



# Disseminated fusariosis after allogenic hematopoietic stem cell transplantation: case report

A. Gantner<sup>1</sup> · J. B. Hagemann<sup>2</sup> · B. Grüner<sup>1</sup> · G. Walther<sup>3</sup> · A. Neagoie<sup>1</sup> · V. Wais<sup>1</sup> · H. Döhner<sup>1</sup> · E. Sala<sup>1</sup>

Received: 21 April 2024 / Accepted: 12 August 2024 / Published online: 26 August 2024  
© The Author(s) 2024

## Abstract

In allogenic stem cell recipients, invasive fungal disease is a common yet dreaded complication with high mortality. Among these, fusariosis is especially complex to treat due to high intrinsic resistance and few antimycotic options, requiring close cooperation of all involved departments. We here report an instructive case of disseminated fusariosis after allogenic stem cell transplantation with fatal outcome despite maximum treatment.

**Keywords** Allogenic hematopoietic stem cell transplantation · Fusariosis · *Fusarium* · Fungal infection

## Case report

A 65-year-old male with a heavily pre-treated high-risk myelofibrosis bearing an ASXL-1 mutation underwent an allogeneic stem cell transplantation (allo-HSCT) from a mismatched (9/10) unrelated donor in 08/2020 after a myeloablative conditioning regimen with Treosulfan 14 g/m<sup>2</sup> d1-3, Fludarabine 40 mg/m<sup>2</sup> d1-4 and anti-thymocyte globulin 30 mg/kg. The post-transplant follow-up was complicated due to a poor graft function with continuous transfusion-dependency and grade III-IV neutropenia requiring stimulation with growth factors, which was treated with a stem cell boost. Due to the development of a steroid-refractory acute graft versus host disease (GvHD), the patient underwent further immune suppressive treatment with ruxolitinib during the subsequent follow-up after allo-HSCT.

In February 2021, after a blunt trauma of the right foot, the patient presented with a superficial wound next to the

toenail of the right hallux. In the performed swabs *Fusarium solani* was detected. Initial treatment was performed with local application of ciclopirox by the patient's dermatologist and clinical improvement was reported. Four weeks later, the patient developed abdominal pain. Since an ultrasound examination revealed no pathologies, computed tomography (CTI) and magnetic resonance tomography imaging (MRI) were performed, and multiple hepatic lesions suspicious of malignant origin were detected. We admitted the patient to the transplant ward for further diagnostics. During the hospitalization, the patient developed erysipelas on the right foot spreading to the lower leg. Due to persistent neutropenia, continued immunosuppression and eminently elevated CRP levels an empiric antibiotic therapy with meropenem (1000 mg three times per day) and clindamycin (600 mg three times a day) was started. A liver biopsy revealed no malignant cells, but the presence of septate fungal elements. Lactophenol blue staining revealed septate hyphae with branched and unbranched conidiophores. Phialides produced both single-celled, ovoid microconidia and large, slightly curved, tapering macroconidia with up to four septa, which are characteristic for the genus *Fusarium*. The isolate was molecular biologically identified as *F. solani* species complex. Cultural grown *Fusarium* (*F.*) spp. (Fig. 1a, b) were processed for molecular identification. Sequencing of the translation elongation factor 1 $\alpha$  (TEF) identified the isolate as *F. keratoplasticum* (Syn. *Neocosmospora keratoplastica*), a member of the *F. solani* species complex (FSSC). The TEF sequence is stored in GenBank (accession number OR861623) and

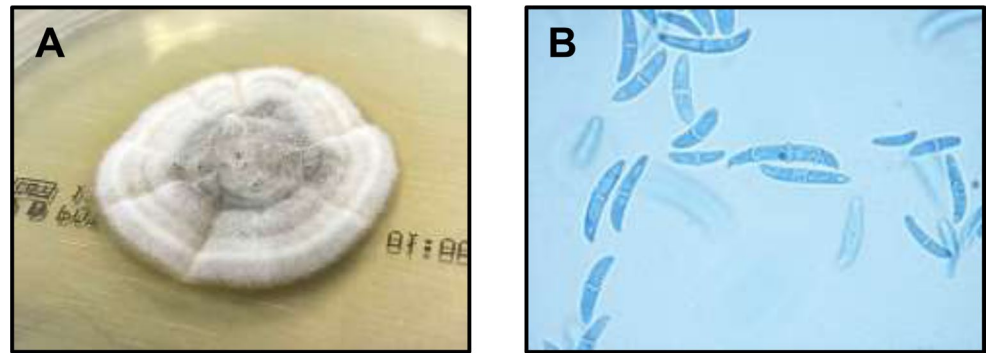
✉ A. Gantner  
andrea.gantner@uniklinik-ulm.de

<sup>1</sup> Department of Internal Medicine III, University Hospital Ulm, Albert-Einstein-Allee 23, D-89081 Ulm, Germany

<sup>2</sup> Institute of Medical Microbiology and Hygiene, University Hospital of Ulm, Albert-Einstein-Allee 23, D-89081 Ulm, Germany

<sup>3</sup> National Reference Center for Invasive Fungal Infections (NRZMyk), Leibniz Institute of Natural Product Research and Infection Biology–Hans Knöll Institute, Jena, Germany

**Fig. 1** *Fusarium keratoplasticum* isolated from a clinical sample (A) Colony growth on Sabouraud-agar after five days of incubation at 30 °C, 5%CO<sub>2</sub>. A cottony surface, darker center and a lighter periphery are common features. (B) Lactophenol blue staining with typical large, slightly curved, tapering macroconidia with up to four septa, which are characteristic for *Fusarium* spp



the corresponding isolate (NRZ-2021-330) is deposited in the Jena Microbial Research Collection (JMRC). Antifungal susceptibility testing by microdilution according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) protocol revealed the following minimum inhibitory concentrations (MICs): amphotericin B 2 mg/L, isavuconazole > 8 mg/L, itraconazole > 8 mg/L, posaconazole > 8 mg/L, voriconazole > 8 mg/L, anidulafungin > 8 mg/L, and caspofungin > 8 mg/L.

To clarify the extent of systematic spread of the invasive fusariosis, positron emission tomography (PET)-MRI was performed. Here, additional subcutaneous lesions in the ipsilateral lower leg and multiple intramuscular lesions in the thigh were detected (Fig. 2), retrospectively suggesting fungal dissemination from the initial skin lesion of the right foot.

The patient had received standard antifungal prophylaxis with posaconazole with continuous blood levels within therapeutic range above 1000 µg/l after allo-HSCT, which we switched to a combined intravenous therapy regimen of liposomal amphotericin B (5 mg/kg) plus voriconazole (loading dose 6 mg/kg, 4 mg/kg afterwards). Due to persistent neutropenia with a neutrophil count ranging from 0,2 G/l to 1,2 G/l, granulocyte colony stimulating factor was added. Lymphopenia was also detected, with a lymphocyte count ranging from 0,1 to 0,5 G/l. After a month of intensive antifungal treatment, abdominal CTI showed a stabilization of the hepatic lesions, so surgical resection of the affected liver segments was performed under continued antifungal treatment. Dose adjustment of liposomal amphotericin B to 3 mg/kg was necessary due to progressive renal impairment whereas voriconazole dosage was adjusted to 5 mg/kg on the account of decreased levels in drug monitoring. One month later, in a restaging PET-MRI, a mixed response with residual activity of the subcutaneous lesions and new bipulmonary pleural effusion was observed. Thoracocentesis was performed and *F. keratoplasticum* was subsequently isolated in the pleural effusion as well. According to evidence for other invasive mycoses with pleural affection, local instillation of amphotericin B was initiated under continuation

of the systemic antifungal treatment with amphotericin B liposomal and voriconazole [1–3].

At that time, the patient experienced a severe recurrence of the systemic GvHD, so dosage of immunosuppressive treatment, especially steroids, had to be escalated. Under increased immunosuppression, the invasive fusariosis rapidly progressed with worsening of the lung involvement and persistent cultural evidence of *F. keratoplasticum* in the pleural effusion. Furthermore, bacterial infections with *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* emerged, so the patient died 14 weeks after initial diagnosis despite maximal antifungal treatment, due to multiorgan failure caused by uncontrolled bacterial and fungal infection in sustained neutropenia.

## Discussion

Invasive fungal diseases (IFD) are serious complications in allo-HSCT recipients and are associated with high morbidity and mortality. Cumulative incidence lies around 10% [4, 5], and while invasive aspergillosis is the most frequently reported IFD [4], mucormycosis and fusariosis seem to be the second and third most common mould infections, respectively [5–7]. While the incidence of fusariosis is low, mortality is high despite optimal concerted treatment, ranging from 50 to 70% [8, 9].

Cutaneous fusariosis makes up around 70% of cases, particularly in immunocompromised patients, and can either be the primary site of inoculation or a secondary result in systemic dissemination [10]. At the time of clinical presentation, several cutaneous and subcutaneous lesions were observed in our patient, and the likely route of fungal dissemination could be retrospectively reconstructed: *F. keratoplasticum* was first detected in the cutaneous sample of the right hallux, then multiple skin lesions along the right leg, and finally in the liver and in the right pleural cavity were subsequently demonstrated by PET-MRI.

Treatment of invasive fusariosis is challenging. The interpretation of the antifungal susceptibility testing is difficult, mainly due to the absence of break points, to the

**Fig. 2** Images of the initial PET-MRI showing lesions with increased metabolism in liver, intramuscular in the gluteal region and subcutaneous on the medial right lower leg



poor correlation of in-vitro susceptibility data with clinical response, and to multiple intrinsic drug resistances including azoles, echinocandins, and polyenes, which taken together often hamper optimal antifungal therapy [11]. Currently, voriconazole and amphotericin B are considered as first-line antifungal treatment options and combination regimens are also applied [12–15]. Breakthrough fungal infections under posaconazole prophylaxis are reported in around 1–4% of patients, with fusariosis accounting for about 1% of entities in this patient clientele. Whilst lowering the incidence of hitherto more frequent invasive fungal pathogens like *Candida* spp. and *Aspergillus* spp., the broad use of posaconazole as primary antifungal prophylaxis in immunocompromised patients seems to increase the incidence of fusariosis and mucormycosis [6, 7]. Sub-therapeutic posaconazole serum concentration is a major risk factor for infections due to isolates with acquired posaconazole

resistance, but breakthrough invasive fungal diseases have also been reported in patients with appropriate serum concentration [6, 16]. Furthermore, numerous *Fusarium* spp. especially of the FSSC are known to have intrinsically high MICs for posaconazole [17]. On the other side, as Nucci and colleagues showed in a relatively large multicentric retrospective study there seems to be no strict correlation between the MIC distribution and the probability of survival of immunocompromised patients developing an invasive fusariosis [18], so that therapeutic decisions should not be at least only based on the MIC profile of a specific *Fusarium* spp. isolate.

Surgical treatment is considered the therapeutic option of choice whenever possible [12, 13, 15]. In our case, surgical infectious source control and reduction of fungal burden was only possible for the hepatic lesions, while the multiple cutaneous and subcutaneous lesions could not be removed.

Apart from surgical treatment, reconstitution of immunocompetence is considered essential to control fungal infection [12], whereas especially neutropenia is a known risk factor of unsuccessful therapy [7]. In our case the patient had neutropenia and furthermore did not experience T-cell immune reconstitution after transplantation, also considering that termination of immunosuppression was not possible due to severe, steroid-refractory GvHD.

As penetration of systemically administered liposomal amphotericin B into pleural fluid is low [19], local application of non-liposomal amphotericin B can be considered in addition. Local administration of amphotericin B in pleural cavities is usually well tolerated and complete remission of fungal evidence has been reported [1–3].

## Conclusion

IFD remains a major cause of early death after allo-HSCT. While the prevalence of *Candida* spp. infections has decreased after the introduction of azole-based antifungal prophylaxis, there is an increasing number of invasive infections due to *Fusarium* spp. and *Mucorales* [5, 6, 20]. Surgical treatment and improvement of a patient's immune status are the main backbones for a successful therapy of invasive fusariosis. It has to be considered that surgical treatment could often be difficult due to anatomical peculiarities and/or to the localisation of the fungal infection. On the other side due to the occurrence of acute or chronic GvHD, immunosuppressive treatment is mandatory and impairs the fitness of the immune system, both the innate and the adaptive one. For systemic antifungal treatment of invasive fusariosis, voriconazole and liposomal amphotericin B are currently recommended as substances of choice, and additional local instillation of amphotericin B should be discussed in compartments with restricted bioavailability for its liposomal counterpart, if surgical treatment is not possible. The increasing importance of invasive mycoses leads to an urgent need for new diagnostic and therapeutic options in medical mycology. This is also relevant against the background of global warming, which requires the adaptation of hitherto harmless saprophytic fungi to higher temperatures that could eventually support their survival on or in the human body - underline the urgent need for new diagnostic and therapeutic options in medical mycology. Several novel approaches like olorofim, an inhibitor of the fungal dihydroorotate dehydrogenase, or fosmanogepix are currently under evaluation and might beneficially influence the prognosis of invasive mycoses in the near future [20]. With only few therapeutic options available, uncommon approaches as local instillation should always be evaluated. Still, this case shows that even maximum treatment with

combination of antifungal agents, surgery, local instillation and withdrawal of immunosuppression is bound to fail if treatment is started after disseminated and invasive infection in immunocompromised patients. Therefore, awareness needs to be raised in the physicians not used in caring for immunocompromised patient for this rare, but highly aggressive disease, which can present as a harmless cutaneous infection but can reach, especially if not promptly treated, a high mortality rate, ranging from 50 to 70% of affected patients.

**Author contributions** Gantner A.: Data retrieval and manuscript preparation; Hagemann JB: provision of microbiological background, manuscript revision, Grüner B: provision of infectiological background, manuscript revision; Walther G: provision of microbiological background, manuscript revision, Neagoie A: clinical supervision, manuscript revision; Wais V.: clinical supervision, manuscript revision; Döhner H: clinical supervision, manuscript revision, Sala E.: clinical supervision, manuscript preparation.

**Funding** No funding was received to assist with the preparation of this manuscript.

Open Access funding enabled and organized by Projekt DEAL.

**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Consent to participate** Informed consent was obtained as part of consent to the registry studies: “MPNSG Bio” (approved by the ethical review board of the University of Ulm, Application No: 100/13) and “EBMT/DRST-Register” (approved by the ethical review board of the University of Ulm, Application No: 345/21).

**Consent to publish** Informed consent was obtained as part of consent to the registry studies: “MPNSG Bio” (approved by the ethical review board of the University of Ulm, Application No: 100/13) and “EBMT/DRST-Register” (approved by the ethical review board of the University of Ulm, Application No: 345/21).

**Competing interests** The authors declare no competing interests.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

- Qian Z, Yeye Z, Pan C, e Jie C. «REPORT-Pleural lavage of amphotericin B for treatment of empyema caused by *Candida albicans* infections: A case report,» *Pakistan journal of pharmaceutical sciences*, pp. 2757–2759, November 2019.
- Baquero-Artigao F, García-Miguel MJ, Hernández F, del Hernández Ne. «Combined systemic and intrapleural treatment of *Aspergillus* pulmonary empyema after invasive aspergillosis,» *Pediatr Infect Dis J*, pp. 471–473, Mai 2003.
- Bonatti H, Lass-Floerl C, Angerer K, Singh N, Lechner M, Stelzmueller I, Singh R, Schmid T, e Geltner C. «Successful management of postpneumectomy *Aspergillus* pleural empyema by combined surgical and anti-fungal treatment with voriconazole and caspofungin,» *Mycoses*, pp. 448–454, September 2010.
- Kontoyiannis D, Marr K, Park B, Alexander B, Anaissie E, Walsh T, Ito J, Andes D, Baddley J, Brown J, Brumble L, Freifeld A, Hadley S, Herwaldt L e, Kauffman C. «Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database,» *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, pp. 1091–1100, 15 April 2010.
- Girmenia C, Raiola AM, Picocchi A, Algarotti A, Stanzani M, Cudillo L, Pecoraro C, Guidi S, Iori AP, Montante B, Chiusolo P, Lanino E, Carella AM, Zucchetti E, Bruno B, Irrera G, Patriarca F, Baronciani D, Musso M, Prete A, Risitano AM, Russo D, Mordini N, Pastore D, Vacca A, Onida F, Falcioni S, Pisapia G, Milone G, Vallisa D, Olivieri A, Bonini A, Castagnola E, Sica S, Majolino I, Bosi A, Busca A, Arcese W, Bandini G, Bacigalupo A, Rambaldi A e Locasciulli A. «Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO),» *Biol Blood Marrow Transplant.*, pp. 872–80, June 2014.
- Lerolle N, Raffoux E, Socie G, Touratier S, Sauvageon H, Porcher R, Bretagne S, Bergeron A, Azoulay E, Molina JM. E Lafaurie M. «Breakthrough invasive fungal disease in patients receiving posaconazole primary prophylaxis: a 4-year study,» *clinical microbiology and infection*, November 2014.
- Takahiro Matsuo S, Wurster Y, Jiang K, Sasaki J, Tarrand RE, Lewis e Dimitrios P, Kontoyiannis. «Invasive fusariosis in patients with leukaemia in the era of mould-active azoles: increasing incidence, frequent breakthrough infections and lack of improved outcomes,» *Journal of Antimicrobial Chemotherapy*, pp. 297–306, February 2024.
- Riches M, Trifilio S, Chen M, Ahn KW, Langston A, Lazarus H, Marks D, Martino R, Maziarz R, Papinicolou G, Wingard J. J.-A. Young e C. Bennett. «Risk Factors and Impact of non-*Aspergillus* mold infections (NAMI) following Allogeneic HCT: A CIBMTR Infection and Immune Reconstitution analysis,» *Bone Marrow Transplantation*, pp. 277–282, Februar 2016.
- Muhammed M, Anagnostou T, Desalermos A, Kourkoumpetis TK, Carneiro HA, Glavis-Bloom J, Coleman JJ, e Mylonakis E. «Fusarium infection: report of 26 cases and review of 97 cases from the literature». *Med (Baltim)* pp.:305–16, November 2013.
- Nucci AE. October M, «Cutaneous infection by *Fusarium* Species in healthy and immunocompromised hosts: implications for diagnosis and Management». *Clin Infect Dis*, 15 2002.
- Zhao B, He De, Wang L. «Advances in *Fusarium* drug resistance research,» *J Glob Antimicrob Resist*, pp. 215–219, Mar 2021.
- Tortorano AM, Richardson M, Roilides E, van Diepeningen A, Caira M, Munoz P, Johnson E, Meletiadis J, Pana ZD, Lackner M, Verweij P, Freiburger T, Cornely OA, Arian-Akdagli S, Danaoui E, Groll AH, Lagrou K, Chakrabarti A, Lanternier F, Pagano L, Skiada A, Akova M, Arendrup MC, Boekhout T, Chowdhary A, Cuenca-Estrella M, Guinea J, Guarro J, de Hoog S, Hope W, Kathuria S, Lortholary O, Meis JF, Ullmann AJ. Petrikos G e Lass-Flörl C, «ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others,» *Clinical Microbiology and Infection*, pp. 27–46, 2014.
- Ruhnke M, Cornely O, Schmidt-Hieber M, Alakel N, Boell B, Buchheidt D, Christopeit M, Hasenkamp J, Heinz W, Hentrich M, Karthaus M, Koldehoff M, Maschmeyer G, Panse J, Penack O, Schleicher J, Teschner D, Ullmann A, Vehreschild M, von Lilienfeld-Toal M. F. Weissinger e S. Schwartz, «Treatment of invasive fungal diseases in cancer patients-Revised 2019 Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO),» *Mycoses*, pp. 653–682, Juli 2020.
- Hoenigl M, Salmanton-García J, Walsh T, Nucci M, Neoh C, Jenks J, Lackner M, Sprute R, Al-Hatmi A, Bassetti M, Carlesse F, Freiburger T, Koehler P, Lehmbecher T, Kumar A, Prates J, Richardson M, Revankar S, Slavin M, Stemler J, Spiess B, Taj-Aldeen S, Warris A, Woo P, Young J, Albus K, Arenz D, Arsic-Arsenijevic V, Bouchara J, Chinniah T, Chowdhary A, de Hoog G, Dimopoulos G, Duarte R, Hamal P, Meis J, Mfinanga S, Queiroz-Telles F, Patterson T, Rahav G, Rogers T, Rotstein C, Wahyuningsih R. D. Seidel e O. Cornely, «Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology & the American Society for Microbiology,» *The Lancet. Infectious diseases*, pp. e246-e257, August 2021.
- Al-Hatmi AMS, Bonifaz A, Ranque S, Sybren de Hoog G. Verweij PE e Meis JF, «Current antifungal treatment of fusariosis». *Int J Antimicrob Agents*, 2017.
- Lamoth F, Chung SJ, Damonti L, e Alexander BD. «Changing Epidemiology of Invasive Mold Infections in Patients Receiving Azole Prophylaxis,» *Clinical Infectious Diseases*, Juni 2017.
- Walther G, Zimmermann A, Theuersbacher J, Kaerger K, von Lilienfeld-Toal M, Roth M, Kampik D. G. Geerling E O. Kurzai, «Eye infections caused by filamentous Fungi: Spectrum and Antifungal susceptibility of the Prevailing agents in Germany». *J Fungi*, p. 511, 2021.
- Marcio Nucci J, Jenks GR, Thompson M, Hoenigl MCdos, Santos F, Forghieri JC, Rico. April, Valentina Bonuomo, Leyre López-Soria, Cornelia Lass-Flörl, Anna Candoni, Carolina Garcia-Vidal, Chiara Cattaneo, Jochem Buil, Ricardo Rabagliati, Maria Pia Roiz, Carlota Gudiol, Nicola Fracchiolla, Maria Isolina Campos-Herrero, Mario Delia, Francesca Farina, Jesus Fortun, Gianpaolo Nadali, Enric Sastre, Arnaldo L Colombo, Elena Pérez Nadales, Ana Alastruey-Izquierdo e Livio Pagano, «Do high MICs predict the outcome in invasive fusariosis?». *J Antimicrob Chemother*, p. 1063–9, 2021.
- Moriyama B, Torabi-Parizi P, Pratt AK, Henning SA, Pennick G, Shea YR, Roy Chowdhuri S, Rinaldi MG, Barrett AJ e, Walsh TJ. «Pharmacokinetics of liposomal amphotericin B in pleural fluid,» *Antimicrobial agents and chemotherapy*, pp. 1633–1635, April 2010.
- Lamoth F, Lewis RE, e Kontoyiannis DP. «Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective,» *Clinical infectious diseases*, pp. 534–544, August 2022.