Clinical and Laboratory Characteristics of Patients with Nontuberculous *Mycobacterium* Bloodstream Infection in a Tertiary Referral Hospital in Beijing, China

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Abstract

Background: Nontuberculous *Mycobacterium* (NTM) bloodstream infection (BSI) is relatively rare. We aimed in this study to evaluate the clinical characteristics, laboratory evaluation, and outcomes of patients with NTM BSI.

Methods: We retrospectively reviewed the clinical records of inpatients with NTM BSI at our institution between January 2008 and January 2015 and recorded clinical parameters including age, gender, underlying disease, clinical manifestation, organs involved with NTM disease, species of NTM, laboratory data, treatment and outcome of these patients. We also reviewed the reported cases and case series of NTM BSI by searching PubMed, EMBASE, and Wanfang databases. Data of normal distribution were expressed by mean ± standard deviation (SD). Data of nonnormal distribution were expressed by median and interquartile range (IQR).

Results: Among the ten patients with NTM BSI, the median age was 51 years (IQR 29–57 years) and three patients were males. Eight patients were immunocompromised, with underlying diseases including human immunodeficiency virus (HIV) infection (one patient), rheumatic diseases (two patients), breast cancer (one patient), myelodysplastic syndrome (two patients), and aplastic anemia (two patients). Other organ(s) involved were lung (two patients), endocardium (two patients), brain, spinal cord, and soft tissue (one each patient). The median lymphocyte was 0.66×10^9/L (IQR $0.24–1.93 \times 10^9$/L). The median cluster of differentiation 4 (CD4) cell count was 179/mm^3 (IQR 82–619/mm^3). Five patients died (three with hematological diseases, one with breast cancer, and one with rheumatic disease), three recovered, and two were lost to follow-up.

Conclusions: We reported all cases in our hospital diagnosed with bloodstream NTM infection that was rarely reported. In this group of patients, patients usually had a high fever and could have multiple organ involvements. All patients with poor prognosis had underlying diseases.

Key words: Bloodstream Infection; Hematogenous Disseminated; Nontuberculous *Mycobacterium*

Introduction

Mycobacterium includes *Mycobacterium tuberculosis* (MTB) and nontuberculous *Mycobacterium* (NTM). NTM are ubiquitous microorganisms in the environment. Most NTM is found in wet soil, natural waters, and even in tap water.[1] They are not common causes of invasive diseases in immunocompetent individuals. Diseases and therapies that reduce cell-mediated immunity increase the risk of NTM disease. Acquired immunodeficiency syndrome (AIDS), cancer, and hematologic and solid organ transplants have been identified as associated with NTM disease. More recently, immunosuppressive drugs including anti-tumor

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necrosis factor biologics have been associated with NTM disease in population-based studies.[2] NTM disease has also been reported in patients with rheumatic and autoimmune diseases, such as in those with systemic lupus erythematosus (SLE).[3]

Extrapulmonary NTM disease, including disseminated, skin, and catheter-related disease, is more common in immunosuppressed patients compared to immunocompetent patients.[2] However, hematogenous disseminated NTM or NTM bloodstream infection (BSI) is a severe form of NTM disease as overall in-hospital mortality was reported to be 41.7% in AIDS patients.[4] However, relevant reports on NTM BSI are scarce with most published data emerging from the human immunodeficiency virus (HIV) infected patients.[4-6] To add to the knowledge regarding NTM BSI among the general population and immunocompromised patients admitted to the general hospital and to arouse clinicians to pay more attention to this severe form of NTM disease, we retrospectively evaluated all patients with NTM BSI who were admitted to our institution, a major national referral hospital in Beijing, China, between January 2008 and January 2015.

Methods

Study subjects

We searched the electronic database in the clinical microbiology laboratory at our institution and found 58 reports of positive *Mycobacterium* species from peripheral blood samples between January 2008 and January 2015. Forty-eight cases of MTB were excluded. For the remaining ten patients included in the final analysis, information including demographics, underlying diseases, clinical presentation, laboratory data, time of positive culture results, type of antimicrobial directed NTM therapy, and outcomes was collected from the medical records. This study was reviewed and approved by the Institutional Review Board at our institution and waiver of consent was granted because this was a retrospective and observational study.

We also reviewed the past case reports and case series of NTM BSI by searching the PubMed, EMBASE, and Wanfang databases up to February 29, 2016. We used the search terms "*Non-tuberculous Mycobacterium*," and "bloodstream infection," or "bacteremia" or "blood culture" or "hematogenous disseminated." The inclusion criterion was open published full texts, English or Chinese, and NTM BSI diagnosed by positive blood cultures.

Laboratory diagnosis

The laboratory diagnosis of NTM from blood was performed as following. Peripheral blood cultures were collected and inoculated into a liquid culture method (BacT ALERT MP [BioMerieux] from 2008 to 2010 and BD MGIT 960 [BD] after 2010). When a positive culture of *Mycobacterium* species was confirmed, MTB colloidal gold method of kabely kit was used to identify MTB or NTM. Then, chip hybridization was performed for species identification.

Statistical analysis

We used the Kolmogorov-Smirnov test to check if variants followed normal distribution. Measurement data of normal distribution were expressed by mean ± standard deviation (SD), and measurement data of nonnormal distribution were expressed by median and interquartile range (IQR). Statistical analysis was performed by the SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics are summarized in Table 1. Among the ten patients included, three patients were males and the median age was 51 years (IQR 29–57 years). Eight patients were immunocompromised, with underlying conditions including HIV infection (one patient, with a cluster of differentiation 4 [CD4] cell count of 15/mm^3), rheumatic diseases (two patients), breast cancer (one patient), aplastic anemia (AA, two patients), and myelodysplastic syndrome (MDS, two patients). The median peak temperature was 39.8°C (IQR 39.3–40.0°C). Three patients had night sweats, and eight patients had weight loss. Six patients had other organ(s) involvement, and they all had underlying diseases. Other organ(s) involvement included the lung in three patients, endocardium in two patients, brain, spinal cord, and soft tissue in one each patient. Two patients had more than one organ involved.

The laboratory examinations are shown in Table 2. The median leukocyte was 9.72 × 10^9/L, (IQR 0.86–21.08 × 10^9/L). The median lymphocyte was 0.66 × 10^9/L, (IQR 0.24–1.93 × 10^9/L). The median thrombocyte was 94 × 10^9/L, (IQR 41–303 × 10^9/L). The median hemoglobin was 65 g/L, (50–89 g/L). All patients had increased erythrocyte sedimentation rate with a median of 135 mm/h (IQR 59–140 mm/h). Eight patients had hypersensitive C-reactive protein examination, and the median value was 171.15 mg/L (IQR 61.31–202.73 mg/L). Eight patients had T-cell and B-cell subsets tests, and the median CD4 counts were 179/mm^3 (IQR 82–619/mm^3) and the median CD8 counts were 422/mm^3 (IQR 167–517/mm^3).

Among the eight patients who had a T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK) done before diagnosis, one patient of *Mycobacterium kansasii* BSI had a positive result with 32 spots forming cells/10^6 peripheral blood mononuclear cells.

Mycobacterium intracellulare was identified in two patients, *Mycobacterium abscessus/chelonae* complex was also identified in two patients, *Mycobacterium fortuitum* and *Mycobacterium kansasii* were identified in one patient. The median time to positive culture was 11.5 days (IQR 6.8–18.8 days) in the study. Three species were rapidly grown mycobacteria (RGM).

All the patients were diagnosed and treated in-hospital. Till the last follow-up in November 2015 (the median follow-up time was 43 months, [IQR 16–63 months]), two patients were lost to follow-up, five patients died, three patients improved after anti-NTM treatment. One patient received

Table 1: Demographics, underlying diseases, organs involved, laboratory data, treatment, and outcome of the ten patients in our hospital

Cases	Age (years)/ gender	Underlying conditions	Other organs involved	Identification of NTM	Treatment	Outcome
1	58/male	HIV-infected	Lung, brain, and spinal cord	NA	Isoniazid, clarithromycin, levofloxacin, ethambutol, amikacin	Improved
2	21/female	AA	Endocardium	*M. fortuitum*	Amikacin, cefoxitin, SMZ/TMP, minocycline, clarithromycin, and linezolid	Died
3	45/male	None	No	NA	Clarithromycin, ethambutol, amikacin, and levofloxacin	Lost to follow-up
4	58/female	MDS	Lung, marrow	NA	Rifampicin, isoniazid, ethambutol, pyrazinamide, amikacin, and moxifloxacin	Died
5	32/female	SLE	No	*M. kansasii*	Ethambutol, clarithromycin, and moxifloxacin (resistant to INH)	Improved
6	56/female	Breast cancer	No	NA	Moxifloxacin, amikacin, and clarithromycin	Died
7	21/female	AA	Soft tissue	*M. intracellulare*	Azithromycin, rifampicin, ethambutol, amikacin, and moxifloxacin	Died
8	57/female	MDS	Lung	*M. intracellulare*	Isoniazid, rifampicin, ethambutol, and levofloxacin	Lost to follow-up
9	41/male	TA	Endocardium	*M. abscessus*	Clarithromycin, ethambutol, imipenem, levofloxacin, and amikacin	Died
10	56/female	None	No	*M. chelonae*/ *M. abscessus*	Clarithromycin, ethambutol, imipenem, and moxifloxacin	Improved

NTM: Nontuberculous *Mycobacterium*; HIV: Human immunodeficiency virus; NA: Not available; AA: Aplastic anemia; SMZ/TMP: Sulfamethoxazole/ trimethoprim; INH: Isoniazid; MDS: Myelodysplastic syndrome; SLE: Systemic lupus erythematosus; TA: Takayasu arteritis; *M. fortuitum*: *Mycobacterium fortuitum*; *M. kansasii*: *Mycobacterium kansasii*; *M. intracellulare*: *Mycobacterium intracellulare*; *M. chelonae*: *Mycobacterium chelonae*; *M. abscessus*: *Mycobacterium abscessus.*

Table 2: Laboratory examinations (routine blood test, ESR, and hsCRP) of the ten patients in-hospital

Cases	Leukocyte ($\times 10^9$/L)	Lymphocytes ($\times 10^9$/L)	Hemoglobin (g/L)	Platelet ($\times 10^9$/L)	ESR (mm/h)	hsCRP (mg/L)
1	19.10	0.57	51	364	140	177.34
2	0.50	0.28	47	6	140	NA
3	27.00	2.98	71	790	140	226.52
4	0.98	0.19	56	71	140	NA
5	11.28	0.76	78	283	130	16.32
6	7.30	1.84	88	82	28	59.21
7	12.00	0.25	59	51	140	174.30
8	0.25	0.02	46	9	39	168.00
9	8.16	0.74	109	105	66	67.59
10	47.25	2.20	92	275	108	211.20

ESR: Erythrocyte sedimentation rate, normal range: <20 mm/h; hsCRP: Hypersensitive C-reactive protein, normal range: <3 mg/L; NA: Not available.

2.5 years of anti-NTM drugs, one patient received one year of anti-NTM drugs, and one patient was still on treatment which started one year ago. Among the three patients, one had no underlying diseases and one had SLE with the SLE disease activity index of zero at diagnosis of NTM BSI. The remaining one with HIV infection received empiric anti-tuberculosis (TB) treatment before the result of the blood culture. All the patients who died during follow-up had underlying diseases, with hematological diseases in three patients (AA in two patients and MDS in one patient) and breast cancer and rheumatic disease (Takayasu Arteritis, TA) in one patient. The species of NTM among patients who died were *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium intracellulare*.

Discussion

In the study, we reported all cases diagnosed in our institution with NTM BSI which were rarely reported before, especially in China. The data showed that patients with NTM BSI were mostly immunocompromised and usually had multiple organ involvement. The prognosis was poor.

It is known that biological agents such as infliximab increase the risk of *tuberculosis*. Less is known about its association with the development of *Mycobacterium* other than tuberculosis (MOTT) infection.[7] Besides the use of infliximab, a rapidly increasing number of people face challenging conditions such as HIV infection, rheumatic diseases, and cancers. This growing proportion of the immunocompromised population is at risk for severe forms of *Mycobacterium* infection, especially dissemination and BSI with poor outcomes.[1] The biological variation among NTM is great regarding the potential to cause clinical diseases in predisposed hosts and to affect various target organs or tissues.[1] The course of disease and development of

infection depends on the characteristics of the NTM species, the presence of predisposing host factors, and the clinical setting.[8] Autosomal mutations and X-linked mutations have been reported to confer susceptibility to disseminated nontuberculous mycobacterial infection. GATA binding protein 2 deficiency and anti-interferon-γ autoantibodies also give rise to disseminated infection.[9]

T-cell and B-cell subsets examined in our group of patients showed a low median CD4 count (179/mm^3), and routine blood test showed low median lymphocytes (0.66×10^9/L), which might be the reason why these patients were susceptible to NTM infections.

We conducted a literature review to obtain a broader perspective of the topic. A total of 179 papers were initially spotted out, six duplicate papers were excluded first. Thirty-nine papers were excluded by title screening for no relation with NTM BSI. Three were excluded for being written in neither English nor Chinese. During abstract viewing, another 57 papers of MTB BSI were excluded, 41 papers which were not cases or case series were excluded, and five papers which were meeting abstracts with no full texts were then excluded. After full-paper evaluation, 16 were excluded because they did not meet the diagnostic criterion. Finally, 12 papers including 22 cases were included [Table 3]. The process was shown as a flow chart in Figure 1. Table 3 summarized the 22 cases reported[7,10-20] which were compared with patients in our hospital.

Among the two groups of patients, most patients were immunocompromised in both groups (80% and 91%). Among patients in our hospital, lung was the most common organ involved, followed by endocardium, brain, spinal cord, and soft tissue. Among cases previously reported, lung was also the most common organ involved, followed by gut, endocardium, and subcutaneous implantable cardioverter defibrillator insertion site. Some patients had more than one organ involved. The most common species of NTM was *Mycobacterium chelonae/abscessus* in our group, and *Mycobacterium mucogenicum* in cases reported, and distribution of other species of NTM varied in the two groups. After the treatment, the proportion of patients died in the study was higher than cases reported. One reason to explain this might be the sample size of both groups. In addition, Peking Union Medical College Hospital is the national center for complicated and severe diseases in China. Patients admitted to our hospital often had severe and complicated conditions, which might be another reason for the poorer prognosis. Overall, in previously reported case group, 23–50% of patients died. We also observed that all patients who died had underlying diseases and/or received immunosuppressive therapy in both groups, including hematological diseases, rheumatic diseases, solid tumors, HIV infection, and interstitial pneumonia. In the study, patients who died had *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium intracellulare* BSI. In reported cases, among the five patients who died, two patients had *Mycobacterium mucogenicum* BSI, one each patient had

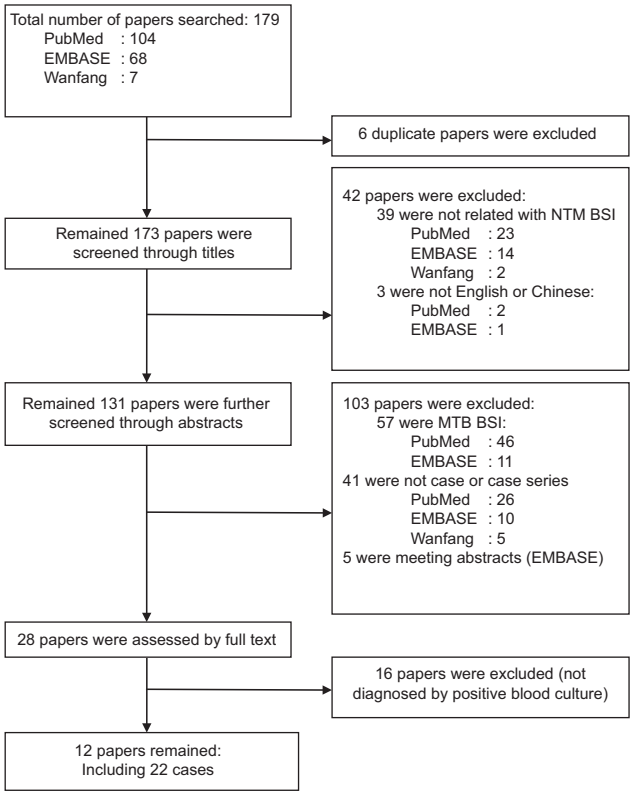

Figure 1: The flowchart for the result of literature search. NTM: Nontuberculous *Mycobacterium*; BSI: Bloodstream infection; MTB: *Mycobacterium tuberculosis*.

Mycobacterium abscessus, Mycobacterium chelonae, and *Mycobacterium arupense* BSI. As Kotilainen *et al.*[21] showed in a study of 167 non-HIV adult patients with NTM disease, patients with pulmonary *Mycobacterium avium* complex (MAC) had a significantly lower risk of death as compared to patients with pulmonary infection of other NTM (hazard ratio [*HR*] 0.50, 95% confidence interval [*CI*] 0.33–0.77, $P = 0.002$). Moreover, when compared to patients with pulmonary infection caused by RGM, the risk of death was lower with pulmonary MAC patients (*HR* 0.47, 95% *CI* 0.25–0.87, $P = 0.020$). In another study by Hsieh *et al.*[6] of AIDS patients, 22 cases of disseminated TB and 15 cases of disseminated MAC were analyzed, the patients with disseminated TB survived much longer than patients with disseminated MAC (mean survival, 96 vs. 22 weeks, $P = 0.008$). However, these were all AIDS patients, which were different from the study subjects. Therefore, the final outcomes might vary due to different forms of NTM disease, different species of NTM, and different health conditions of the patients. Further studies might be done to analyze possible risk factors related to poor prognosis.

Ten patients with central venous catheters in haemato-oncology unit were considered to be caused by contaminated water supply. The species identified were *Mycobacterium mucogenicum* in nine patients and *Mycobacterium neoaurum* in one patient.[12,20] This usually occurred in immunocompromised hosts, especially in patients with underlying malignancies. Water is the main

Table 3: Demographics, underlying diseases, organs involved, laboratory data, treatment, and outcome of the 22 patients in the literature review

Cases	Age (years)/ gender	Underlying conditions	Other organs involved	Identification of NTM	Treatment	Outcome
1[7]	36/female	Crohn's disease	Lung	*M. avium* complex	Rifampin, ethambutol, ciprofloxacin, and azithromycin	Improved
2[10]	30/male	Intravenous drug use	Endocardium	*M. neoaurum*	Tobramycin, azithromycin, and moxifloxacin	Lost to follow-up
3[11]	76/male	Interstitial pneumonia	Lung	*M. abscessus*	Imipenem, cilastatin, amikacin, levofloxacin, and clarithromycin	Died
4[12]	62/female	NHL	None	*M. mucogenicum*	Multiple including clarithromycin	Died
5[12]	46/female	AML	None	*M. mucogenicum*	Ceftazidime, gentamicin, and teicoplanin	Improved
6[12]	41/male	AML	None	*M. neoaurum*	Meropenem	Improved
7[12]	42/male	NHL	None	*M. mucogenicum*	Ciprofloxacin and clarithromycin	Improved
8[12]	40/female	AML	None	*M. mucogenicum*	Ciprofloxacin	Improved
9[13]	16/male	ALL	None	*M. mucogenicum*	Meropenem, teicoplanin, and gentamicin	Improved
10[14]	22/male	HIV-infected	Gut	MAC	Azithromycin and ethambutol	Improved
11[14]	32/female	HIV-infected	Gut, lung	MAC	Azithromycin, amikacin, ethambutol, and sparfloxacin	Improved
12[15]	59/female	None	Subcutaneous ICD insertion site	*M. mageritense*	Ciprofloxacin and clarithromycin	Improved
13[16]	41/female	Rheumatic heart disease	Endocardium	*M. chelonae*	Rifampicin, clarithromycin, amikacin, and levofloxacin	Died
14[17]	26/male	Sickle cell disease; T1DM	None	*M. terrae* complex	Imipenem and amikacin	Improved
15[18]	55/male	HIV-infected	Lung	*M. arupense*	Clarithromycin, ethambutol, and rifabutin	Improved
16[18]	40/male	HIV-infected	None	*M. arupense*	Clarithromycin, ethambutol, and rifabutin	Died
17[19]	30/male	HIV-infected	Gut	*M. avium*	None (lost to follow-up when diagnosed)	Lost to follow-up
18[20]	15/male	ALL, Burkitt lymphoma	None	*M. mucogenicum*	Amikacin	Improved
19[20]	3/male	ALL	None	*M. mucogenicum*	Clarithromycin and ciprofloxacin	Improved
20[20]	5/male	Rhabdomyosarcoma	None	*M. mucogenicum*	None (died before the culture results were available)	Died
21[20]	5/female	Neuroblastoma	None	*M. mucogenicum*	Clarithromycin and ciprofloxacin	Improved
22[20]	17.5/male	AA	None	*M. mucogenicum*	Clarithromycin	Improved

NTM: Nontuberculous *Mycobacterium*; NHL: Non-Hodgkin lymphoma; AML: Acute myelocytic leukemia; ALL: Acute lymphoblastic leukemia; ICD: Implantable cardioverter defibrillator; HIV: Human immunodeficiency virus; T1DM: Type 1 diabetes mellitus; AA: Aplastic anemia; MAC: *Mycobacterium avium* complex; *M. mucogenicum*: *Mycobacterium mucogenicum*; *M. avium*: *Mycobacterium avium*; *M. arupense*: *Mycobacterium arupense*; *M. terrae*: *Mycobacterium terrae*; *M. neoaurum*: *Mycobacterium neoaurum*; *M. chelonae*: *Mycobacterium chelonae*; *M. mageritense*: *Mycobacterium mageritense*; *M. abscessus*: *Mycobacterium abscessus*.

source of NTM, which can be controlled by chlorination and monitoring of bacterial growth. In hospitals with hematology and oncology departments where patients are immunocompromised and with intravascular catheters, adequate disinfection of medical devices and water supply system should be ensured to avoid nosocomial outbreaks.[12,22]

In the study, eight patients had a T-SPOT.TB assay before the diagnosis of NTM BSI. As interferon-γ releasing assays (IGRAs) examine the MTB specific antigen early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10), all NTM infected samples would have negative results, but one patient had false positive result due to *Mycobacterium kansasii*. According to Adams *et al.*,[23] two NTM that affect humans, *Mycobacterium marinum* and *Mycobacterium kansasii*, contain the ESAT-6 or CFP-10 antigens used in the IGRA assays. Infection with either of these NTM has been shown to produce positive results in assays using these antigens.

There are also some limitations in the study. This is a retrospective study of small samples in a single center. The institution is a center for complicated and severe diseases in China. Patients in the hospital are often difficult to diagnose when admitted to hospital and in more severe conditions. Therefore, the findings might not be representative of patients in other places.

In summary, as the immunocompromised population is increasing, MOTT infection should be paid attention to including BSI. Physicians should pay attention to this severe form of NTM infection, especially in patients with underlying diseases, high fever, and multiple organ involvement. Not only blood culture of aerobic and anaerobic bacteria but also blood culture of *Mycobacterium* should be performed.

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Conflicts of interest

There are no conflicts of interest.

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