Original Article

Cytomegalovirus viremia is associated with poor outcomes in AIDS patients with disseminated nontuberculous mycobacterial disease

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SUMMARY   Both cytomegalovirus (CMV) viremia and disseminated nontuberculous mycobacterial (NTM) disease are common opportunistic infections in AIDS patients. Whether concurrent CMV viremia is associated with mortality in patients with AIDS and disseminated NTM disease is unknown. Subjects were patients with AIDS and disseminated NTM disease seen at a single center from January 2015 to April 2021. Data were retrospectively collected. Differences in demographics and clinical characteristics and hospitalization survival rates were compared between patients with disseminated NTM and with CMV viremia or not. Subjects were 113 AIDS patients with disseminated NTM who were seen at this Hospital from January 2015 to April 2021. Twenty-six of the patients had CMV viremia and 87 did not. The median age was 36 years (interquartile range [IQR] 29-42) and 108 patients were male (96%). The median CD4 count was 7 cells/µL (IQR 3-17). The median plasma CMV viral load was 9,245 IU/mL (IQR 3147-45725). The serum albumin of patients with CMV viremia was significantly lower than that of patients without CMV viremia ($P = 0.03$). Compared to patients without CMV viremia (81.6%), patients with CMV viremia had a significantly poorer prognosis ($P = 0.01$). Cox regression analysis indicated that the risk of a poor prognosis in patients with CMV viremia was 4.7 times higher than that in patients without CMV viremia ($P = 0.003$), and patients with CD8 more than 250/µL had a better prognosis ($P = 0.02$). CMV viremia increases the risk of a poor prognosis in patients with AIDS and a disseminated NTM infection. A routine CMV DNA test should be performed on patients with AIDS and disseminated NTM disease in order to reduce the risk of death.

Keywords   AIDS, disseminated, nontuberculous Mycobacteria, Cytomegalovirus, clinical characteristics, outcomes

1. Introduction

Nontuberculous Mycobacteria (NTM) are ubiquitous in the environment and usually infect immunocompromised populations (*1,2*). A disseminated NTM infection mostly occurs in HIV-infected patients with a CD4 count below 50/µL (*3*). In the pre-antiretroviral therapy (ART) era, up to 43% of AIDS patients were reported to be infected with disseminated NTM, and especially those with severe immunodeficiency (*4*). The most common NTM is *Mycobacterium avium*-intracellulare complex, which accounted for 71% of pulmonary NTM infections in Australia, followed by 54% in Asia, 52% in North America, 51% in South Africa, 37% in Europe, and 31% in South America (*5*). In the post-ART era, the rate

of NTM infections and their mortality have gradually decreased in AIDS patients in developed countries (*5*). In Asia, Africa, and Latin America, the rate of NTM infection in AIDS continues to rise, and NTM infection is a key reason for the increased hospitalization and mortality of AIDS patients (*6,7*). In Shanghai, China, the rate of NTM identification among AIDS patients is also increasing. A retrospective study by the current authors' team found that NTM accounted for 41 (41/101, 41%) of the isolates identified using 16S rDNA sequencing in 2014, 64 (64/137, 47%) in 2015, and 72 (72/162, 44%) in 2016 (*8*).

CMV is a double-stranded DNA virus belonging to the herpes virus family that can cause disseminated or localized end-organ disease in HIV-infected patients

with advanced immunosuppression (*9*). Positivity for CMV in HIV-infected people is much higher than that in HIV-negative people. CMV viremia, as a better indicator of active disease, has a prevalence of 2% to 23% in African cohorts living with HIV (*10*). Those with cell-mediated immunodeficiencies or undergoing cell-mediated immunosuppression cannot mount an adequate immune response to CMV and therefore are at the highest risk of CMV viremia (*11*). Ward *et al.* (*12*) found that CMV viremia was associated with a trend toward increased mortality in persons living with HIV who had tuberculosis, and particularly in older patients.

Few studies have examined co-infections with disseminated NTM and CMV, and most of the literature is in the form of case reports. Little is known regarding whether active CMV replication contributes to an increased risk of death in patients with AIDS and a disseminated NTM infection. The current study compiled serum CMV DNA results from patients with AIDS and a disseminated NTM infection at the Shanghai Public Health Clinical Center (SPHCC), it compared the differences in clinical characteristics and prognosis, and it retrospectively determined whether CMV viremia was a risk factor for a poor prognosis in patients with AIDS and a disseminated NTM infection.

2. Methods

2.1. Ethical statement

Ethical approval was granted by the Ethics Committee of the SPHCC (Ethics approval No. 2017-S022-04). The committee decided to waive the need for written informed consent from the participants in this study since the data were collected retrospectively and anonymous.

2.2. Study populations and clinical data

Data from January 1, 2015 to April 30, 2021 were retrospectively collected. Subjects were 113 patients with a disseminated NTM infection identified *via* blood culture (106), hydrothorax (2), lymph node aspiration (4), or ascites (1) in patients seen at the SPHCC. Electronic medical records were searched for HIV-positive patients diagnosed with a disseminated NTM infection. An NTM infection was identified based on testing negative for the MPT64 antigen or 16S rRNA (to identify the species of NTM). CMV DNA was detected in accordance with the method reported in the literature (*13*). Based on CMV DNA results, patients were divided into two groups: patients with CMV viremia (CMV DNA > 2,000 copies/mL) and patients without CMV (CMV DNA < 2,000 copies/mL). Laboratory tests (blood routine test, biochemistry, procalcitonin (PCT), CD4 and CD8 cell count, and C-reactive protein (CRP)) and outcomes during hospitalization were analyzed.

A blood culture or some other type of pathogen detection was performed along with a blood routine test, biochemistry, and cellular immunity as well as measurement of PCT and CRP. Mycobacterium was cultured and detected using the BACTEC MGIT 960 system, and it was operated in accordance with the manufacturer's instructions. In this study, a disseminated NTM infection was immediately treated with a combination of rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z) administered according to guidelines (*14,15*). For a severe infection, empirical treatment was given by adding macrolides and fluoroquinolones to the HREZ regimen. When the species was identified as NTM, H and Z were discontinued and amikacin were added to the regimen depending on the patient's clinical status. Patients were divided into those who survived and those with a poor prognosis (death or terminal discharge) depending on the final clinical outcome.

2.3. Statistical analysis

A Mann-Whitney test (for numeric variables) and Fisher's exact test (for categorical variables) were used to compare demographic and clinical characteristics between patients with CMV viremia and those without CMV viremia.

Cox regression analysis was used to analyze the risk factors for survival and define the outcome variables: 1 = death or terminal discharge, 0 = normal discharge; Time variable: duration of hospitalization. Independent variables: CMV viremia (0 = negative, 1 = positive), age (1 = < 35 years, 2 = ≥ 35 years), gender (1 = male, 2 = female), white blood cell count (1 = < 4.0×10^9/L, 2 = ≥ 4.0×10^9/L), neutrophil count (1 = < 3.5×10^9/L, 2 = ≥ 3.5×10^9/L), hemoglobin (Hb) level (1 = < 90 g/L, 2 = ≥ 90 g/L), serum albumin (Alb) level (1 = < 30 g/L, 2 = ≥ 30 g/L), CRP level (1 = < 50 mg/L, 2 = ≥ 50 mg/L), PCT level (1 = < 0.25 ng/mL, 2 = ≥ 0.25 ng/mL), erythrocyte sedimentation rate (ESR) (1 = < 75 mm/h, 2 = ≥ 75 mm/h), CD4 cell count (1 = < 10 cells/uL, 2 = ≥ 10 cells/uL), CD8 cell count (1 = < 250 cells/uL, 2 = ≥ 250 cells/uL), 1,3-β-D-glucose (BDG) level (1 = < 12pg/mL, 2 = ≥ 12 pg/mL), the time of ART (0 = within 30 days, 1 = more than 30 days). The variables included in the multivariate model were selected based on a significance level of *P* < 0.1 in univariate analysis. For survival analysis, patient survival was calculated in days from admission to death, terminal discharge, or normal discharge after admission, whichever occurred first. The difference was statistically significant when *P* < 0.05. Data were analyzed using IBM SPSS version 22.0 (IBM SPSS, Inc., Armonk, NY, USA), and survival was plotted using GraphPad Prism version 7.0.

3. Results

3.1. Patient selection and the demographic and clinical

characteristics of patients with AIDS and disseminated NTM disease

Data on 113 patients with a disseminated NTM infection seen at the SPHCC from January 2015 to April 2021 were analyzed. Twenty-six patients had CMV viremia and 87 did not. For details on patient selection, see Figure 1. The median age was 36 years (IQR 29-42) and 108 patients were male (96%). The median CD4 count was 7 cells/μL (IQR 3-17). Of the total patients, 89% (101/113) had CD4 < 50 cells/μL and 97% (110/113) had CD4 < 100 cells/μL. The median plasma CMV viral load was 9245 IU/mL (IQR 3147-45725). The serum albumin level in patients with CMV viremia was significantly lower than that in patients without CMV viremia ($P = 0.03$). The median CD4 count did not differ between patients with CMV viremia and patients without CMV viremia ($P = 0.37$). Compared to patients without CMV viremia, patients with CMV viremia had a significantly poorer prognosis ($P = 0.01$). Other clinical characteristics such as the CD8 cell count, the ratio of CD4/CD8 cells, blood culture conversion in days, the duration of hospitalization, and the proportion of patients receiving ART over 3 months later did not differ significantly between patients with CMV viremia and patients without CMV viremia (Table 1).
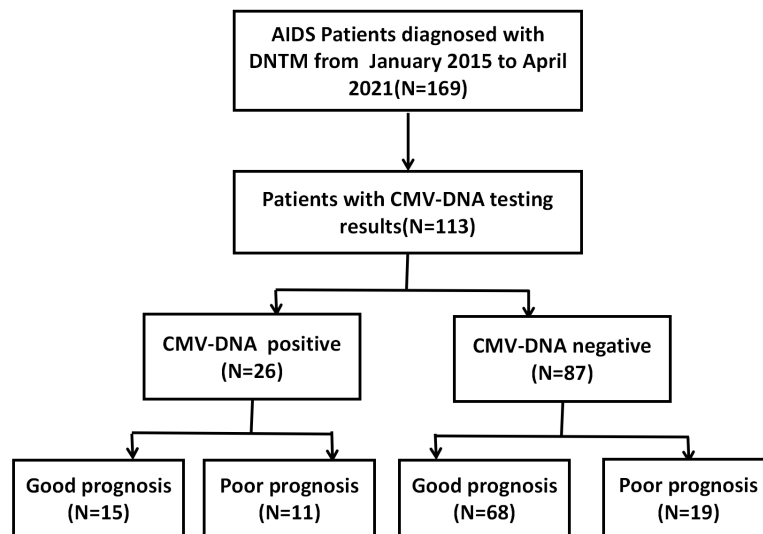

Figure 1. The flow chart for selection of eligible patients.

Table 1. The demographic and clinical characteristics of patients with AIDS and disseminated NTM disease

Demographic and clinical data	Normal range	Total cases ($n = 113$)	CMV viremia ($n = 26$)	No CMV viremia ($n = 87$)	P value
Age (years)	-	36 (29-42)	35 (29-49)	36 (29-41)	0.89
Male (%)	-	108 (95.6)	25 (96.2)	83 (95.4)	0.87[※]
WBC count (×10⁹/L)	3.5-9.5	4.0 (2.7-5.4)	4.5 (3.1-5.8)	4.0 (2.5-5.3)	0.26
Neutrophil count (×10⁹/L)	1.8-6.30	3.2 (1.9-4.5)	3.3 (2.4-4.7)	3.1 (1.8-4.2)	0.31
Hemoglobin (g/L)	115-150	87 (69-106)	85 (63-96)	91 (71-106)	0.15
CD4 (cells/uL)	41-1,590	7 (3-17)	6 (1-14)	7 (3-19)	0.37
CD8 (cells/uL)	19-1,140	258 (109-468), [§]$N = 108$	262 (67-384) [§]$N = 25$	254 (120-487) [§]$N = 83$	0.42
Ratio of CD4/CD8 cells	0.9-3.6	0.03 (0.01-0.09) [§]$N = 108$	0.03 (0.01-0.06) [§]$N = 25$	0.03 (0.12-0.09) [§]$N = 83$	0.95
Serum albumin (g/L)	40-55	30 (25-33)	27 (21-31)	31 (25-34)	0.03
CRP (mg/L)	0-10	50.7 (18.7-99.5) [§]$N = 96$	73.9 (22.1-117.2) [§]$N = 22$	39.9 (17.7-95.6) [§]$N = 74$	0.21
PCT (ng/mL)	0-0.05	0.25 (0.10-0.94) [§]$N = 106$	0.24 (0.09-3.80) [§]$N = 24$	0.26 (0.11-0.87) [§]$N = 82$	0.76
ESR (mm/h)	0-15	75 (57-94) [§]$N = 67$	79 (65-105) [§]$N = 15$	75 (56-94) [§]$N = 52$	0.56
BDG (pg/mL)	< 60	12 (10-120) [§]$N = 108$	26 (10-127) [§]$N = 24$	12 (10-114) [§]$N = 84$	0.64
Culture conversion (days)	-	14 (10-21)	14 (10-28)	14 (10-21)	0.57
Hospitalization (days)	-	19 (12-36)	16 (10-33)	21 (12-38)	0.27
ART > 30 days	-	24 (21.2)	3 (11.5)	21 (24.1)	0.17[※]
Poor prognosis	-	27 (23.9)	11 (42.3)	16 (18.4)	0.01[※]

[※]According to Fisher's exact test, otherwise according to the Mann-Whitney test; [§]N indicates the number of patients for whom clinical data were analyzed. WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; BDG:1,3-β-D-glucose; NTM: nontuberculous mycobacteria; CMV: cytomegalovirus; ART: antiretroviral therapy.

Table 2. COX regression analysis for patients with AIDS and disseminated NTM disease

Variables	Crude HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Gender	Reference	--	--			
Female	1.63	0.38-6.88	0.51			
WBC	Reference	--	--			
$\geq 4.0 \times 10^9$/L	0.64	0.30-1.38	0.26			
Neutrophil	Reference	--	--			
$\geq 3.5 \times 10^9$/L	0.81	0.37-1.77	0.60			
PCT	Reference	--	--			
≥ 0.25 ng/mL	1.38	0.63-3.00	0.42			
ESR	Reference	--	--			
≥ 75 mm/h	1.10	0.36-3.44	0.86			
Albumin	Reference	--	--			
≥ 30 g/L	0.56	0.25-1.26	0.16			
CD4	Reference	--	--			
≥ 10/uL	0.49	0.20-1.23	0.13			
Age	Reference	--	--			
≥ 35 years	0.51	0.24-1.09	0.08	0.98	0.37-2.58	0.97
Hemoglobin	Reference	--	--	--	--	--
≥ 90 g/L	0.43	0.19-0.98	0.04	0.50	0.18-1.40	0.19
CRP	Reference	--	--	--	--	--
≥ 50 mg/L	2.41	0.99-5.88	0.05	1.62	0.58-4.51	0.36
BDG	Reference	--	--	--	--	--
≥ 12pg/mL	0.50	0.22-1.13	0.09	0.52	0.19-1.42	0.20
ART	Reference	--	--	--	--	--
≥ 30 days	0.27	0.06-1.13	0.07	0.57	0.12-2.79	0.49
CD8	Reference	--	--	--	--	--
≥ 250/uL	0.44	0.19-1.02	0.06	0.29	0.10-0.85	0.02
CMV viremia	Reference	--	--	--	--	--
YES	2.71	1.26-5.86	0.01	4.68	1.68-13.05	0.003

WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate; BDG:1,3-β-D-glucose; NTM: nontuberculous mycobacteria; CMV: cytomegalovirus; ART: antiretroviral therapy.
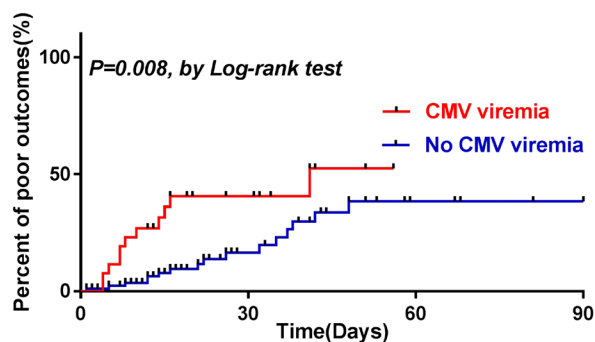

Figure 2. Survival analysis of patients with AIDS and disseminated NTM disease.

3.2. Comparison of the survival rate of patients with AIDS and disseminated NTM disease with and without CMV viremia

Of 113 patients with a disseminated NTM infection, 27 had a poor prognosis and 86 were discharged normally. Twelve patients died in hospital and 15 received a terminal discharge. In the patients with a disseminated NTM infection, the species was identified in 29 patients.

M. avium was detected in 25, M. intracellulare was detected in 2, *M. kansasii* was detected in 1, and *M. haemophilum* was detected in 1.

Cox regression analysis indicated that the risk of a poor prognosis in patients with CMV viremia was 4.7 times higher than that in patients without CMV viremia (*P* = 0.003), and patients with a CD8 cell count of more than 250 cells/uL had a better prognosis (*P* = 0.02), as shown in Table 2. Survival analysis indicated that patients with AIDS and a disseminated NTM infection had a longer survival and better prognosis than patients with AIDS, CMV viremia, and a disseminated NTM infection (Figure 2).

4. Discussion

The current results revealed that CMV viremia is associated with a nearly 5-fold increase in mortality in patients with AIDS and a disseminated NTM infection. This is a novel finding that corroborates CMV viremia as a detrimental biomarker in patients with AIDS and a disseminated NTM infection, irrespective of the presence or absence of end-organ CMV disease.

In China, population-based data indicate that the proportion of NTM among all mycobacterial isolates has increased from 11% to 23% (*16*). Isolates of NTM from patients with AIDS have also increased in recent years, and prognosis is poor without rapid identification and appropriate antibiotic therapy (*8*). Disseminated NTM disease, a key AIDS-defining opportunistic infection, is associated with significant morbidity and

mortality and with shorter survival. Both NTM disease and CMV disease are caused by intracellular pathogens requiring Type 1 T helper (Th1) cell immunity for protection (*17*). Viral infections can increase the production of Type 1 interferons (*e.g.*, interferon-alpha), which may subsequently impair Th1 cytokine (*e.g.*, interferon-gamma) responses (*18*).Thus, a concomitant infection with CMV could potentially counteract protective Th1 immune responses to a mycobacterial infection (*19*). The stimulation of peripheral blood mononuclear cells with CMV antigens results in lower levels of interferon-gamma and tumor necrosis factor alpha in CMV-seropositive versus CMV-seronegative patients (20).

CMV reactivation is associated with a higher mortality in AIDS patients with severe immunodeficiency (*21*). Two studies in different settings (Thailand (*22*) and South Africa (*23*)) confirmed that CMV viremia was associated with an increased risk of death despite prompt initiation of ART. Active CMV replication with viremia is associated with an over 2-fold increase in mortality in severely immunocompromised persons living with HIV who have cryptococcal meningitis (*24*). Looking specifically at patients with CMV viremia, those receiving preemptive anti-CMV therapy and in whom CMV DNA is no longer detectable have a better survival rate (*21*). Therefore, timely detection of a CMV infection and active anti-CMV treatment may improve patient prognosis. A routine CMV DNA test should be performed on patients with AIDS and disseminated NTM disease who have a low CD4 count.

Baseline serum albumin < 25g/L was an independent predictor of mortality in the competing risk model of patients with HIV and end-stage renal failure (*25*). The role of serum albumin in predicting illness and death is heavily influenced by inflammation (*26*). CMV replication have been shown to drive inflammation, and CMV coinfection may partially explain the inflammation noted in HIV-infected patients receiving ART (*27*). The current study found that the serum albumin level in patients with CMV viremia was lower than that in patients without CMV viremia, which also reflects the fact that an inflammatory reaction caused by CMV intensified the decrease in serum albumin. A variety of opportunistic infections occur at the same time, increasing the disease burden in patients. Excessive wasting of the body also leads to a decrease in serum albumin. Therefore, improved nutrition should be encouraged for patients with more complications. CMV viremia did not cause significant differences in other laboratory results. However, other reasons for the low level of serum albumin such as impaired liver synthesis and nephropathy were not noted, and this flaw may undermine the aforementioned explanation.

In this study, patients with AIDS and disseminated NTM disease who had a CD8 cell count of more than 250 cells/uL had a better prognosis. A study has reported that the CD8 counts may predict prognosis independent of the CD4 counts (*28*). In most cases, the end stage of HIV infection can cause both CD4 and CD8 depletion (*29*). The CD8 cell count may also indicate poor outcomes for AIDS patients with severe opportunistic infections since the low CD4 cell count in people infected with HIV is one of the main reasons for co-infection of NTM and CMV. The incidence of new cases of CMV end-organ disease has declined by ≥ 95% with the advent of ART (*30,31*). Therefore, early diagnosis of HIV infection and timely ART are crucial.

There are several limitations to this study. First, this study was a retrospective one, so many patients with HIV and a disseminated NTM infection were tested for CMV DNA. This may have reduced the sample size and produced bias in analysis. Second, some laboratory results are missing, reducing the statistical power. Third, data on HIV RNA were not collected in this study, so the impact of the HIV burden on prognosis could not be evaluated in more detail. Last, this was a single-center study, and caution should be exercised when extrapolating the current findings to the whole population in areas with a high incidence of NTM disease.

In conclusion, CMV viremia increases the risk of a poor prognosis in patients with AIDS and a disseminated NTM infection. A routine CMV DNA test should be performed on patients with AIDS and disseminated NTM disease in order to reduce the risk of death.

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