Medical Mycology Case Reports 32 (2021) 4–9

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Case Report

Fulminant *Rhizomucor pusillus* mucormycosis during anti-leukemic treatment with blinatumomab in a child: A case report and review of the literature

Sarah Schober [a], Karin Melanie Cabanillas Stanchi [a], Anna Riecker [a], Matthias Pfeiffer [a], Ilias Tsiflikas [b], Gesa Wiegand [c], Leticia Quintanilla-Martinez [d], Susanne Haen [d], Martin Ebinger [a], Peter Lang [a], Rupert Handgretinger [a], Michaela Döring [a,*]

[a] University Children's Hospital Tuebingen, Department I – General Pediatrics, Hematology/Oncology, Hoppe-Seyler-Str.1, 72076, Tuebingen, Germany
[b] Department of Diagnostic and Interventional Radiology, University Hospital Tuebingen, Hoppe-Seyler-Str. 3, 72076, Tuebingen, Germany
[c] University Children's Hospital Tuebingen, Department II – Pediatric Cardiology, Intensive Care Medicine and Pulmonology, Hoppe-Seyler-Str. 3, 72076, Tuebingen, Germany
[d] Institute of Pathology and Neuropathology and Comprehensive Cancer Centre, University Hospital Tuebingen, Liebermeister-Str. 8, 72076, Tuebingen, Germany

ARTICLE INFO

Keywords:
Mucormycosis
Pediatric patients
Rhizomucor pusillus
Acute lymphoblastic leukemia relapse
Allogeneic hematopoietic stem cell transplantation

ABSTRACT

This is the first published case report of a child with acute lymphatic leukemia developing a fatal mucormycosis during blinatumomab treatment. The patient showed multiple, systemic thromboembolic lesions with ischemia, bleeding and infarction in almost all organs. The child succumbed to increased brain pressure resulting in cerebral herniation. This case particularly illustrates the fulminant progression and huge challenges of diagnosing and treating mucormycosis in children with hemato-oncological diseases during treatment with targeted therapeutic antibodies (blinatumomab).

1. Introduction

Rhizomucor pusillus is a mucormycete that can induce fatal, opportunistic infections in immunocompromised patients. Despite being the third most common invasive fungal infection after aspergillosis and candidiasis, mucormycosis is still a rare disease. Mucormycetes can be found in soil and decaying organic structures all over the world. Infections by *Rhizomucor* spp. are rare in humans, but mostly caused by *R. pusillus* [1]. There are 28 (10 pediatric) published cases of mucormycosis associated with *R. pusillus* [2,3]. The hyphae are highly angio-invasive and can cause hemorrhage, thrombosis, infarction and necrosis in any organ [1]. The overall mortality rate of mucormycosis is very high, at roughly 47% in all patients and up to 80% in hematopoietic stem cell transplantation (HSCT) recipients. The outcome depends on the underlying disease, the location of infection and the time to diagnosis and treatment [1,4,5].

Mucormycosis can cause fatal, opportunistic infections in immunocompromised hosts such as transplant recipients, patients with hematological or malignant diseases [6]. Immunocompetent persons are hardly infected [1,4,7]. In the special risk group of HSCT recipients pretreatment with antifungal medication not suitable against mucormycosis is related to an even higher risk of infection [5].

A 70% increase in the appearance of mucormycosis between 1940 and 2000 is described, especially among patients with hemato-oncological underlying diseases or after HSCT [1,5]. The incidence in allogeneic HSCT recipients is stated at roughly 0.3% up to 2.5% [5].

The most frequent locations of infection are rhino-orbito-cerebral and pulmonary [2]. The course of the disease is progressive and rapidly invasive, with often no more than a few days between diagnosis and death [1]. Considering the fast progression of the disease, early diagnosis and treatment are vital for best outcomes. Mucormycosis is difficult to diagnose and identifying the fungus is often challenging. Thus, many cases are only identified after an autopsy has been performed.

To date, the best treatment is the combination of surgery and antifungal medication. The gold standard for drug therapy is liposomal amphotericin B [2]. Most azoles are not effective against mucormycosis, except for posaconazole [1,5,8]. In high-risk pediatric patients (with

* Corresponding author.
E-mail address: michaela.doering@med.uni-tuebingen.de (M. Döring).

https://doi.org/10.1016/j.mmcr.2020.12.002
Received 2 November 2020; Received in revised form 21 December 2020; Accepted 21 December 2020
Available online 29 December 2020

cancer or after HSCT) high-dose liposomal amphotericin B (5–10 mg per kg BW) or liposomal amphotericin B in combination with caspofungin or with posaconazole are suggested according to the guidelines for treatment of invasive fungal disease in pediatric oncology patients [9]. There are promising results with isavuconazole which might play a more prominent role in the future [2].

Generally, data concerning treatment options in mucormycosis substantially relies on retrospective case reports, animal models and *in vitro* studies. There is a lack of prospective clinical trials, especially in children. This is the first published case report of a child with a second relapse of acute lymphatic leukemia (ALL) developing a fulminant mucormycosis during blinatumomab treatment. Blinatumomab is a monoclonal antibody with dual specificity for $CD3^+$ cells (T cells) and $CD19^+$ cells (B cells). This immunologic binding leads to T-cell mediated apoptosis in B cells. Destroying all B cells and causing neutropenia frequently blinatumomab is associated with a risk of infections such as mucormycosis although it is less immune-suppressing than standard chemotherapy. The unique addition of this case report to the few existing descriptions is the rapid sequence of unfortunate events and circumstances resulting in a fatal situation. Therefore, it is the aim of this case report to increase clinicians' awareness of this lethal disease and the need for immediate action.

2. Case

A seven-year-old boy was referred to the University Children's Hospital Tuebingen for treatment with a monoclonal bi-specific T-cell engager (blinatumomab) after a second relapse of pre-B-ALL. The first relapse had been treated with allogeneic HSCT from an unrelated HLA-compatible donor. Upon admission (day 0), his blood values were already compromised (hemoglobin 8.5 g/dl, thrombocytes 13.000/µl and WBC (white blood cells) 940/µl with 50/µl neutrophils, CRP (C-reactive protein) 6.83 mg/dl, ferritin 182 µg/dl). The patient was presented in a chronically reduced general condition with cachexia, dry skin, pallor, multiple hematomas and a hepatosplenomegaly. Antibiotic, antiviral, and antifungal chemoprophylaxis was performed with ceftriaxone, teicoplanin, acyclovir and caspofungin. Even prior to the antibody treatment, the patient complained about pain in the left flank which had to be treated with continuous infusion of morphine (max. 15 µg/kg BW per hour). The pain aggravated on day +5 of blinatumomab treatment. The ultrasound scan did not show any pathology apart from the known hepatosplenomegaly. Suddenly on day +6 the boy seemed somnolent and sleepy. First an overdose of morphine was assumed.

However, even after dose reduction the boy reacted with delay and only opened his eyes when addressed. Hence, a cerebral side effect of blinatumomab was presumed. On the same evening, the neurological condition of the patient worsened again. A cerebral CT scan as well as an MRI scan was performed. The imaging showed multiple cerebral hemorrhages (Fig. 1). Due to cardio-respiratory decompensation, the boy was transferred to the intensive care unit, where he received mechanical ventilation and catecholamine therapy. Blinatumomab treatment was stopped. At the time, the blood count had dropped considerably (hemoglobin 6.7 g/dl, thrombocytes 49.000/µl and WBC 120/µl with 20/µl neutrophils) and the CRP had risen to 23.13 mg/dl (ferritin 1439 µg/dl). The echocardiography showed multiple thrombi in the left and right ventricle. Thus, thromboembolic events were presumed as the cause of the cerebral lesions. An endocarditis with multiple septic embolisms was suspected, since the boy had suffered an endocarditis earlier. Consequently, the antibiotic regimen was intensified with meropenem, teicoplanin, and gentamicin. The antimycotic treatment (caspofungin 1 × 50 mg/day) was continued. CT scans of the thorax, abdomen and pelvis were performed 12 h later. They revealed multiple, systemic thromboembolic lesions with ischemia, bleeding and infarction in both lungs, the heart, both kidneys, the liver, the intestines and in multiple muscles (Fig. 2). A bone marrow aspiration showed bone marrow aplasia with lymphatic blasts. Cerebral pressure was rising. The etiology of the lesions was still unknown at that time. A few hours later, the patient succumbed to cerebral herniation. The patient died in the intensive care unit seven days after starting blinatumomab treatment (day +7) and about 24 hours after the first neurological symptoms appeared. The autopsy showed an invasive mycosis of *R. pusillus* as the cause of death (Figs. 3–5). The macroscopic and microscopic examination of several organs including the lungs led to the suspicion of a systemic fungal infection. *R. pusillus* was then identified via PCR-based methods.

3. Discussion

Mucormycosis is an emerging, severe infection in immunocompromised patients characterized by high mortality. Today's knowledge about the disease is mainly based on retrospective analyses, case reports and literature reviews.

In the first literature review summarizing the published information on mucormycosis in children with underlying hemato-oncological diseases, 82 cases were identified (1958–2007). Around 90% of the presented children suffered from leukemia, as did the boy in this case report. Looking at the development of mortality rates, an encouraging decrease from 100% (1950–1959) to 25.8% (2000–2007) can be observed. Disseminated disease was associated with a worse outcome and surgical treatment with better prognosis. *Rhizomucor* was identified in 9.1% of the cases. Neutropenia and steroid treatment were identified as risk factors [10].

Twelve pediatric cases from Germany and Austria were reported to

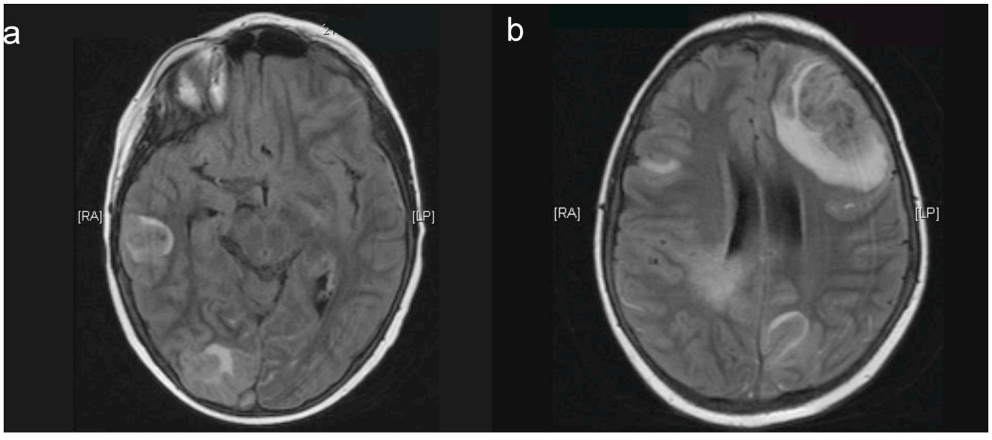

Fig. 1. Cerebral infiltration of the mucormycosis.
Head MRI (**a** + **b**, transversal FLAIR – fluid-attenuated inversion recovery) reflecting the cerebral lesions due to septic embolic infarctions and bleeding.

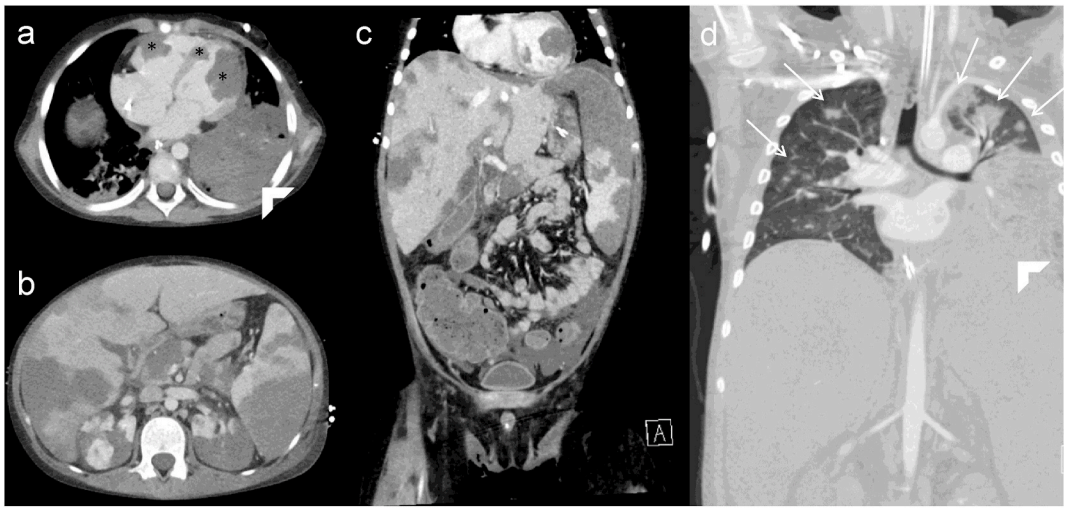

Fig. 2. Imaging of the disseminated mucormycosis
CT images in portal venous phase (**a** + **b** transversal reformations, **c** + **d** coronal reformation) illustrate huge right and left ventricular thrombi (*) in the heart and multiple septic embolic infarctions in the myocardium, liver, pancreas, spleen and both kidneys. Furthermore, there are focal areas of consolidation with surrounding ground-glass opacity (halo sign) in both lungs (white arrows) and attendant atelectasis of left lower lobe (white arrowhead) as radiological manifestations of pulmonary mucormycosis.

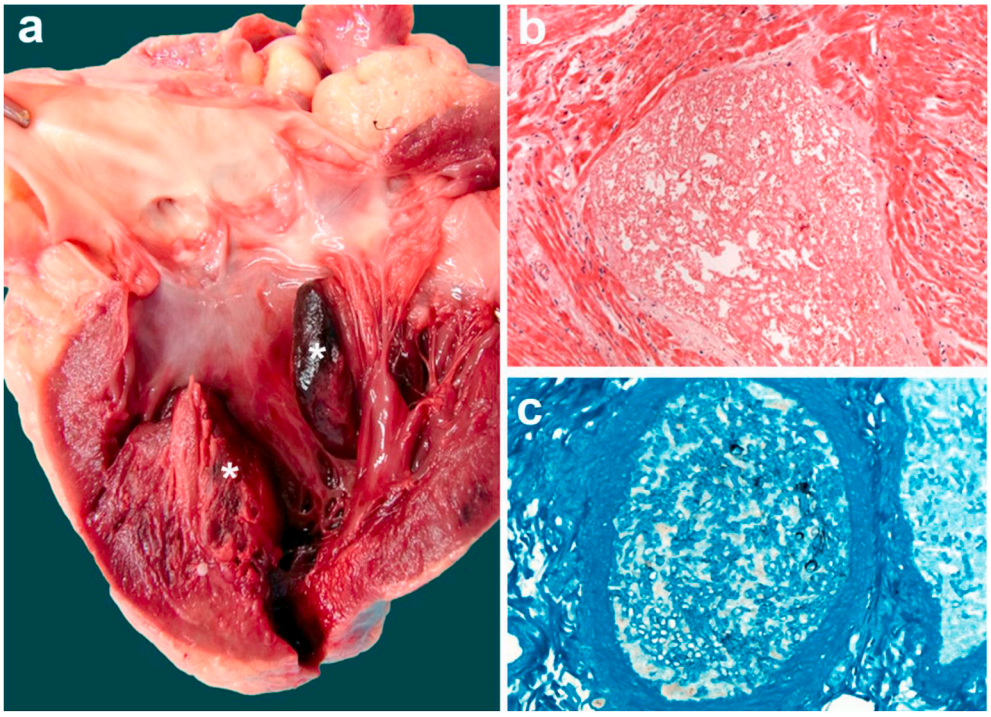

Fig. 3. Autopsy of the heart.
a) Macroscopy view of the left ventricle with aortic valve and origin of the right coronary artery. Note a parietal thrombus in the endocardium (*), locally infiltrating the myocardium (*). **b**) Myocardium with a vascular occlusion of coronary artery. **c**) Grocott stain demonstrates a coronary artery containing many fungal hyphae within the vessel-forming thrombosis. The culture revealed the presence of *R. pusillus*.

the Working Group on Zygomycosis of the European Confederation of Medical Mycology (ECMM) between 2004 and 2008. Eight children suffered from an underlying hematological disease or had received HSCT. Half of them had been treated with steroids, six of eleven patients had been neutropenic and one-third of the affected children had received antifungal medication with caspofungin or voriconazole prior to the infection. The overall mortality rate was stated at 67%. All children with disseminated disease died [11].

In a report from two registries on mucormycosis in children (2005–2014, 15 countries, 63 cases) the results seem to be similar. 46% suffered from hematological malignancies (55% ALL) and 15.9% were HSCT recipients. Almost half of the children suffered from neutropenia and the lungs were the most common location of infection (19%), whereas dissemination was recorded in 38.1% of the cases. The overall mortality in these children was 33.3%. Patients with HSCT, dissemination and an age of less than one year, were associated with higher risk of death [12].

Looking more closely only at the mucormycosis caused by *R. pusillus,* an analysis of 22 cases shows that the rate of immunocompromised patients is even higher in this subgroup (91%) [13]. Disseminated infection was reported in 40.9% of these cases, with a mortality of 78% (overall mortality rate in *R. pusillus* infections: 46%) [13]. Interestingly, in 68% of the *R. pusillus* cases, a nosocomial or health care-related infection (e.g. associated with IV catheters, injection sites,

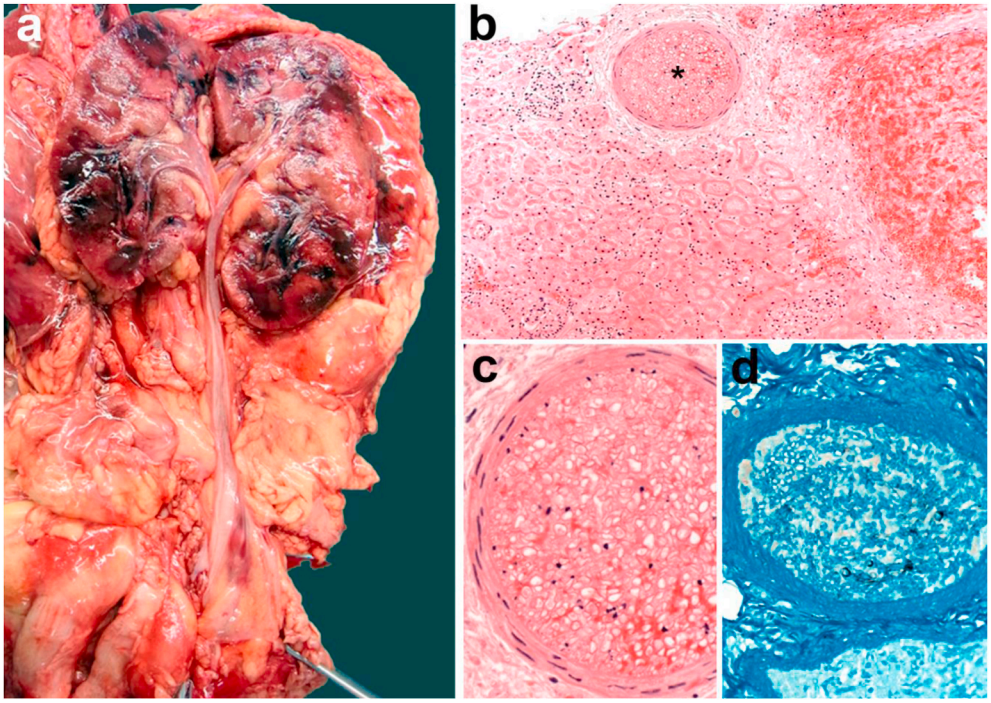

Fig. 4. Autopsy of abdominal organs (kidney).
a) Macroscopic view of the left kidney with multiple infarcts. **b**) H&E stain of the kidney showing extensive tubular necrosis secondary to hemorrhagic infarct and one occluded artery (*). **c**) Higher magnification revealing many fungal hyphae within the vessel producing a thrombus. **d**) Grocott stain highlights the fungal hyphae.

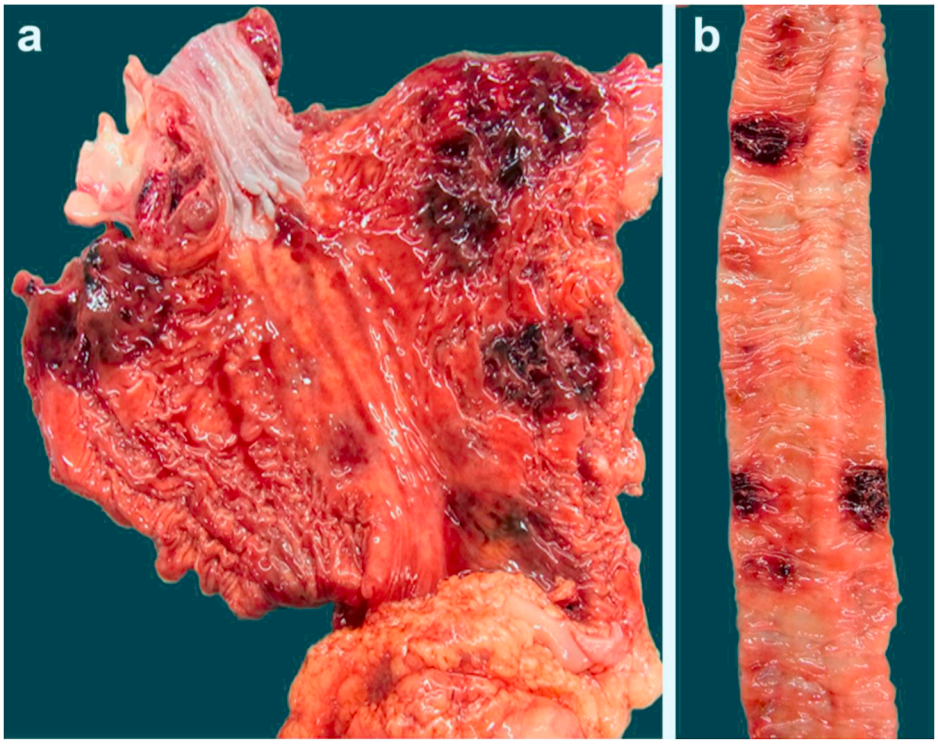

Fig. 5. Autopsy of abdominal organs (stomach, colon).
a) Macroscopic view of the stomach. **b**) Colon segment showing multiple ulcerations.

construction work) could not be excluded and had been described previously [8,13,14].

Table 1 provides an overview of pediatric case reports of mucormycosis caused by *R. pusillus* and underlying hemato-oncological disorder (Table 1).

Comparing this data to the case presented here, it can be concluded that the patient was part of the typical high-risk group for a deadly mucormycosis (ALL, neutropenia, disseminated disease). Consistent with the literature, the diagnosis in the presented case was not identified until an autopsy was performed. Universal fungal PCR of the tracheal secretion could not detect any fungal infection, even on the day the patient died. This emphasizes the diagnostic challenges associated with mucormycosis. In the post-mortem, molecular pathological analyses revealed a disseminated infection with proof of *R. pusillus* in the lungs

Table 1
Published pediatric case reports of mucormycosis caused by *R. pusillus* with underlying hematological disease.

patient	underlying disease	location	treatment	outcome	reference
girl, 14 years	ALL, after HSCT, neutropenia	disseminated intracardial thrombus, infectious emboli of multiple organs	fluconazole, caspofungin, voriconazole, amphotericin B	died	[15]
girl, 12 years	hemophagocytic lymphohistiocytosis	disseminated	antibiotics	died	[3]
girl, 10 years	severe aplastic anemia	disseminated, thromboembolisms of several organs	prophylactic fluconazole	died	[7]
boy, 19 years	acute myeloid leukemia relapse	liver	local surgery, amphotericin B, posaconazole, deferasirox	survived	[16]
boy, 16 years	acute myeloid leukemia	disseminated	antifungal therapy	died	[6]
boy, 15 years	ALL	soft tissues, rhino-cerebral	amphotericin B, posaconazole	survived	[8]
boy, 11 years	ALL	nasal, sinus tissues	amphotericin B	survived	[14]
boy, 3 years	ALL, second relapse (after HSCT)	perineum, cerebral	amphotericin B, voriconazole	died	[17]
boy, 18 years	acute leukemia	lung, kidney	amphotericin B	died	[18]
boy, 21 months	ALL	soft tissues	amphotericin B, debridement, rifampicin	survived	[19]

and other organs.

As the lungs are the most common location in patients with malignancies, one might speculate that the lungs were the original location of the infection. However, the source of infection in the boy remains unclear. A health care-related infection cannot be excluded either.

Due to lack of awareness of the deadly infection, the patient discussed in this case report did not receive standard treatment for mucormycosis (liposomal amphotericin B ± surgery). Instead, the boy was treated with caspofungin as an antifungal prophylaxis for candidiasis and aspergillosis, as the most common invasive fungal infection after HSCT [17]. Caspofungin is not suitable for the treatment of mucormycosis as monotreatment. There are several descriptions of breakthrough filamentous fungal infections (one out of four with *R. pusillus*) in pediatric oncological patients receiving caspofungin [17]. By using caspofungin or voriconazole as a prophylactic treatment, resistant fungi such as *R. pusillus* can cause severe infections as in the described case [15]. Since posaconazole seems to be effective in mucormycosis, a general switch from caspofungin, voriconazole or fluconazole to posaconazole as the standard prophylactic antimycotic treatment should be considered. However, there are also reports about breakthrough infections under prophylaxis with posaconazole [5].

In the ECMM report, 39% of the cases were treated with amphotericin B, 7% with posaconazole and 21% with both. In 2011, the mortality rate was stated at 47% (27% in children), which is an improvement compared to 66–76% in 1990 and 94% prior to 1970 [4]. In ECMM's study, one of the factors associated with mortality was treatment with caspofungin prior to diagnosis [4]. Furthermore, delay of amphotericin B treatment (more than 6 days, resulting in a two-fold mortality increase), cytopenia, and active malignancy are also associated with higher mortality. Retrospectively, all of these factors were present in the current case and might have contributed to the fatal outcome.

To the best of our knowledge, this is the first case of a child developing a fulminant mucormycosis during blinatumomab treatment. The combination of targeted therapy (blinatumomab) and reduced immunocompetence after HSCT resulted in an increased vulnerability to opportunistic infections. Furthermore, this case draws attention to one key factor that mucormycosis is a life-threatening and progressive infection. Since 2017, the blinatumomab treatment has been part of the standard treatment of ALL in the AIEOP-BFM-2017 protocol.

Knowledge about associated invasive fungal infections is limited. In three trials invasive fungal diseases were stated in 8 of 501 patients (fusarium n=2, aspergillus n=1, candida n=1, mucor n=1, pneumocystis n=1, unspecified n=2) [20]. To the best of our knowledge there is no data concerning invasive fungal infections in pediatric patients during blinatumomab treatment.

Unfortunately, there is a lack of prospective studies regarding antifungal prophylaxis in new targeted therapies such as blinatumomab. It is important that clinicians take into consideration opportunistic and difficult-to-treat infections such as mucormycosis to increase the chances of patients' survival. Consequently, prophylactic treatment with an antimycotic medication covering mucormycetes (liposomal amphotericin B) should be considered in high-risk patients.

Declaration of competing interest

No conflicts of interest are declared. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Acknowledgements

None.

References

[1] A.G. Freifeld, P.C. Iwen, Zygomycosis. Semin Respir Crit Care Med. 25 (2) (2004) 221–231.
[2] Villanueva P. Francis JR, P. Bryant, C.C. Blyth, Mucormycosis in children: review and recommendations for management, J Pediatric Infect Dis Soc 7 (2) (2018) 159–164.
[3] J. Dien Bard, A. Mangahis, T.C. Hofstra, J.M. Bender, First case report of bloodstream infection by Rhizomucor pusillus in a child with hemophagocytic lymphohistiocytosis, Med Mycol Case Rep 5 (2014) 20–23.
[4] A. Skiada, L. Pagano, A. Groll, S. Zimmerli, B. Dupont, K. Lagrou, et al., Zygomycosis in europe: analysis of 230 cases accrued by the registry of the European confederation of medical Mycology (ECMM) working group on zygomycosis between 2005 and 2007, Clin. Microbiol. Infect. 17 (12) (2011) 1859–1867.
[5] C. Robin, A. Alanio, C. Cordonnier, Mucormycosis: a new concern in the transplant ward? Curr. Opin. Hematol. 21 (6) (2014) 482–490.
[6] P.E. Verweij, W.J. van der Velden, J.P. Donnelly, N.M. Blijlevens, A. Warris, [Invasive zygomycosis in patients treated for haematological malignancies], Ned. Tijdschr. Geneeskd. 151 (47) (2007) 2597–2602.
[7] N.J. Rawlinson, B. Fung, T.G. Gross, A.M. Termuhlen, M. Skeens, A. Garee, et al., Disseminated Rhizomucor pusillus causing early multiorgan failure during hematopoietic stem cell transplantation for severe aplastic anemia, J. Pediatr. Hematol. Oncol. 33 (3) (2011) 235–237.
[8] D. Garner, K. Machin, Investigation and management of an outbreak of mucormycosis in a paediatric oncology unit, J. Hosp. Infect. 70 (1) (2008) 53–59.
[9] A.H. Groll, E. Castagnola, S. Cesaro, J.H. Dalle, D. Engelhard, W. Hope, et al., Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric

patients with cancer or allogeneic haemopoietic stem-cell transplantation, Lancet Oncol. 15 (8) (2014) e327–e340.
[10] W. Dehority, J. Willert, A. Pong, Zygomycetes infections in pediatric hematology oncology patients: a case series and review of the literature, J. Pediatr. Hematol. Oncol. 31 (12) (2009) 911–919.
[11] J. Dabritz, A. Attarbaschi, K. Tintelnot, N. Kollmar, B. Kremens, F.D. von Loewenich, et al., Mucormycosis in paediatric patients: demographics, risk factors and outcome of 12 contemporary cases, Mycoses 54 (6) (2011) e785–e788.
[12] Z.D. Pana, D. Seidel, A. Skiada, A.H. Groll, G. Petrikkos, O.A. Cornely, et al., Invasive mucormycosis in children: an epidemiologic study in European and non-European countries based on two registries, BMC Infect. Dis. 16 (1) (2016) 667.
[13] M.Z. Gomes, R.E. Lewis, D.P. Kontoyiannis, Mucormycosis caused by unusual mucormycetes, non-Rhizopus, -Mucor, and -Lichtheimia species, Clin. Microbiol. Rev. 24 (2) (2011) 411–445.
[14] A. del Palacio Hernanz, J. Fereres, S. Larregla Garraus, A. Rodriguez-Noriega, F. Sanz Sanz, Nosocomial infection by Rhizomucor pusillus in a clinical haematology unit, J. Hosp. Infect. 4 (1) (1983) 45–49.
[15] S.M. Kivivuori, R. Karikoski, P. Koukila-Kahkola, V.J. Anttila, U.M. Saarinen-Pihkala, Zygomycosis presenting a major clinical challenge: case report on Rhizomucor pusillus infection in a stem-cell-transplant recipient, Mycopathologia 172 (3) (2011) 241–245.
[16] A. Busca, F. Marmont, F. Locatelli, G. Limerutti, M.T. Sorrentino, A. Barbui, et al., Combined antifungal therapy, iron chelation and surgical resection as treatment of hepatic zygomycosis in a patient with haematological malignancy, Mycoses 53 (3) (2010) 275–278.
[17] S.K. Morris, U.D. Allen, S. Gupta, S.E. Richardson, Breakthrough filamentous fungal infections in pediatric hematopoetic stem cell transplant and oncology patients receiving caspofungin, Can. J. Infect Dis. Med. Microbiol. 23 (4) (2012) 179–182.
[18] G. St-Germain, A. Robert, M. Ishak, C. Tremblay, S. Claveau, Infection due to Rhizomucor pusillus: report of four cases in patients with leukemia and review, Clin. Infect. Dis. 16 (5) (1993) 640–645.
[19] M.E. Ryan, D. Ochs, J. Ochs, Primary cutaneous mucormycosis: superficial and gangrenous infections, Pediatr. Infect. Dis. 1 (2) (1982) 110–114.
[20] T.S.Y. Chan, Y.L. Kwong, Systemic trichosporonosis mimicking disseminated varicella zoster viral infection during blinatumomab therapy, Ann. Hematol. 97 (2) (2018) 371–373.