Case Report: Mycobacterium avium Complex Infection as a Cause of Fever of Unknown Origin in HIV Disease

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ABSTRACT

Fever of unknown origin (FUO) is a common presenting complaint in patients with HIV disease. This article presents a case where Mycobacterium avium Complex (MAC) infection is identified as the cause of FUO in a patient with late stage HIV disease, and reviews the diagnostic and therapeutic strategy for effective management of this condition. MAC is an atypical mycobacterium which causes disseminated disease in up to 50% of HIV patients at some point during their illness. Studies have found it to be responsible for FUO in up to 21% of cases where a cause of fever could be identified. Blood cultures are a sensitive method of detecting MAC infection, and a single positive blood culture is diagnostic for disseminated MAC disease. Current laboratory techniques allow identification of MAC in the blood within 7 to 14 days of collection. The most effective treatment protocol for dissemi-nated MAC disease involves a three drug regimen of rifabutin, ethambutol and clarithromycin, that leads to rapid clearance of the organism from the blood and significant reduction in the severity of symptoms. Primary prophylaxis with clarithromycin has also been shown to reduce the incidence of MAC infection in HIV patients. Given that MAC has been found to have a significant impact on the mortality of HIV patients, it is important to maintain high diagnostic suspicion when evaluating patients with FUO so that treatment may begin promptly to improve patients' quality of life and prolong survival.

CASE HISTORY

A 54 year old janitor with late stage AIDS presented to the Infectious Disease Clinic at the QEII Health Sciences Centre in early December of 1996 with intermittent fever of one week duration. The fever occurred every night, and ranged from 38.5 to 39.6 degrees. Prior to this he had felt well. He experienced intermittent fatigue, but no specific symptoms to suggest a local cause of the fever. He reported no cough, sputum production, or urinary tract symptoms; his appetite was good and his weight was stable. Tylenol was minimally effective at lowering his temperature. On examination, the patient had severe oral thrush and oral hairy leucoplakia; there were enlarged nodes in the axillae bilaterally.

The patient's HIV disease was diagnosed in December of 1994, subsequent to an episode of Pneumocystis carinii pneumonia. Since then he had been receiving trimethoprim-sulfamethoxazole, one double strength tablet daily, as secondary Pneumocystis prophylaxis . He had also been on trials of zidovudine (AZT) and ddC. During the past two years he had experienced severe oral thrush, occasional mucosal ulcers, ddC-associated peripheral neuropathy, and extensive Molluscum contagiosum over the face, neck and right arm. There had been no previous history of fever. For the past six months his CD4 counts had been less than 80/mm 3 . At the time of presentation with FUO he was taking saquinavir 300mg tid, and 3TC 150 mg tid.

Preliminary investigations showed white blood cells 4.3x10 9 /l; hemoglobin 138g/l; platelets 257x10 9 /l; creatinine, calcium, uric acid, bilirubin, alkaline phosphatase, ALT, AST, LDH, CK, total protein, and serum amylase were all normal. Blood cultures for aerobes, anaerobes, and CMV were negative. A chest radiograph revealed a pleural plaque involving the right lung which was present 1 year previously. A Mantoux test was negative at that time, and the patient had no other history of exposure to Mycobacterium tuberculosis. A gallium 67 scan of the chest and abdomen revealed gallium avid lesions in the left cervical chain, and paraortic region of the abdomen. There was no uptake in the lungs. Blood cultures for MAC were positive and diagnosis of disseminated MAC was made in January 1997.

The patient was immediately started on clarithromycin 500mg bid, rifampin 600mg od, and ethambutol 1200 mg od. However, one month later he continued to experience fever up to 39 degrees Celsius at least every other night, and night sweats. Blood cultures taken at that time were negative for Cryptococcus and CMV; a repeat chest radiograph was also negative. Repeat cultures for MAC were positive. However, to exclude the possibility of a drug interaction between rifampin and saquinavir as being responsible for the persistent fever, the patient's antiretroviral medications, saquinavir and 3TC, were discontinued.

The fever persisted for two more weeks. The patient's antimycobacterial medications were then changed from rifampin 600 mg od, to rifabutin 150mg bid plus clarithromycin and ethambutol as before. Naprosyn 250mg bid was also prescribed to lower the temperature as a comfort measure.

Within the next two weeks the patient became afebrile. He was no longer experiencing night sweats and his weight had increased. At this time the patient's CD4 count was 25/mm 3 and viral load was 1.3x10 6 RNA copies/ ml. Antiretroviral therapy, including D4T and indinavir, were reinitiated.

FEVER IN PATIENTS WITH HIV DISEASE

Fever of uncertain origin (FUO) can be defined as fever, with a temperature greater than 38.2 degrees Celsius, for at least 4 weeks prior to hospital admission, and uncertainty of diagnosis after 3 days, despite appropriate investigations (3). FUO is a common occurrence during advanced HIV disease, and often presents a diagnostic challenge to physicians. Patients may experience fever for a prolonged period before presenting for medical care, and without any localizing symptoms (1). In three observational studies of patients with advanced HIV disease

performed over 9, 15 and 27 month periods, FUO occurred in 46%, 8.2%, and 21% of patients respectively (2, 3, 4). However, a specific cause of the fever could be identified in an average of 86% of cases (range 83% to 88%). Atypical mycobacterium was determined to be one of the most common causative agents of FUO in each study along with Pneumocystis carinii and lymphoma. Mycobacterium avium complex (MAC) infection accounted for up to 31% of all cases of FUO. Other less common causes of FUO in these studies included Mycobacterium tuberculosis, toxoplasmosis, disseminated CMV, leishmaniasis, and drugs.

Fever in HIV patients should not be attributed to HIV infection itself. Diagnostic evaluation should be aggressive, and is most effectively guided by clinical symptoms, associated conditions, and stage of HIV disease. Investigations found to have high diagnostic yield include blood, urine and sputum cultures for mycobacteria, lymph node aspiration and biopsy, and bone marrow biopsy. Investigations that may be diagnostic in a low percentage of cases of FUO include abdominal ultrasound, and serology for toxoplasmosis or leishmaniasis (3).

It should be remembered that the effective yield of these investigations may vary depending on the prevalence of the possible etiologic agents in the community to which the patient belongs.

MYCOBACTERIUM AVIUM COMPLEX INFECTION IN PATIENTS WITH AIDS

Mycobacterium avium Complex (MAC) is a serologic complex of Mycobacterium avium and Mycobacterium intracellulare. Infection with MAC is extremely common in the late stages of HIV disease. In one study which followed 1006 HIV positive patients over a three year period, the incidence of MAC was 21% in the first year and 43% by the end of the second year (5). It is generally felt that at least 50% of patients with HIV disease will develop MAC infection at some time. The risk of infection increases linearly with decreasing CD4 counts below 100/ mm 3 , and with previous Pneumocystis pneumonia, severe anaemia, or interruption of antiretroviral therapy. There does not appear to be an association between age, gender, or race and the risk of MAC infection (6).

Prior to dissemination, the gastrointestinal and respiratory tracts are the major sites of initial MAC colonization following exposure to MAC organisms from food, water, soil and animal sources (6). However, dissemination and tissue invasion has been reported to occur in the absence of prior colonization. Bacteremia may initially be intermittent, most likely reflecting a lighter bacterial load. Although it is also associated with shorter periods of clinical signs and symptoms, intermittent bacteremia inevitably progresses to continuous high grade bacteremia with ongoing mycobacterial replication and tissue infiltration. Involvement of multiple organs results in the characteristic clinical signs and symptoms of disseminated disease (7). Up to 85% of patients with MAC infection present with fever. Other frequently described clinical manifestations include weight loss, intra abdominal lymphadenopathy, and hepatosplenomegaly. Night sweats, diarrhea, nausea and vomiting, and abdominal pain have also been reported. Laboratory tests may show anemia with hemoglobin as low as 8.5 g/dl, and elevated levels of alkaline phosphatase (6).

Without treatment, the duration of survival after diagnosis of disseminated MAC has been reported to range from 107 days to 139 days (6, 8). MAC infection itself has not yet been determined to be directly responsible for the reduced life expectancy of AIDS patients. Instead, the insidious and progressive nature of the infection leads to physiologic abnormalities that diminish the quality of life and shorten survival for these patients.

DIAGNOSIS

High diagnostic suspicion for MAC should be maintained in evaluation of HIV patients presenting with FUO. A single positive blood culture is considered evidence for disseminated MAC disease. Mycobacteria recovered from other normally sterile body tissues including bone marrow, liver, lymph nodes, and from CSF or brain tissue, may precede recovery of organisms from the blood and should also be interpreted as indicative of disseminated disease. Blood cultures are the most convenient and frequently used method for detection. Unfortunately, intermittent bacteremia in the presence of disease may delay positive identification of MAC by this method (7).

Stool and respiratory tract secretions may also be used for culture. When positive, screened cultures of stool and sputum often predict disseminated disease. However, they are not as sensitive as blood cultures for detection of actual disseminated disease and the negative predictive value is poor (9).

Currently, the radiometric BACTEC TB system is the most effective method of detecting MAC organisms in the blood. The sensitivity of this system is 94%, and allows positive identification of cultures in 7 to 14 days compared to up to 3 weeks by conventional culture medium. Using the BACTEC method, the level of bacteremia appears to correlate inversely with the time to positive blood cultures. The BACTEC system can also be used in susceptibility testing to evaluate synergistic interactions between medications or drug resistance (10).

TREATMENT AND CLINICAL COURSE OF DISSEMINATED MAC

Previous monotherapy protocols for MAC infection used rifabutin or clarithromycin. However, relapse due to drug resistant strains was a frequent problem, especially with clarithromycin monotherapy (reviewed in 10). A recent randomized clinical trial has found that a three drug regimen of rifabutin 300 mg od, ethambutol 15 mg/kg/d and clarithromycin 1000 mg od, is an effective treatment for MAC infection (11). Sixty-one percent of patients taking this three drug regimen became blood culture negative by four weeks, and there were no relapses during the 16 weeks trial period. There was also a significant reduction in the severity of MAC associated symptoms, in particular less weight loss, by twelve weeks. High dose rifabutin, 600 mg od, was associated with a similar blood clearance rate of MAC, but was also related to a higher incidence of uveitis compared to 300 mg rifabutin once daily. A four drug regimen of rifampin, ethambutol, clofazimine, and ciprofloxacin, was also evaluated, and found to be less effective with a blood clearance of 29% by 4 weeks. In addition, the combination of rifabutin 300 mg od with ethambutol and clarithromycin was associated with a decreased incidence of clarithromycin resistance.

Among the various treatments available for mycobacterium infection, it is not clear at this time which therapeutic regimen is superior as different drug combinations work better for different patients. However, it is generally recommended that if initial treatment with one of the regimens described above does not improve symptoms within 2 to 4 weeks, an alternative treatment, such as the addition of azithromycin 500 mg po qd, should be attempted (12).

PROPHYLAXIS FOR MAC

Some controversy surrounds the issue of whether prophylactic drug therapy for MAC infection actually contributes to a better prognosis for patients compared to surveillance and treatment of disease when it occurs. Recent evidence from a randomized clinical trial found that primary prophylactic treatment of MAC with clarithromycin 500 mg po bid was associated with prolonged survival independent of CD4 count (13). As compared to the placebo group, patients in the clarithromycin prophylaxis group experienced a 69% reduction in risk for disseminated MAC infection. Six percent of patients in the clarithromycin group developed MAC infection compared to 16% in the placebo group. Additionally, a 23% reduction in the risk of hospitalization among the clarithromycin treated patients suggests that clarithromycin may also act to prevent other common infections that contribute to morbidity and mortality in HIV infected patients. The risk of selecting for drug-resistant organisms may be a deterrent to clarithromycin prophylaxis, however, the risk tends to be greatest in patients with very low CD4 counts (<=25/mm 3), and with prolonged prophylaxis (13).

As an alternative to clarithromycin, prophylaxis with weekly azithromycin 1200 mg po was associated with a 60% reduction in the risk of MAC infection compared to placebo (14). Weekly doses of azithromycin may result in greater compliance among patients compared to clarithromycin prophylaxis which must be taken daily. Azithromycin may also be associated with lower cost and less toxicity (15). Importantly, the low frequency of clarithromycin resistant isolates in patients who developed MAC infection despite azithromycin prophylaxis suggests that an effective treatment option would still be available for those in whom prophylaxis has failed.

For patients who are unable to tolerate clarithromycin or azithromycin prophylaxis, rifabutin has been shown to significantly reduce the risk of MAC bacteremia in patients with CD4 counts below 200/mm 3 . The currently recommended dose for rifabutin prophylaxis is 300 mg po qd (16).

The 1996 Stanford Guide to HIV/AIDS Therapy recommends initiation of primary MAC prophylaxis when CD4 counts fall below 75/mm 3 (12). Secondary prophylaxis to prevent recurrence is always necessary as recurrence is virtually universal without chronic suppression. Clarithromycin or azithromycin plus ethambutol in treat-ment doses is the suggested regimen for chronic post treatment suppression (1).

CONCLUSION

The patient presented in this case report had multiple positive blood cultures for MAC indicative of persistent disseminated disease. For patients with previous MAC infection, the most common cause of relapsing fever is recurrent MAC disease (1). However, in the absence of a positive blood culture in the face of recurrent fever and low CD4 counts, other possibilities such as lymphoma or disseminated CMV infection must also be considered.

The incidence of MAC infection is increasing among HIV/AIDS patients. This is due to more effective management of opportunistic infections previously associated with a high risk of mortality, and with better surveillance and reporting of successful treatment regimens. More patients with low CD4 counts are surviving longer, thus increasing the risk of acquiring MAC. Unfortunately, disseminated MAC disease has been shown to be an independent risk factor for mortality in HIV/AIDS patients (6). Therefore, it is important to maintain a high index of suspicion during management of patients with late stage AIDS or persistent fever of unknown origin given the proven clinical benefit of prophylactic therapy and available treatment regimens. Where appropriate, prophylaxis or treatment for MAC should be promptly initiated to improve quality of life and increase survival time.

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REFERENCES

1. Sullivan et al. Fever in patients with HIV infection. Inf Dis Clin-ics of NA 1996;10(1).
2. Sepkowitz, K. A., Telzah, E. E., Carrow, M., Armstrong, D. Fever amoung patients with advanced human immunodeficiency virus infection. Arch Int Med 1993; 153:1909-1912.
3. Miralles, P. et al. Fever of uncertain origin in patients infected with human immunodeficiency virus. Clin Inf Dis 1995; 20: 872-875.
4. Bissuel, F., Leport, C., Perronne, C., Longuet, P., Vilde, J.L. Fever of unknown origin in human immunodeficiency virus infected patients: A critical analysis of a retrospective series of 57 cases. J Int Med 1994;236(5):529-535.
5. Nightingale, S. D., Byrd, T. B., Southern, P.M. et al. Incidence of Mycobacterium avium intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Inf Dis 1992;165:1082-1085.
6. Benson, C. A. Disease due to Mycobacterium avium Complex in patients with AIDS: Epidemiology and Clinical Syndrome. Clin Inf Dis 1994;18 (suppl 3):S218-222
7. Benson, C. A. and J.J. Ellner. Mycobacterium avium complex infection in AIDS. Clin Inf Dis 1993;17:7-20.
8. Jacobson, M. A., Hopwell, P. C., Yajko, D. M., et al. Natural history of Mycobacterium avium complex infection in AIDS. J Inf Dis 1991;164:

994-998.
9. Havlik, J. A., Metchock, B., Thompson, S. E., et al. A prospective evaluation of Mycobacterium avium complex colonization of the respiratory and gastrointestinal tracts of persons with human immunodeficiency virus infection. J Inf Dis 1993; 168:1045-1048.
10. Inderlied C. B., Kemper, C. A., and Bermudez, L. E. M. et al., The Mycobacterium avium complex. Clin Microbiol Rev. 1993;6; 266-310.
11. Shafran, S. D. et al A comparison of two regeimens for the treatment of Mycobacterium avium complex in AIDS: Rifabutin, Ethambutol, and Clarithromycin versus Rifampin, Ethambutol, Cofazimine, and Ciprofloxacin. N Eng J Med 1996; 335:377- 383.
12. Sanford Guide to HIV/AIDS Therapy 5th Ed. 1996.
13. Pierce, M. et al. A randomized trial of Clarithromycin as prophylaxis against disseminated Mycobacterium avium comples in-fections in patients with advanced AIDS. N Eng J Med 1996: 335:384-391.
14. Oldfield, E. C. Dickison, G. Chung, R. et al. Once weekly azithromycin for the prevention of Mycobacterium avium complex infection in AIDS patients. In: Program and Abstracts of the Third conference on Retroviruses and Opportunistic Infections, Washington, D. C. 1996:90. abstract.
15. Havlir, D. V. et al. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin or both. N Eng J Med 1996; 335:392-398.
16. Nightingale, S. D., Cameron, D. W., Gordin, F. M. et al.Two controlled trials of rifabutin prophylaxis against Mycobacterium avium complex infection in AIDS. N Eng J Med 1993;329:828- 833.