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Review Article

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Disseminated Nontuberculous Mycobacteria in HIV-Infected Patients

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Abstract

Nontuberculous mycobacteria are ubiquitous in the environment and are increasingly implicated in human diseases worldwide. Currently, there are more than 150 species of Mycobacterium and it is likely that more will be discovered. The rapid increase in identified species in recent years is due to improved culturing techniques and more precise differentiations of species. The application of highly active antiretroviral therapy for the treatment of HIV disease dramatically reduced rates of all opportunistic infections including nontuberculous mycobacteria. Despite this decline, nontuberculous mycobacterium remains one of the most commonly encountered opportunistic infections in AIDS patients.

Disseminated nontuberculous mycobacteria infections are seen exclusively among immunocompromised hosts, including those with AID. Disseminated disease is most commonly seen in association with profound immunosuppression. In HIV infected patients, dissemination does not typically occur unless the CD-4+ T-lymphocyte count is below 50/uL. Structural lung disease, such as chronic obstructive pulmonary disease, silicosis, pneumoconiosis or prior TB infection, predisposes to pulmonary infection. Nodular bronchiectasis is very strongly associated with nontuberculous mycobacteria infections. Disseminated Mycobacterium avium complex disease was one of the first opportunistic infections recognized as part of the syndrome of AIDS .Interest in disseminated Mycobacterium avium and nontuberculous mycobacteria infections increased as a result of the HIV epidemic, and therapeutic strategies to treat and prevent these diseases must be focused. Prevention and treatment regimens were lifelong because cure of nontuberculous mycobacteria was not achievable in AIDS patients with profound immune suppression.

Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment and are increasingly implicated in human diseases worldwide [1]. The hydrophobicity of NTM results in preferential aerosolization from water, and many of these organisms are resistant to high temperature and is relatively resistant to low pH [2, 3]. Given these characteristics of NTM it is not surprising that drinking water, household plumbing, peat rich soils, brackish marshes, and drainage water are reservoirs of NTM [4]. Water systems in hospitals, hemodialysis centers, and dental offices have particularly high rates of mycobacterium colonization [5].

Currently, there are more than 150 species of Mycobacterium and it is likely that more will be discovered. The rapid increase in identified species in recent years is due to improved culturing techniques and more precise differentiations of species. Species differentiation improved dramatically with the development of molecular techniques that enabled the detection of differences in the *16S rRNA* gene [6]. This gene is highly conserved amongst species and slight differences characterize different species.

NTM are most commonly classified by growth rate, either slowly growing or rapidly growing. The most common organism associated with pulmonary disease is the *Mycobacterium avium* complex (MAC), a slow growing NTM that encompasses many subspecies including *avium, silvaticum, hominissuis, and paratuberculosis, as well as the species intracellulare, arosiense, chimaera, colombiense, marseillense, timonense, bouchedurhonense, and ituriense*.

Disseminated NTM infections are seen exclusively among immunocompromised hosts, including those with AIDS [7-9]. Disseminated disease is most commonly seen in association with profound immunosuppression. In HIV infected patients, dissemination does not typically occur unless the CD-4+ T-lymphocyte count is below 50/uL [10]. Structural lung disease, such as chronic obstructive pulmonary disease (COPD), silicosis, pneumoconiosis or prior TB infection, predisposes to pulmonary infection. Nodular bronchiectasis is very strongly associated with NTM infections.

Disseminated *Mycobacterium avium* complex (MAC) disease was one of the first opportunistic infections recognized as part of the syndrome of AIDS [11]. Interest in disseminated MAC and nontuberculous mycobacteria (NTM) infections increased as a result of the HIV epidemic, and therapeutic strategies to treat and prevent these diseases must be focused [12-14]. Prevention and treatment

regimens were lifelong because cure of NTM was not achievable in AIDS patients with profound immune suppression.

The application of highly active antiretroviral therapy (HAART) for the treatment of HIV disease dramatically reduced rates of all opportunistic infections including NTM [15, 16]. Despite this decline, NTM remains one of the most commonly encountered opportunistic infections in AIDS patients [16]. Disease resulting from NTM now occurs in the following settings: in patients not receiving antiretroviral therapy, in patients who are intolerant or failing antiretroviral therapy, and in the early period following the initiation of HAART prior to immune recovery. HAART also altered the clinical approach to MAC and led to the recognition of new clinical syndromes

Pathogenesis in HIV-infected patients

Disseminated MAC is most likely a result of primary infection rather than reactivation. In vitro evidence showing that MAC can bind and invade intestinal cell lines supports the animal models showing that colonization of the gastrointestinal or respiratory tracts precedes disseminated disease [15]. The precise immune defect predisposing HIV infected patients to disseminated disease is unknown. *In vitro*, cells from HIV infected patients are able to ingest M avium and respond to interferon gamma [16]. Reduction in host production of cytokines, such as interferon gamma, increased production of M avium growth promoting cytokines, such as interleukin (IL)-6, may favor dissemination of NTM in HIV infection [14]. The propensity for developing disseminated NTM disease in HIV infected patients is dependent not only on the level of the host's immunity but also on the virulence of the organism. Support for this is found in the increased isolation of certain serotypes in disseminated disease and the fact that transfection of a plasmid into a no plasmid-containing strain of M avium is associated with increased intracellular replication [8]. Intracellular survival of M avium is enhanced by inhibition of phagosome-lysozyme fusion, and localization of the organism to less acidic vacuoles within the cell favors long-term survival [9]. Similar to other opportunistic infections, the development of MAC is associated with a more rapid progression of HIV disease and subsequent death. Many opportunistic infections, including disseminated M avium, activate lymphocytes. Because productive HIV infection requires cellular activation, HIV replication increases when an opportunistic infection develops. In one study, HIV RNA plasma levels increased after the onset of disseminated MAC [3]. Increased HIV replication within macrophages has also been reported in patients with disseminated disease [6].

Mycobacterium Avium Complex

The *Mycobacterium avium complex* includes both *M avium and M intracellulare*, which together account for the majority of disease-causing species of NTM in the HIV-infected patient. M avium is the most common cause of NTM disease in patients with AIDS [17, 18]. The presence of MAC in the sputum or stool of patients with AIDS prior to the development of disseminated disease suggests that infection results from inhalation or ingestion [17, 19]. Profound immunocompromise is the major risk for the development of disseminated MAC [20]. A number of studies demonstrate that the median CD4 cell count is consistently less than 50 cells/mm3 at the time that disseminated disease is diagnosed. In one prospective observational study of HIV-infected patients cultured monthly for MAC, the incidence of infection for patients with less than 200 CD4 cells/ mm3 was 43% after 2 years. In the subgroup of patients with less than 10 CD4 cells/mm3, the incidence of infection was 39% at 1 year [21]. Another risk factor for MAC is increased HIV RNA levels is being greater than 100,000 copies/ml was associated with a threefold increase in the risk of developing MAC in patients with CD4 < 75 cells/mm3 [22]. One of the interesting observations of NTM disease in HIV-infected patients is the low frequency of disease in Africa despite the presence of NTM in the environment. Evidence of environmental exposure to MAC occurring in humans in Africa is supported by the finding that skin test reactivity to *M avium* is as common in Kenya as it is in certain areas of the United States [17]. A number of explanations have been put forth to explain this observation. Comorbidities may result in death prior to progression of HIV disease to a state of immune compromise that is associated with NTM disease. Another theory put forth to explain the low incidence of disease is that exposure to other mycobacterial pathogens such as M tuberculosis or *M bovis* (in bacillus Calmette-guerin [BCG]) provides cross-protective immunity to MAC. This theory is supported by the low reported incidence of disease in countries such as Sweden, where childhood vaccination with BCG was common [23].

Nontuberculous Mycobacteria Other Than MAC

Most NTM disease in HIV-infected patients other than MAC is caused by *M kansasii* [24]. Some of the other NTM encountered in HIV-infected patients include *M chelonei, M fortuitum M gordonae, M malmoense, M marimum and M xenopi*. All of these organisms are capable of causing disseminated disease with a symptom complex resembling MAC [17]. These organisms are often contaminants or colonizers; however, when the typical symptoms are present, isolation of one of these organisms from a normally sterile site provides strong evidence for a true infection.

M kansasii

The source of infection remains unclear, although the presence of the organism in tap water has been well documented [25]. *M kansasii* infection usually occurs in severely immunosuppressed patients (CD4 counts >50 cells/ mm3) and typically presents with isolated pulmonary disease (± 70%). Disseminated disease is less common than that seen in MAC, with only approximately 20% having only extra pulmonary manifestations. Those with disseminated disease were typically the most severely immunocompromised [17].

M Gordonae

Mycobacterium gordonae is a slow growing mycobacterium usually found in soil, tap water, and as laboratory contaminant. It is occasionally implicated in different infections in immunosuppressed patients. In contrast, there have been few case reports of active infection in immunocompetent individuals. *M gordonae* is a ubiquitous organism and is usually considered a contaminant when recovered in culture. Although considered to be an organism with low pathogenicity, there have been reports of both pulmonary and disseminated disease in the immunocompromised host [26]. Although the clinician is often unable to distinguish the type of NTM from the chest radiograph, the finding most commonly noted in AIDS patients with NTM (excluding *M kansasii*) is an interstitial pattern that may be localized or diffuse. Cavitary disease has been reported to be very rare in this immunosuppressed population.

M Genovese

M Genovese is a newly recognized pathogen in HIV-infected patients. It was first described in a patient with AIDS in 1990 [26].

Some investigators have suggested that the true prevalence may be underestimated because of difficulties experienced when culturing the organism. Patients infected with M Genovese are usually severely immunocompromised (average CD4 count of 50 cells/mm3) and present with nonspecific symptoms of fever, wasting, abdominal pain, and diarrhea. Physical findings include hepatosplenomegaly, anemia, and abdominal lymphadenopathy. Pulmonary involvement is rare, if it exists at all. The findings on abdominal CT scan are also nonspecific with lymphadenopathy (retroperitoneal, mesenteric, and peri-pancreatic), splenomegaly and diffuse proximal small bowel thickening being the well-described features [27].

M xenopi

Mycobacterium xenopi is a non-tuberculous mycobacterium responsible for lung disease, especially in north-east France, south-east UK and in Ontario, Canada. *M xenopi* is a commonly found organism and is often considered a contaminant. *Mycobacterium xenopi* is a water related mycobacterium, recognized as a human pathogen with low pathogenicity in 1965. It was first cultured in immunocompromised patients with lymphoma, renal transplants, or HIV infection in which a haematogenous spread of the microorganism is suggested. The principal risk group appears to be young severely immunocompromised individuals in whom *M xenopi* infection probably occurs as an opportunistic infection together with other microorganisms and is even disseminated at times. It has increasingly been recognized as a cause of pulmonary infection among those with impaired immunity or chronic lung disease in whom it can colonise the airways [28].

Reports of an increasing incidence are probably the result of more sensitive tests becoming available. The clinical features of M xenopi infection in the HIV-infected patient include both disseminated disease and pulmonary manifestations. Pulmonary disease typically occurs in those with pre-existing pulmonary disease [29]. Its usual feature is an apical cavitary process in patients with obstructive pulmonary disease. However, other features have been described. Mycobacterium xenopi infections can present in two ways, either with cough, malaise, weight loss and haemoptysis over a period of months, or with chronic dyspnoea, weight loss and chronic cough with chest radiographic abnormalities over a period of years. Radiographic abnormalities in no tuberculosis mycobacterial infections are numerous and include mediastinal or hilar adenopathy, heterogeneous and linear pulmonary areas of increased opacity, cavitation, and miliary nodules. M xenopi infections are difficult to treat and there is no standard treatment [30].

Conclusion

Disseminated NTM infections are seen exclusively among immunocompromised hosts, including those with AIDS. Disseminated disease is most commonly seen in association with profound immunosuppression. Most NTM disease in HIV-infected patients is caused By *Mycobacterium avium complex* and NTM other than MAC which includes *M chelonei, M fortuitum M gordonae, M malmoense, M marimum and M xenopi*. All of these organisms are capable of causing disseminated disease with a symptom complex resembling *Mycobacterium avium complex*. These organisms are often contaminants or colonizers; however, when the typical symptoms are present, isolation of one of these organisms from a normally sterile site provides strong evidence for a true infection. The propensity for developing disseminated NTM disease in HIV infected patients is dependent not only on the level of the host's immunity but also on the virulence of the organism.

No tuberculosis mycobacterium is under reportable because most health professionals and researchers consider as contaminants. All health professionals and researchers should aware of no tuberculosis mycobacterium as the major public health problems in human especially in HIV patients and immonocompromised patients.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contribution

GT and GG wrote and edited the manuscript. All authors read and approved the final manuscript.

References

1. Parker BC, Ford MA, Gruft H, Falkinham JO (1983) Epidemiology of infection by nontuberculous mycobacteria. IV. Preferential aerosolization of Mycobacterium intracellular from natural waters. Am Rev Respir Dis 128: 652-656.
2. Bodmer T, Miltner E, Bermudez LE (2000) Mycobacterium avium resists exposure to the acidic conditions of the stomach. FEMS Microbiol Lett 182: 45-49.
3. Kirschner RA Jr, Parker BC, Falkinham JO (1992) Epidemiology of infection by nontuberculous mycobacteria. Mycobacterium avium, Mycobacterium intracellulare, and Mycobacterium scrofulaceum in acid, brown-water swamps of the southeastern United States and their association with environmental variables. Am Rev Respir Dis 145: 271-275.
4. Falkinham JO (2013) Ecology of nontuberculous mycobacteria-where do human infections come from? Semin Respir Crit Care Med 34: 95-102.
5. Phillips MS, von Reyn CF (2001) Nosocomial infections due to nontuberculous mycobacteria. Clin Infect Dis 33: 1363-1374.
6. Tortoli E (2003) Impact of genotypic studies on mycobacterial taxonomy: the new mycobacteria of the 1990s. Clin Microbiol Rev 16: 319-354.
7. Von Reyn CF, Arbeit RD, Horsburgh CR, Ristola MA, Waddell RD, et al. (2002) Sources of disseminated Mycobacterium avium infection in AIDS. J Infect 44: 166-170.
8. Ristola MA, von Reyn CF, Arbeit RD, Soini H, Lumio J, et al. (1999) High rates of disseminated infection due to non-tuberculous mycobacteria among AIDS patients in Finland. J Infect 39: 61-67.
9. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, et al. (2007) ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175: 367-416.
10. Schulze-Robbecke R, Janning B, Fischeder R (1992) Occurrence of mycobacteria in biofilm samples. Tuber Lung Dis 73: 141-144.
11. Aberg JA, Yajko DM, Jacobson MA (1998) Eradication of AIDS related disseminated Mycobacterium avium complex after twelve months anti-mycobacterial therapy combined with highly active antiretroviral therapy. J Infect Dis 178: 1446-1449.
12. Benson CA, Ellner JJ (1993) Mycobacterium avium_ Complex infection and AIDS: advances in theory and practice. Clin Infect Dis 17: 7-20.
13. Bermudez LE, Petrofsky M, Kolonoski P, Young LS (1992) An

animal model of mycobacterium avium complex disseminated infection after colonization of the intestinal tract. J Infect Dis 165: 75-79.

14. Chaisson RE, Moore RD, Richman DD, Keruly J, Creagh T (1992) Incidence and natural history of Mycobacterium avium complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. Am Rev Respir Dis 146: 285-289.
15. Chaisson RE, Benson CA, Dube MP, Heifets LB, Korvick JA, et al. (1994) Clarithromycin therapy for bacteremic Mycobacterium avium complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. Annals Internal Med 121: 905-911.
16. Chaisson RE, Keiser P, Pierce M, Fessel WJ, Ruskin J, et al. (1997) Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic Mycobacterium avium complex disease in patients with HIV infection. AIDS 11: 311-317.
17. Cinti SK, Kaul DR, Sax PE, Crane LR, Kazanjian PH (2000) Recurrence of Mycobacterium avium infection in patients receiving highly active antiretroviral therapy and ant mycobacterial agents. Clin Infect Dis 30: 511-514.
18. Corbett EL, Churchyard GJ, Hay M, Herselman P, Clayton T, et al. (1999) The impact of HIV infection on Mycobacterium Kansasii disease in South African gold miners. Am J Respir Crit Care 160: 10-14.
19. Dube MP, Torriani FJ, See D, Havlir DV, Kemper CA, et al. (1999) Successful short-term suppression of clarithromycin-resistant Mycobacterium avium complex bacteremia in AIDS. California Collaborative Treatment Group. Clin Infect Dis 28: 136-138.
20. Dunne M, Fessel J, Kumar P, Dickenson G, Keiser P, et al. (2000) A randomized, double blind trial comparing azithromycin and clarithromycin in the treatment of disseminated Mycobacterium avium infection in patients with HIV. CID 31: 1245-1252.
21. Eckburg PB, Buadu EO, Stark P, Sarinas PS, Chitkara RK, et al. (2000) Clinical and chest radiographic findings among persons with sputum culture positive for Mycobacterium gordonae. Chest 117: 96-102.
22. El-Sadr WM, Burman WJ, Grant LB, Matts JP, Hafner R, et al. (2000) Discontinuation of prophylaxis for Mycobacterium avium complex disease in HIV infected patients who have a response to antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med 342: 1085-1092.
23. Gordin FM, Sullam PM, Shafran SD, Cohn DL, Wynne B, et al. (1999) Randomized placebo controlled study of rifabutin added to a regimen of Clarithromycin and Ethambutol for treatment of disseminated infection with mycobacterium avium complex. Clin Infect Dis 28: 1080-1085.
24. Sturgill-Koszycki S, Schlesinger PH, Chakraborty P, Haddix PL, Collins HL, et al. (1994) Lack of acidification in Mycobacterium phagosomes produced by exclusion of the vesicular proton-ATPase. Science 263: 678-681.
25. Williams PL, Currier JS, Swindells S (1999) Joint effects of HIV 1 RNA levels and CD4 lymphocyte cells on the risk of specific opportunistic infections. AIDS 13: 1035-1044.
26. Wolinski E (1992) Mycobacterial diseases other than tuberculosis. Clinical Infectious Diseases 15: 1-12.
27. Yates MD, Pozniak A, Uttley AH, Clarke R, Grange JM (1997) Isolation of enviromental mycobacteria from clinical specimens in South East England, 1973-1993. Internatl J Tuberc Lung Dis 1: 75-80.
28. Damsker B, Bottone EJ, Deligdisch L (1982) Mycobacterium xenopi: infection in an immunocompromised host. Hum Pathol 13: 866-870.
29. Young LS, Wiviott L, Wu M, Kolonoski P, Bolan R, et al. (1991) Azithromycin for treatment of Mycobacterium avium-intracellulare complex infection in patients with AIDS. Lancet 338: 1107-1109.
30. Contrevas MA, Cheung OT, Sanders DE, RS Goldstein (1988) Pulmonary infection with nontuberculous mycobacteria. Am Rev Respir Dis 137: 149-152.

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