 Proven/Probable Cases. Open Forum Infect Dis. 2017 Sep 26;4(4):ofx200. doi: 10.1093/ofid/ofx200. PMID: 29766015; PMCID: PMC5946886.

9. Chowdhary A, Meis JF, Guarro J, de Hoog GS, Kathuria S, Arendrup MC, Arikan-Akdagli S, Akova M, Boekhout T, Caira M, Guinea J, Chakrabarti A, Dannaoui E, van Diepeningen A, Freiberger T, Groll AH, Hope WW, Johnson E, Lackner M, Lagrou K, Lanternier F, Lass-Flörl C, Lortholary O, Meletiadis J, Muñoz P, Pagano L, Petrikkos G, Richardson MD, Roilides E, Skiada A, Tortorano AM, Ullmann AJ,

Verweij PE, Cornely OA, Cuenca-Estrella M; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect. 2014 Apr;20 Suppl 3:47-75. doi: 10.1111/1469-0691.12515. PMID: 24483780.

10. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, Clancy CJ, Wingard JR, Lockhart SR, Groll AH, Sorrell TC, Bassetti M, Akan H, Alexander BD, Andes D, Azoulay E, Bialek R, Bradsher RW, Bretagne S, Calandra T, Caliendo AM, Castagnola E, Cruciani M, Cuenca-Estrella M, Decker CF, Desai SR, Fisher B, Harrison T, Heussel CP, Jensen HE, Kibbler CC, Kontoyiannis DP, Kullberg BJ, Lagrou K, Lamoth F, Lehrnbecher T, Loeffler J, Lortholary O, Maertens J, Marchetti O, Marr KA, Masur H, Meis JF, Morrisey CO, Nucci M, Ostrosky-Zeichner L, Pagano L, Patterson TF, Perfect JR, Racil Z, Roilides E, Ruhnke M, Prokop CS, Shoham S, Slavin MA, Stevens DA, Thompson GR, Vazquez JA, Viscoli C, Walsh TJ, Warris A, Wheat LJ, White PL, Zaoutis TE, Pappas PG. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020 Sep 12;71(6):1367-1376. doi: 10.1093/cid/ciz1008. PMID: 31802125; PMCID: PMC7486838.

11. Morrison VA, Weisdorf DJ. Alternaria: a sinonasal pathogen of immunocompromised hosts. Clin Infect Dis. 1993 Feb;16(2):265-70. doi: 10.1093/clind/16.2.265. PMID: 8443305.

12. Levy I, Stein J, Ashkenazi S, Samra Z, Livni G, Yaniv I. Ecthyma gangrenosum caused by disseminated Exserohilum in a child with leukemia: a case report and review of the literature. Pediatr Dermatol. 2003 Nov-Dec;20(6):495-7. doi: 10.1111/j.1525-1470.2003.20608.x. PMID: 14651568.

13. Avivi I, Oren I, Haddad N, Rowe JM, Dann EJ. Stem cell transplantation post invasive fungal infection is a feasible task. Am J Hematol. 2004 Jan;75(1):6-11. doi: 10.1002/ajh.10447. PMID: 14695626.

14. Adler A, Yaniv I, Samra Z, Yacobovich J, Fisher S, Avrahami G, Levy I. Exserohilum: an emerging human pathogen. Eur J Clin Microbiol Infect Dis. 2006 Apr;25(4):247-53. doi: 10.1007/s10096-006-0093-3. Erratum in: Eur J Clin Microbiol Infect Dis. 2006 Apr;25(4):254-6. PMID: 16511679.

15. Mullane K, Toor AA, Kalnicky C, Rodriguez T, Klein J, Stiff P. Posaconazole salvage therapy allows successful allogeneic hematopoietic stem cell transplantation in patients with refractory invasive mold infections. Transpl Infect Dis. 2007 Jun;9(2):89-96. doi: 10.1111/j.1399-3062.2007.00208.x. PMID: 17461992.

16. Togitani K, Kobayashi M, Sakai M, Uemura Y, Taguchi H, Morita T, Sugihara S, Sano A, Nishimura K. Ethmoidal sinusitis caused by Exserohilum rostratum in a patient with malignant lymphoma after non-myeloablative allogeneic peripheral blood stem cell transplantation. Transpl Infect Dis. 2007 Jun;9(2):137-41. doi: 10.1111/j.1399-3062.2007.00212.x. PMID: 17462000.

17. Kohashi S, Toyama T, Hashimoto N, Sakurai M, Kato J, Kikuchi T, Koda Y, Sugita K, Hasegawa N, Yarita K, Kamei K, Okamoto S, Mori T. Sinusitis caused by Exserohilum rostratum after cord blood transplantation for myelodysplastic syndrome: A case report and literature review. Transpl Infect Dis. 2018 Feb;20(1). doi: 10.1111/tid.12805. Epub 2017 Dec 13. PMID: 29119669.

18. Drozd-Sokolowska JE, Sokolowski J, Wiktor-Jedrzejczak W, Niemczyk K. Sinusitis in patients undergoing allogeneic bone marrow transplantation - a review. Braz J Otorhinolaryngol. 2017 Jan-Feb;83(1):105-111. doi: 10.1016/j.bjorl.2016.02.012. Epub 2016 Apr 22. PMID: 27184506.

19. Savage DG, Taylor P, Blackwell J, Chen F, Szydlo RM, Rule SA, Spencer A, Apperley JF, Goldman JM. Paranasal sinusitis following allogeneic bone marrow transplant. Bone Marrow Transplant. 1997 Jan;19(1):55-9. doi: 10.1038/sj.bmt.1700601. PMID: 9012932.

20. Johnson PJ, Lydiatt WM, Huerter JV, et al. Invasive Fungal Sinusitis following Liver or Bone Marrow Transplantation. American Journal of Rhinology. 1994;8(2):77-84. doi:10.2500/105065894781874485

21. Berlinger NT. Sinusitis in immunodeficient and immunosuppressed patients. Laryngoscope. 1985 Jan;95(1):29-33. doi: 10.1288/00005537-198501000-00009. PMID: 3880849.

22. Savage DG, Taylor P, Blackwell J, Chen F, Szydlo RM, Rule SA, Spencer A, Apperley JF, Goldman JM. Paranasal sinusitis following allogeneic bone marrow transplant. Bone Marrow Transplant. 1997 Jan;19(1):55-9. doi: 10.1038/sj.bmt.1700601. PMID: 9012932.

23. Chowdhary A, Meis JF, Guarro J, de Hoog GS, Kathuria S, Arendrup MC, Arikan-Akdagli S, Akova M, Boekhout T, Caira M, Guinea J, Chakrabarti A, Dannaoui

E, van Diepeningen A, Freiberger T, Groll AH, Hope WW, Johnson E, Lackner M, Lagrou K, Lanternier F, Lass-Flörl C, Lortholary O, Meletiadis J, Muñoz P, Pagano L, Petrikkos G, Richardson MD, Roilides E, Skiada A, Tortorano AM, Ullmann AJ, Verweij PE, Cornely OA, Cuenca-Estrella M; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect. 2014 Apr;20 Suppl 3:47-75. doi: 10.1111/1469-0691.12515. PMID: 24483780.

24. Falci DR, Pasqualotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. Infect Drug Resist. 2013 Oct 22;6:163-74. doi: 10.2147/IDR.S51340. PMID: 24187505; PMCID: PMC3810441.

25. Cordonnier C, Rovira M, Maertens J, Olavarria E, Faucher C, Bilger K, Pigneux A, Cornely OA, Ullmann AJ, Bofarull RM, de la Cámara R, Weisser M, Liakopoulou E, Abecasis M, Heussel CP, Pineau M, Ljungman P, Einsele H; Voriconazole for Secondary Prophylaxis of Invasive Fungal Infections in Patients With Allogeneic Stem Cell Transplants (VOSIFI) study group; Infectious Diseases Working Party, European Group for Blood and Marrow Transplantation. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. Haematologica. 2010 Oct;95(10):1762-8. doi: 10.3324/haematol.2009.020073. Epub 2010 Jul 15. PMID: 20634495; PMCID: PMC2948103.

26. Revankar SG, Patterson JE, Sutton DA, Pullen R, Rinaldi MG. Disseminated phaeohyphomycosis: review of an emerging mycosis. Clin Infect Dis. 2002 Feb 15;34(4):467-76. doi: 10.1086/338636. Epub 2002 Jan 9. PMID: 11797173.

27. Derber C, Elam K, Bearman G. Invasive sinonasal disease due to dematiaceous fungi in immunocompromised individuals: case report and review of the literature. Int J Infect Dis. 2010 Sep;14 Suppl 3:e329-32. doi: 10.1016/j.ijid.2010.04.003. Epub 2010 Jul 1. PMID: 20594890.

28. Werbel WA, Baroncelli R, Shoham S, Zhang SX. Angioinvasive, cutaneous infection due to Colletotrichum siamense in a stem cell transplant recipient: Report and review of prior cases. Transpl Infect Dis. 2019 Oct;21(5):e13153. doi: 10.1111/tid.13153. Epub 2019 Aug 13. PMID: 31357231; PMCID: PMC7370837.

29. Lee SH, Sun HY, Ko BS, Chang SC. Breakthrough invasive fungal infection under the use of posaconazole and voriconazole. J Formos Med Assoc. 2016 May;115(5):384-5. doi: 10.1016/j.jfma.2015.03.008. Epub 2015 Apr 17. PMID: 25891760.

30. Sato E, Togawa A, Masaki M, Shirahashi A, Kumagawa M, Kawano Y, Ishikura H, Yamashiro Y, Takagi S, To H, Kobata K, Takeshita M, Kusaba K, Sueoka E, Tamura K, Takamatsu Y, Takata T. Community-acquired Disseminated Exophiala dermatitidis Mycosis with Necrotizing Fasciitis in Chronic Graft-versus-host Disease. Intern Med. 2019 Mar 15;58(6):877-882. doi: 10.2169/internalmedicine.1706-18. Epub 2018 Nov 19. PMID: 30449799; PMCID: PMC6465022.

31. Watanabe N, Gotoh A, Shirane S, Hamano Y, Hirai Y, Shimizu M, Nakamura A, Matsumoto K, Morita K, Mori T, Ohsaka A, Komatsu N. Breakthrough Exophiala dermatitidis infection during prophylactic administration of micafungin during second umbilical cord blood transplantation after graft failure. Transpl Infect Dis. 2018 Apr;20(2):e12833. doi: 10.1111/tid.12833. Epub 2018 Feb 12. PMID: 29359870.

32. Teixeira AB, Trabasso P, Moretti-Branchini ML, Aoki FH, Vigorito AC, Miyaji M, Mikami Y, Takada M, Schreiber AZ. Phaeohyphomycosis caused by Chaetomium globosum in an allogeneic bone marrow transplant recipient. Mycopathologia. 2003;156(4):309-12. doi: 10.1023/b:myco.0000003563.29320.95. PMID: 14682456.

33. Lundstrom TS, Fairfax MR, Dugan MC, Vazquez JA, Chandrasekar PH, Abella E, Kasten-Sportes C. Phialophora verrucosa infection in a BMT patient. Bone Marrow Transplant. 1997 Nov;20(9):789-91. doi: 10.1038/sj.bmt.1700969. PMID: 9384484.

34. Baddley JW, Moser SA, Sutton DA, Pappas PG. Microascus cinereus (Anamorph scopulariopsis) brain abscess in a bone marrow transplant recipient. J Clin Microbiol. 2000 Jan;38(1):395-7. doi: 10.1128/JCM.38.1.395-397.2000. PMID: 10618123; PMCID: PMC88731.

35. Krisher KK, Holdridge NB, Mustafa MM, Rinaldi MG, McGough DA. Disseminated Microascus cirrosus infection in pediatric bone marrow transplant recipient. J Clin Microbiol. 1995 Mar;33(3):735-7. doi: 10.1128/jcm.33.3.735-737.1995. PMID: 7751387; PMCID: PMC228024.

36. Emmens RK, Richardson D, Thomas W, Hunter S, Hennigar RA, Wingard JR, Nolte FS. Necrotizing cerebritis in an allogeneic bone marrow transplant recipient due to Cladophialophora bantiana. J Clin Microbiol. 1996 May;34(5):1330-2. doi: 10.1128/jcm.34.5.1330-1332.1996. PMID: 8727934; PMCID: PMC229013.

37. 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 Jul;45(1):56-61. doi: 10.1067/mjd.2000.113691. PMID: 11423835.

38. Liu AW, Bateman AC, Greenbaum A, Garvin K, Clarridge J, Grim J. Cutaneous phaeohyphomycosis in a hematopoietic stem cell transplant patient caused by Alternaria rosae: First case report. Transpl Infect Dis. 2017 Jun;19(3). doi: 10.1111/tid.12698. Epub 2017 May 4. PMID: 28295973.

39. Hagiya H, Maeda T, Kusakabe S, Kawasaki K, Hori Y, Kimura K, Ueda A, Yoshioka N, Sunada A, Nishi I, Morii E, Kanakura Y, Tomono K. A fatal case of Exophiala dermatitidis disseminated infection in an allogenic hematopoietic stem cell transplant recipient during micafungin therapy. J Infect Chemother. 2019 Jun;25(6):463-466. doi: 10.1016/j.jiac.2018.12.009. Epub 2019 Jan 22. PMID: 30679025.

APÊNDICE

Table 1: Reported cases of IFDS in immunocompromised patients who underwent allogeneic HSCT.

Case no.	Author (Reference)	Age* (years)	Gender	Underlying disease	Time	Presentation	Pathogen	EORTC/MSG Classification	Treatment	Outcome
1	Morison et al[11]	13	Male	ALL	Post-HSCT	Nasal septum, sinus	*Alternaria* species	Proven	Surgery, AMB, flucytosine, rifampin	Survived
2	Levy et al[12]	8	Male	ALL	Pre-HSCT	Sinus, lung, skin	*Exserohilum* species	Proven	AMB, L-AMB, itraconazole	Died of infection from *Fusarium* species
3	Avivi et al[13]	41	Female	AML	HSCT with active IFDS	Sinus, lung	*Exserohilum* species	Proven	AMB, L-AMB, itraconazole	Died of sepsis and respiratory failure
4	Adler et al[14]	3	Female	ALL	Pre-HSCT	Sinus	*Exserohilum* species	Proven	Surgery, AMB, L-AMB, itraconazole	Survived
5	Mullane et al[15]	33	Male	AML	Pre-HSCT	Sinus, lung	*Alternaria* species	Proven	Voriconazole, L-AMB, Posaconazole	Survived
6	Togitani et al[16]	62	Male	DLBCL	Post-HSCT	Sinus	*Exserohilum rostratum*	Probable	Micafungin, AMB	Died of bacterial bronchopneumonia
7	Kohashi et al[17]	60	Male	MDS	Post-HSCT	Sinus	*Exserohilum rostratum*	Probable	L-AMB	Survived
8	Sinhorelo et al (present case)	21	Female	PNH	Post-HSCT	Sinus	*Colletotrichum* species	Proven	Surgery, L-AMB, Voriconazole	Died of sepsis and respiratory failure

IFDS, invasive dematiaceous fungal sinusitis; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; DLBCL, diffuse large B-cell lymphoma; PNH, paroxysmal nocturnal haemoglobinuria; AMB, amphotericin B; L-AMB, liposomal amphotericin B; HSCT, Hematopoietic stem Cell transplantation. *Age in diagnosis of IFDS.