EBMT

CORRESPONDENCE

Disseminated nontuberculous mycobacterial infections after allogeneic hematopoietic stem cell transplantation: a risk-based strategy for early diagnosis

Bone Marrow Transplantation (2023) 58:956–958; https://doi.org/10.1038/s41409-023-02011-6

TO THE EDITOR:

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms and widely distributed in water and soil [1]. In humans, NTM infections can be localized to the lungs, but can also present as lymphadenopathy, skin/soft tissue, or bone infections. Disseminated NTM infections involve multiple organs and occur in severely immunocompromised hosts, e.g., in persons infected with human immunodeficiency virus (HIV) and low CD4 counts, or with primary immunodeficiencies such as GATA2 deficiency. NTM infections after allogeneic hematopoietic stem cell transplantation (allo-HSCT) are rare with an incidence of 1.7–6.4% [2]. The majority of these cases are localized pulmonary infections, while dissemination is reported in only 0.2% of patients. However, incidence of NTM infections is rising after allo-HSCT [2]. Here, we present four cases of disseminated NTM infections according to the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) definitions [3], occurring in a single center between 2019 and 2022.

Four patients underwent an allo-HSCT with ex vivo αβ T cell depletion and CD19 B cell depletion (see Supplementary data for cases and baseline table). All patients developed acute graft-versus-host disease (GVHD) grade II-IV, treated with prednisolone and CsA. Three out of four patients received ruxolitinib as a second-line treatment. Five to seven months after allo-HSCT, all four patients presented with severe fatigue, wasting, liver enzyme elevations, and cytopenias despite full donor chimerism. All except for patient 2 had a fever at presentation. Imaging showed lymphadenopathy in all patients and pulmonary consolidations in patients 2 and 4. All had positive bone marrow diagnostics for NTM. Ziehl-Neelsen(ZN)-positive granulomas were seen in patients 1, 2, and 3, and subsequent NTM sequencing determined the presence of *M. genavense, M. simiae complex*, and *M. kansasii*, respectively. In patient 4 bone marrow cultures showed the presence of *M. Kansasii* (Fig. 1a). Other affected organs were lymph nodes in patients 1 and 3, duodenum in patient 2 and lungs in patient 4. Antibiotic combinations were suggested in all patients. Unfortunately, none were able to complete treatment because of their poor clinical condition and delay in NTM diagnosis. Patients 1, 2, and 3 died, while patient 4 was at home with the best supportive care at the last follow-up. Details on these cases can be found in Supplementary data.

An obvious but also controversial explanation for the high incidence of disseminated NTM infections presented here, is the deep T cell suppression due to ex vivo αβ T cell-depleted allo-HSCT. Low CD4 counts are a risk factor for NTM infections after allo-HSCT [4]. Alemtuzumab and anti-thymocyte globulin have been implied to enhance the risk of NTM infections by some investigators [5], while others stated that neither of these treatments nor ex-vivo T cell depletion was a risk factor for NTM infection [2, 6].

Acute and chronic GVHD, on the other hand, have been convincingly associated with NTM infections, as GVHD is observed in 40–60% of NTM patients [5]. Older age, cytomegalovirus infection, unrelated/mismatched donors, myeloablative conditioning, neutropenia, and hyperglycemia have been suggested as additional risk factors [2, 7]. However, most of these factors associate with GVHD, implying that GVHD and immunosuppressive drugs used for its treatment are the main underlaying reasons for the increased NTM risk. Of note, within our allo-HSCT cohort, the incidence of gr II–IV GVHD at day 100 is only 26%, whereas all four patients presented here suffered from gr II–IV GVHD.

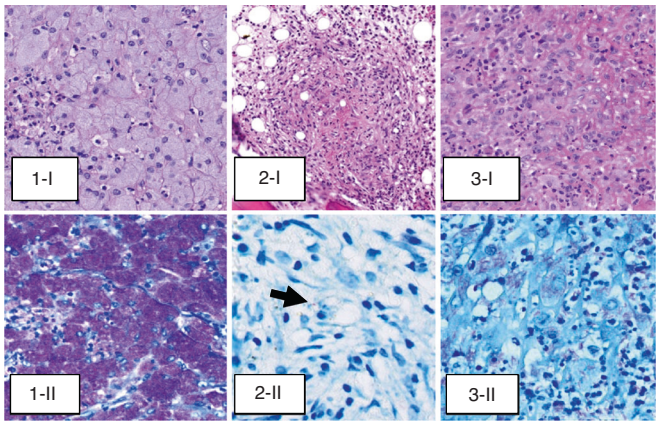
Drugs used to treat GVHD might provide the additional trigger for NTM infections. Prednisolone use was reported to be 8 times higher among NTM cases than in controls [8]. Also ruxolitinib, a JAK/STAT inhibitor, has been associated with disseminated NTM infections post-allo-HSCT [9]. Importantly, three of our four patients received ruxolitinib. JAK/STAT pathway inhibition plays a key role in mycobacterial infection, and patients with STAT1 mutations are very sensitive to mycobacterial infections. Also ibrutinib, a BTK inhibitor that has been approved for treatment of GVHD, has been associated with NTM infections [10].

Treatment of NTM infections requires combinations of antibiotic drugs for a prolonged period up to 12 months [11]. Eradication is not always feasible [1]. Survival of localized NTM infections is 40–50% [2, 7], while disseminated disease has an even poorer prognosis [1]. All patients described here were unable to complete antibiotic therapy, either due to progression of multi-organ failure despite adequate therapy, or to a dismal performance status at the time of NTM diagnosis. The importance of early diagnosis is stressed by the absence of prophylactic, preemptive and empirical antimicrobial strategies. As such, therapy can only be started after definitive diagnosis.

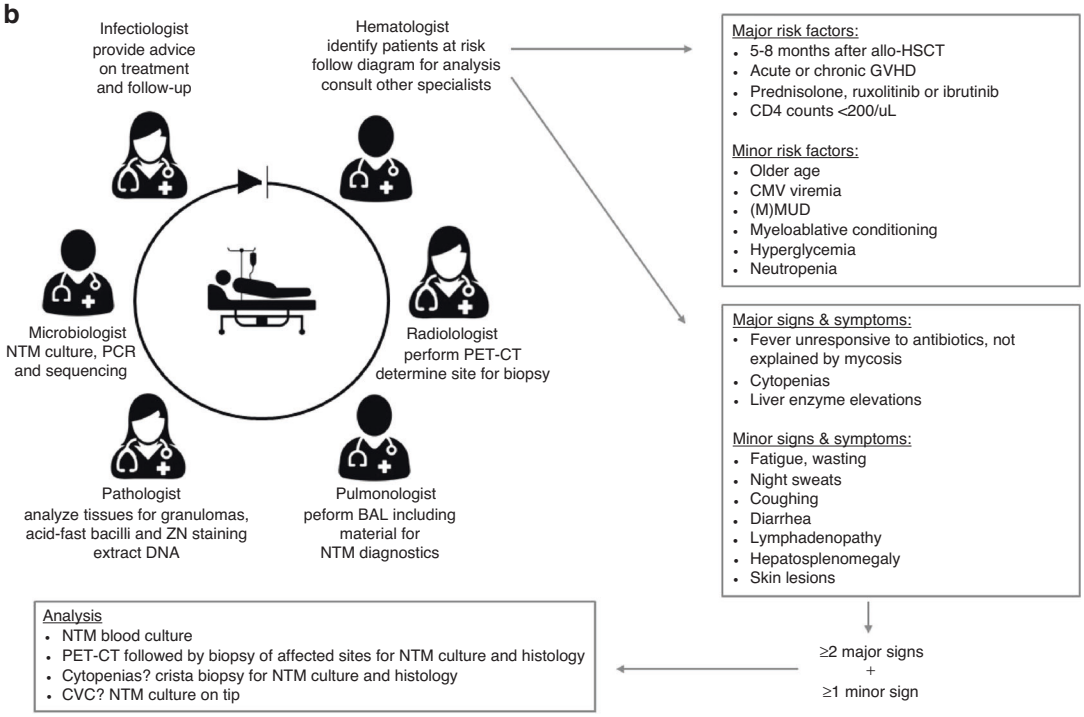
To speed up the diagnostic process, we propose an early, risk-based strategy, starting with identification of patients at risk (Fig. 1b). Major risk factors for disseminated NTM infections were 1) timing 5–8 months post-allo-HSCT, 2) GVHD, 3) use of immunosuppressive therapies, and 4) CD4 counts <200/μL. Minor risk factors are clarified in Fig. 1b, as well as major and minor signs and symptoms of disseminated infections. An important symptom is fever not responsive to antibiotic therapy. NTM infections should always be included in the differential diagnosis of antibiotic-resistant fever after allo-HSCT. Unfortunately, many symptoms are aspecific and will not differentiate between NTM infections and other life-threatening infections: e.g., night sweats, weight loss, and (extreme)

Received: 6 March 2023 Revised: 4 May 2023 Accepted: 12 May 2023
Published online: 20 May 2023

a



b



c

	Patient 1	Patient 2	Patient 3	Patient 4
Major risk factors				
5-8 months after allo-HSCT	+	+	+	+
Acute or chronic GVHD	+	+	+	+
Prednisolone, ruxolitinib or ibrutinib	Pred and ruxo	Pred	Pred and ruxo	Pred and ruxo
Low T cell counts	+	×	+	+
Major signs & symptoms				
Fever	+	-	+	+
Cytopenias	+	+	+	+
Liver enzyme elevations	+	+	+	+
Radiology				
(PET-)CT	Lymphadenopathy	Lymphadenopathy, bronchial consolidations	Lymphadenopathy	Lymphadenopathy, bronchial consolidations
Tissue samples with NTM infection				
Blood	-	+	+	+
Bone marrow	+	+	+	+
Other tissues involved	Lymph nodes	Duodenum	Lymph nodes	Lungs

fatigue. Depending on the organs involved in NTM infections, more specific symptoms will occur. Examples are anemia and neutropenia from bone marrow involvement; lymphadenopathy or hepatosplenomegaly from lymphoreticular involvement; diarrhea, abdominal pain, and elevations of liver enzymes (mostly alkaline phosphatase and gamma-glutyltransferase) from involvement of the gastrointestinal tract; and cough and lung infiltrates from pulmonary involvement.

When ≥2 major signs and ≥1 minor sign are present, further analysis is warranted. These patients deserve mycobacterial blood cultures and positron emission tomography-computed tomography (PET-CT) scan (Fig. 1b). A PET-CT might show FDG-avid

Fig. 1 NTM tissue samples, a risk-based strategy, and clinical characteristics of four patients with disseminated NTM infections. a Tissue samples with NTM infection. The lymph node excision of patient 1 shows on histopathological examination complete effacement of the normal architecture by a diffuse infiltrate of foamy macrophages (1-I: hematoxylin and eosin (H&E) stain, detail), which contain a massive amount of acid-fast bacteria (1-II: Ziehl-Neelsen stain). The bone marrow biopsy of patient 2 contains a granuloma formed by spindle-shaped macrophages (2-I: H&E stain, detail) with only presence of vary rare acid-fast bacteria (2-II: Ziehl-Neelsen stain, arrow). The lymph node excision of patient 3 is completely infiltrated by epitheloid to spindle-shaped macrophages admixed with neutrophilic granulocytes (3-I: H&E stain, detail). Areas of necrosis were present (not shown). In the Ziehl-Neelsen stain (3-II), many acid-fast bacteria can be identified. **b** A risk-based strategy for diagnosis of NTM: a multidisciplinary approach in patients after allo-HSCT. **c** Overview of risk factors, major signs and symptoms, radiology, and sites of NTM detection in the four patients with disseminated NTM. allo-HSCT allogeneic hematopietic stem cell transplantation, GVHD graft versus–host disease, IST immunosuppressive therapy, CMV cytomegalovirus, (M)MUD (mis)matched unrelated donor, (PET-)CT (positron emission tomogramphy-)computed tomography scan, BAL bronchoalveolar lavage, ZN Ziehl-Neelsen, DNA Deoxyribonucleic Acid, NTM nontuberculous mycobacteria, PCR Polymerase chain reaction, CVC central venous catheter, Pred prednisolone, Ruxo ruxolitinib, x data unknown.

lymphadenopathy, pulmonary involvement, or activity in various organs involved in the infection. It can be used to determine sites for biopsy, as well as for follow-up [12]. In addition, diagnostic work-up can be performed on bone marrow in case of cytopenias, on exit sites of venous catheters, and on respiratory samples. Therefore, bronchoalveolar lavage with NTM diagnostics should be performed in patients with respiratory complaints or pulmonary infiltrates on PET-CT.

It is important to send material both to microbiology and pathology departments. Mycobacterial cultures require special media and prolonged incubation as it can take up to 8 weeks for mycobacteria to grow. The pathologist is able to determine the presence of granulomas and acid-fast bacilli on histological samples. A polymerase chain reaction (PCR) on DNA extracted from paraffin-embedded material and subsequent sequencing may allow detection of the pathogen when cultures remain negative. An infectiologist should be involved for advice on the antibiotic regimen of choice, duration of therapy, and follow-up.

In summary, we advocate for increased awareness of disseminated NTM infections after allo-HSCT. Therefore we propose a structured work-up based on risk factors and clinical signs and symptoms, involving a multidisciplinary team of hematologists, infectiologists, pathologists, microbiologists, radiologists, and pulmonologists (Fig. 1b). Advantages of this systematic, multidisciplinary approach include early diagnosis and rapid intervention for this potentially fatal condition. We would like to emphasize that no external validation has been performed, due to the very rare nature of disseminated NTM infections. Whether our approach will lead to improved outcomes, thus remains to be evaluated in future studies.

Laura G. M. Daenen[1]✉, Jan-Tom van der Bruggen[2], Roos J. Leguit[3], Lotte E. van der Wagen[1], Anna van Rhenen[1], Herman F. Wunderink[2], Moniek A. de Witte[1], Anke H. W. Bruns[4,5] and Jurgen Kuball[1,5]

[1]Department of Hematology, University Medical Center, Utrecht, the Netherlands. [2]Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands. [3]Department of Pathology, University Medical Center, Utrecht, the Netherlands. [4]Department of Infectious Diseases, University Medical Center, Utrecht, the Netherlands. [5]These authors contributed equally: Anke H. W. Bruns, Jurgen Kuball. ✉email: l.g.m.daenen-3@umcutrecht.nl

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Al-Anazi KA, Al-Jasser AM, Al-Anazi WK. Infections caused by non-tuberculous mycobacteria in recipients of hematopoietic stem cell transplantation. Front Oncol. 2014;4:311.
2. Beswick J, Shin E, Michelis FV, Thyagu S, Viswabandya A, Lipton JH, et al. Incidence and risk factors for nontuberculous mycobacterial infection after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transpl. 2018;24:366–72.
3. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of non-tuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367–416.
4. Wobma H, Chang AK, Jin Z, Baker C, Garvin J, George D, et al. Low CD4 count may be a risk factor for non-tuberculous mycobacteria infection in pediatric hematopoietic cell transplant recipients. Pediatr Transpl. 2021;25:e13994.
5. Unal E, Yen C, Saiman L, George D, Della-Latta P, van de Ven C, et al. A low incidence of nontuberculous mycobacterial infections in pediatric hematopoietic stem cell transplantation recipients. Biol Blood Marrow Transpl. 2006;12:1188–97.
6. Weinstock DM, Feinstein MB, Sepkowitz KA, Jakubowski A. High rates of infection and colonization by nontuberculous mycobacteria after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transpl. 2003;31:1015–21.
7. Liu YC, Wu CJ, Ko PS, Chien SH, Fan NW, Wang HY, et al. Mycobacterial infections in adult recipients of allogeneic hematopoietic stem cell transplantation: a cohort study in a high endemic area. J Microbiol Immunol Infect. 2020;53:274–82.
8. Dirac MA, Horan KL, Doody DR, Meschke JS, Park DR, Jackson LA, et al. Environment or host? A case-control study of risk factors for Mycobacterium avium complex lung disease. Am J Respir Crit Care Med. 2012;186:684–91.
9. Kompa KG, Trottier CA, Hyman CL, Kohli R. Disseminated mycobacterium avium complex myositis in a patient with graft-versus-host disease. Open Forum Infect Dis. 2022;9:ofac385.
10. Dousa KM, Babiker A, Van Aartsen D, Shah N, Bonomo RA, Johnson JL, et al. Ibrutinib therapy and mycobacterium chelonae skin and soft tissue infection. Open Forum Infect Dis. 2018;5:ofy168.
11. Bergeron A, Mikulska M, De Greef J, Bondeelle L, Franquet T, Herrmann JL, et al. Mycobacterial infections in adults with haematological malignancies and haematopoietic stem cell transplants: guidelines from the 8th European Conference on Infections in Leukaemia. Lancet Infect Dis. 2022;22:e359–e69.
12. Hong SJ, Kim TJ, Lee JH, Park JS. Nontuberculous mycobacterial pulmonary disease mimicking lung cancer: clinicoradiologic features and diagnostic implications. Medicines. 2016;95:e3978.

AUTHOR CONTRIBUTIONS

LGMD was responsible for the literature review, updating reference lists, and creating Fig. 1b/c and the Supplementary table. LGMD, AHWB, and JK wrote the report. JTvdB and HFW gave treatment advice and provided feedback on the report. RJL was the pathologist involved, created Fig. 1a and provided feedback on the report. LEvdW, AvR, and MAdW were involved in treating the patients and provided feedback on the report.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-023-02011-6.

Correspondence and requests for materials should be addressed to Laura G. M. Daenen.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.