A Radical Approach to Acute Lymphoblastic Leukemia Treatment: A Case Study of a Veterinarian Specializing in Livestock who Developed Disseminated Mucormycosis during Induction Therapy

Toshiro Sakai, Ken Sato, Tomoki Kikuchi, Masahiko Obata and Yuichi Konuma

Abstract:
Mucormycosis has emerged as the third-most common fungal mycosis and is one of the most fatal molds. We herein report a case study of a 30-year-old woman who was a veterinarian, specializing in livestock, who developed disseminated mucormycosis during induction therapy for acute lymphoblastic leukemia. We successfully used a radical approach for treatment, including a surgical procedure and allogeneic transplantation, with continuous administration of antifungal agents. Reports of successful treatments are extremely rare, and our case has had the longest documented remission from disseminated disease. We speculate that our case’s occupational environment may represent a risk factor for development of mucormycosis.

Key words: mucormycosis, hematopoietic stem cell transplantation, disseminated disease, dairy workers

(Intern Med 59: 261-266, 2020)
(DOI: 10.2169/internalmedicine.3314-19)

Introduction
Invasive fungal infections (IFIs) are life-threatening complications in patients with hematological malignancies (1). The incidence of mucormycosis has been increasing over the past decade, and this condition is fatal in most patients (2). In clinical situation, hematopoietic stem cell transplantation (HSCT) recipients frequently develop mucormycosis (3). Since rapidly progressive disseminated disease occurs in about 60% of mucormycosis cases, the mortality rate exceeds 58-100% (2, 4). The early diagnosis, prompt administration of appropriate antifungal agents and surgical intervention are known to be critical for the successful treatment of mucormycosis (5). There have been few reports of patients with hematological malignancies in whom HSCT has been conducted after the development of disseminated mucormycosis.

We herein report a case study of a 30-year-old woman who was a veterinarian, specializing in livestock, who developed complicated disseminated mucormycosis during induction therapy for acute lymphoblastic leukemia (ALL). The patient’s occupational environment may represent a risk factor for the development of mucormycosis. We demonstrated the efficacy of a radical treatment approach including allogeneic transplantation for disseminated mucormycosis.

Case Report
A 30-year-old woman who was a veterinarian, specializing in livestock, presented to our hospital because of anemia symptoms and abnormalities on a blood examination in February 2017. She had been caring for dairy cows in a barn until the day before her first visit. The patient’s white blood cell count was 1.6×10^9/L with 21% abnormal cells, and her hemoglobin was 7.6 g/dL. On a bone marrow examination, the abnormal cells were judged to be L2 blastoid cells according to French-American-British (FAB) classification. These cells were positive for CD10, CD19, CD34, and HLA-DR and negative for CD20, indicating a normal karyotype. The patient was therefore diagnosed with B-cell ALL.

The patient started induction therapy according to the CALGB8811 protocol (6) with preventive administration of levofloxacin at 500 mg/day, fluconazole at 200 mg/day and...
April
Achievement of CR left upper lobectomy
CT IV

• liposomal amphotericin B (L-AMB) at 5 mg/kg in

• broad-spectrum antibiotic under the diagnosis of febrile neu-

tropenia: liposomal amphotericin B (L-AMB) at 5 mg/kg in

• blood culture examinations were negative, so we

• sign around the left pulmonary apex region (Fig. 2a) and ab-

• clear. Computed tomography (CT) revealed a reversed halo

• was 99% on room air, and respiratory sounds were

• her body temperature was 38°C, oxygen satu-

• her left shoulder and upper abdomen on day 21 of therapy.

• we immediately discontinued chemotherapy on this day

• body temperature was 38°C, oxygen satu-

• At that time, her body temperature was 38°C, oxygen satu-

• sign around the left pulmonary apex region (Fig. 2a) and ab-

• wide-angle antibiotic under the diagnosis of febrile neu-

• suspected disseminated mucormycosis.

• We immediately discontinued chemotherapy on this day

• combination with mafungin (MCFG). We then increased

• of mucormycosis with the lung as the

• valacyclovir at 500 mg/day (Fig. 1a). She developed pain in

• At that time, her body temperature was 38°C, oxygen satu-

• computed tomography (CT) revealed a reversed halo

• suspected disseminated mucormycosis.

• We immediately discontinued chemotherapy on this day

• day 21 of therapy. At that time, her body temperature was 38°C, oxygen satu-

• sign around the left pulmonary apex region (Fig. 2a) and ab-

• We immediately discontinued chemotherapy on this day

• combination with mafungin (MCFG). We then increased

• of mucormycosis with the lung as the

• valacyclovir at 500 mg/day (Fig. 1a). She developed pain in

• At that time, her body temperature was 38°C, oxygen satu-

• computed tomography (CT) revealed a reversed halo

• suspected disseminated mucormycosis.

• We immediately discontinued chemotherapy on this day

• combination with mafungin (MCFG). We then increased

• of mucormycosis with the lung as the

• valacyclovir at 500 mg/day (Fig. 1a). She developed pain in

• At that time, her body temperature was 38°C, oxygen satu-

• computed tomography (CT) revealed a reversed halo

• suspected disseminated mucormycosis.

• We immediately discontinued chemotherapy on this day

• combination with mafungin (MCFG). We then increased

• of mucormycosis with the lung as the
primary lesion.

To control the main fungal lesions, L-AMB and MCFG were continued, and the patient underwent left upper lobectomy on day 27 following the onset of mucormycosis. This intervention was necessary because of the risk of hemoptysis due to pulmonary lesions with a large cavity in contact with the subclavian artery, with the goal of reducing the risk of further dissemination from the lung to other organs (Fig. 2c). After surgical intervention, three additional consolidation therapies were administered with concurrent antifungal agents at the same dose (Fig. 1b).

In our assessment of the fungal infection activity, a physical examination revealed that the patient’s abdominal findings had disappeared, but her mild fever persisted. A blood examination showed that her C-reactive protein concentration was slightly high, and enhanced CT showed that the abscessed lesion was smaller and encapsulated but still present (Fig. 2d, e). Based on these findings, we deemed the fungal infection activity not completely controlled.

The patient’s renal function gradually worsened, although the ALL remained in complete remission. We predicted that it would be difficult to continue long-term consolidation therapy and maintenance therapy while administering antifungal agents. However, since an HLA-matched sibling donor was available, we decided to carry out bone marrow stem cell transplantation (BMT) six months from the day of mucormycosis onset.

The patient was conditioned with fludarabine (150 mg/m²) and melphalan (140 mg/m²), and both tacrolimus and methotrexate were administered for graft-versus-host disease (GvHD) prophylaxis. Antifungal agents were continued at the same dose before and after transplant. Engraftment was confirmed on day 20 after transplantation. CT showed that the residual fungal lesions were shrinking over time (Fig. 2f, g) and the C-reactive protein level had dropped to zero. Given these findings, we determined the fungal infection activity to be almost gone.

The patient became complicated with bacterial sepsis during myelosuppression but did not develop any transplant-
related complications, including relapse of fungal infections. However, her creatinine level increased from day 60 after transplantation to a maximum of 5 mg/dL. At that time, the antifungal agents were gradually reduced over a period of about 1 month and discontinued entirely on day 273 after the onset of mucormycosis, while tacrolimus was continuously administered. Thereafter, her renal function improved, and her ALL remained in complete remission without mucormycosis recurrence.

She was discharged on day 101 after transplantation and remains in remission from ALL over 1.5 years after BMT without recurrence of mucormycosis.

Discussion

IFIs are frequent life-threatening complications in patients with hematological malignancies. Over the past decade, several new antifungal drugs suitable for clinical use and novel strategies for treating IFIs have been developed (7). In addition, pre-transplant IFI is no longer necessarily a contraindication for transplantation (8). Among IFIs, mucormycosis remains a particularly life-threatening infection associated with high rates of morbidity and mortality (2, 3). There have been few documented cases in which mucormycosis occurred during the early stages of induction therapy in patients with indications for transplantation.

An important point in the present case report is the timing and risk factors for the development of mucormycosis. We suggest the possibility that the patient’s occupational environment (a dairy cattle barn) may have been a risk factor for the fungal infection she acquired. Among veterinarians and dairy farmers, Mucorales species are recognized as important pathogens in cows. Most cases of zygomycosis among cows are caused by mucormycetes, and zygomycosis usually produces focal lesions (e.g., gastric mucormycosis, intestinal zygomycosis or lymphadenitis); fatal zygomycosis has also been reported (9-11). These pathogens are ubiquitous within the environments inhabited by cattle and can be isolated from the air (12, 13). In addition, zygomycetes such as Mucor pusillus and Lichtheimia corymbifera are present in the normal rumen flora (14). Infection can occur from disruption of the normal balance between animals and agents. Such disruptions have been associated with several factors that affect the normal flora in the forestomach, such as ruminal acidosis and broad-spectrum antibiotics. As a result, cattle may develop alimentary mycosis or systemic mycosis (15). We speculate that exposure to factors associated with working in a dairy environment, especially the air, feed and excreta, may be a risk factor for immunocompromised patients. Only one report has focused on the possibility that environmental factors and mucormycosis may be related (16). Our patient was a veterinarian specializing in dairy cows and developed ALL while working in an environment in which she may have inhaled high concentrations of Mucorales spores released from hay, fermented hay and composite feed. We suspect that such exposure was responsible for the onset of mucormycosis during the early stages of induction therapy.

Mucormycosis developing during HSCT has a high mortality rate (2), but recently, there have been reports of successful treatment (17, 18). L-AMB, starting at 5 mg/kg/day, is now preferred as the first-line therapy, and posaconazole has been mentioned as a viable second-line therapy (5, 19). The appropriate treatment duration for mucormycosis is unclear, and urgent surgical debridement is recommended for localized lesions. The benefits of surgery in the setting of disseminated mucormycosis remain unclear (19).

Our literature search revealed 11 case reports of mucormycosis occurring prior to transplantation and allogeneic transplantation (Table 1) (20-28). Eight cases had disease limited to the lungs, and three cases were disseminated. Acute myeloid leukemia was the most common malignancy, and the onset of mucormycosis frequently occurred during induction therapy. These results are consistent with the fact that cases of induction therapy for acute leukemia are classified as a high-risk group for fungal infections according to the Japanese domestic guidelines for the management of deep-seated mycosis (29). In most cases, the time from the diagnosis to transplantation has been reported to be several months. In the disseminated cases, high doses (e.g., 10 mg/kg) of L-AMB were frequently administered for the treatment of mucormycosis prior to HSCT, and surgical intervention was performed in 3 of 4 patients, including the case described here. We summarized the clinical course and outcomes post-HSCT from these reports (Table 2). There was no clear trend in the patient outcome associated with the status at transplantation, conditioning regimens or donor source. Two of the three disseminated cases died from transplantation-related complications. One case died from CMV pneumonia and the other died from idiopathic pneumonia syndrome after developing refractory acute GvHD. Pulmonary complications were the cause of death in both cases. Uryu et al. (30) reported that fungal cell components can trigger lung GvHD in mouse models; in this respect, the outcome of these cases is presumed to be the result of fungal infection affecting local immunity in the lung. The optimal administration period of antifungal agents for treating mucormycosis after transplantation remains unclear. One reason for this uncertainty is difficulty in assessing the disease activity of mucormycosis. In the literature describing the duration of treatment with antifungal agents, three cases finished treatment after engraftment. In two cases, including our own patient, treatment was discontinued due to adverse events that occurred within a few months after engraftment. Three cases received maintenance therapy with a small dose of L-AMB or posaconazole over several months, even after discharge. Based on our experience, we consider that it may be possible to withdraw antifungal drugs within a few months of transplantation if there is no apparent fungal infection activity according to the physical findings and other data, including the C-reactive protein concentration, even if immunosuppressants are being administered following trans-
HM. The clinical course of the present case can be a valuable guide for similar cases. Immunodeficient patients in certain workplaces, especially dairy farms, may be at an increased risk for developing mucormycosis. To confirm this speculation, further epidemiological surveys and statistical analyses will be necessary. In this case report, the urgent and continuous administration of antifungal agents, surgical intervention and allogeneic transplantation made it possible to maintain durable complete remission from both ALL and mucormycosis. Although the appropriate treatment for disseminated cases remains unclear, we hope that this case report will help determine the clinical direction for similar cases in the future.
The authors state that they have no Conflict of Interest (COI).

References

1. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 91: 1068-1075, 2006.
2. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 41: 634-653, 2005.
3. Skaida A, Pagano L, Groll A, 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: 1859-1867, 2011.
4. Ingram CW, Sennesh J, Cooper JN, Perfect JR. Disseminated mucormycosis: report of four cases and review. Rev Infect Dis 11: 741-754, 1989.
5. Kontoyiannis DP, Azie N, Franks B, Horn DL. Prospective antifungal therapy (PATH) alliance(®): focus on mucormycosis. Mycoses 57: 240-246, 2014.
6. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 85: 2025-2037, 1995.
7. Kurosawa M, Yonezumi M, Hashino S, et al. Epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. Int J Hematol 96: 748-757, 2012.
8. Maziarz RT, Brazauskas R, Chen M, et al. Pre-existing invasive fungal infection is not a contraindication for allogeneic HSCT for patients with hematologic malignancies: a CIBMTR study. Bone Marrow Transplant 52: 270-278, 2017.
9. Jensen HE, Olsen SN, Aalbaek B. Gastrointestinal aspergillosis and zygomycosis of cattle. Vet Pathol 31: 28-36, 1994.
10. Chihaya Y, Okada H, Matsukawa K, Matsui Y. Disseminated mycoses in cattle. A study on nine autopsy cases. J Vet Med Sci 54: 485-491, 1992.
11. Tanaka Y, Toyotome T, Inokuma H, et al. Rhinocerebral zygomycosis due to a lichtheimia ramosa infection in a calf: neural spread through the olfactory nerves. Mycopathologia 184: 141-146, 2019.
12. Kotimaa MH, Oksanen L, Koskela P. Feeding and bedding materials as sources of microbial exposure on dairy farms. Scand J Work Environ Health 177: 117-122, 1991.
13. Kosuge J, Goto Y, Shinjo T, Goto A, Kosuke Takatori K. Murcories contamination in cattle feed. Nihon Zyuiski Zasshi (J Japan Veterinary Med Assoc) 55: 281-283, 2002 (in Japanese).
14. Lund A. Yeasts and moulds in the bovine rumen. J. Gen. Microbiol 81: 453-462, 1974.
15. Chihaya Y, Matsukawa K, Ohshima K, et al. A pathological study of bovine alimentary mycosis. 107: 195-206, 1992.
16. Paterson PJ, Marshall SR, Shaw B, et al. Fatal invasive cerebral Absidia corymbifera infection following bone marrow transplantation. Bone Marrow Transplant 26: 701-703, 2000.
17. Rickerts V, Bohme A, Viertel A, et al. Cluster of pulmonary infections caused by Cunninghamella bertholletiae in immunocompromised patients. Clin Infect Dis 31: 910-913, 2000.
18. Ota H, Yamamoto H, Kimura M, et al. Successful treatment of pulmonary mucormycosis caused by Cunninghamella bertholletiae with high-dose liposomal amphotericin B (10 mg/kg/day) followed by a lobectomy in cord blood transplant recipients. Mycopathologia 182: 847-853, 2017.
19. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 102: 433-444, 2017.
20. Slavin MA, Kannan K, Buchanan MR, Sasadeusz J, Roberts AW. Successful allogeneic stem cell transplant after invasive pulmonary mucormycosis. Leuk Lymphoma 43: 437-439, 2002.
21. Avivi I, Oren I, Haddad N, Rowe JM, Dann EJ. Stem cell transplantation post invasive fungal infection is a feasible task. Am J Hematol 75: 6-11, 2004.
22. Salonen JH. Successful management of cerebral and pulmonary mucormycosis with liposomal amphotericin B in a 28-year-old woman with acute lymphoblastic leukemia. Acta Biomed 77: 28-31, 2006.
23. Grigoriadis G, Chang CC, Walker P, et al. Failure of haematopoietic recovery overcome by SCT despite invasive mucormycosis infection. Bone Marrow Transplant 47: 591-592, 2012.
24. Serio B, Rosamilio R, Giudice V, et al. Successful management of pulmonary mucormycosis with liposomal amphotericin B and surgery treatment: a case report. Infez Med 20: 43-47, 2012.
25. Schneidawind D, Nann D, Vogel W, et al. Allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia and pulmonary mucormycosis. Transpl Infect Dis 14: E166-172, 2012.
26. Yuda J, Kato K, Kikushige Y, et al. Successful treatment of invasive zygomycosis based on a prompt diagnosis using molecular methods in a patient with acute myelogenous leukemia. Intern Med 53: 1087-1091, 2014.
27. Suzuki D, Kobayashi R, Hori D, et al. Stem cell transplantation for acute myeloid leukemia with pulmonary and cerebral mucormycosis. Pediatr Int 58: 569-572, 2016.
28. Ochi T, Katayama Y, Okatani T, et al. Successful haploidentical stem cell transplantation with prophylactic administration of liposomal amphotericin B after invasive pulmonary zygomycosis. Med Mycol Case Rep 18: 1-4, 2017.
29. Kohno S, Tamura K, Niki Y, et al. Executive summary of Japanese domestic guidelines for management of deep-seated mycosis 2014. Med Mycol J 57: E117-E163, 2016.
30. Uryu H, Hashimoto D, Kato K, et al. α-Mannan induces Th17-mediated pulmonary graft-versus-host disease in mice. Blood 125: 3014-3023, 2015.

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