The Pathophysiology of Disseminated Mycobacterium avium Complex Disease in AIDS

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Mycobacterium avium complex (MAC) organisms cause disseminated disease in patients with AIDS. The organisms penetrate the gastrointestinal mucosa by unknown mechanisms and are phagocytosed by macrophages in the lamina propria. These cells cannot kill the organisms, and MAC spreads through the submucosal tissue. Lymphatic drainage transports mycobacteria to abdominal lymph nodes, from which the organisms enter the bloodstream. Hematogenous spread can occur to many sites, but spleen, bone marrow, and liver are the most common. Tissue destruction is rare, and most signs and symptoms of MAC disease are due to elaboration of cytokines. MAC is rarely the direct cause of death but increases the risk for superinfection; death may result from malnutrition or other infections.

Bacterial Factors

Virulence factors for MAC have not been well defined. In some ways, no MAC isolates can be considered particularly virulent, since disease in persons with normal immunity is uncommon and usually self limited. Nonetheless, it is clear that some organisms possess unique abilities that others do not to overcome the residual immune defenses of persons with advanced AIDS. Increased virulence has been correlated with transparent colony morphology and the presence of plasmids, but the explanation for increased virulence remains poorly understood [1, 2]. It was recently demonstrated that isolates from AIDS patients have increased replication in vitro compared with replication of environmental isolates; this finding may lead to a better understanding of the mechanisms that lead to disseminated MAC disease.

Route of Acquisition

MAC is acquired from the environment and is not spread from person to person [4]. While the environmental reservoirs from which it is acquired have not been well defined, it is clear that disease can be acquired either by inhalation or ingestion of organisms. These two routes of acquisition lead to pulmonary and gastrointestinal disease, respectively. In healthy hosts, such disease is brief and self limited. Some children may develop cervical lymphadenopathy, while others and adults develop clinical pulmonary disease. In most affected persons, however, infection is not clinically recognized and is apparent only by reactivity to delayed-hypersensitivity skin testing.

It is unknown whether previously infected persons can maintain viable organisms that could reactivate with acquired immunity, as is seen with Mycobacterium tuberculosis; epidemiologic evidence suggests that this is rare. In patients with AIDS, several lines of evidence indicate that most persons with disseminated MAC have recently acquired the organisms [1]. First, although skin tests cannot be assessed directly owing to anergy, the disease is more common than would be predicted by the expected prevalence of positive skin tests to MAC antigens. Second, disease can be detected locally in the gut or lungs prior to dissemination. Third, antibodies to MAC antigens are not seen in AIDS patients with dissemination, suggesting that the patients had not been previously exposed to MAC antigens. In clinical series, the gut is the portal of entry of the organisms in >90% of the cases, and it is this route that will be discussed in this report. Less is known about the events that lead to dissemination from a pulmonary site, but the mechanisms are thought to be analogous.

Adherence of the organisms to the gut wall is the initial event in invasion. The adherence receptors have not been well studied, but some organisms possess greater ability to adhere to intestinal epithelial cells than others [5]. Once adherent, the bacteria
rapidly penetrate the intestinal mucosa. While it appears likely that this occurs through M cells, invasion has not been directly observed and could occur by endocytosis, paracellular transit, or invasion through surfaces damaged by human immunodeficiency virus (HIV) itself or other intestinal pathogens. Penetration of the mucosa occurs rapidly, and solitary organisms are often seen in the lamina propria without apparent mucosal abnormality (figure 1).

**Host Defense Mechanisms**

Once MAC enters the lamina propria, phagocytosis by macrophages occurs readily. Several studies have demonstrated that the ability of macrophages to phagocytose MAC in patients with advanced AIDS is unimpaired. However, intracellular killing does not occur, and organisms multiply within macrophages. This results in the initial appearance of solitary mac-

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**Figure 1.** Solitary mycobacterium, which has not yet been phagocytosed (arrow), in submucosa of colon. Note that colonic mucosal surface is intact. (Photomicrograph courtesy of David Schwartz, Emory University; Grady Memorial Hospital, Atlanta.)
rophages stuffed with acid-fast bacilli. With continued bacterial replication, the host cell ruptures. This process eventually leads to the presence of sheets of macrophages laden with acid-fast bacilli, the classic histologic appearance of MAC disease in AIDS.

Several factors undoubtedly contribute to the killing defect. Macrophages from such patients can be activated by cytokines in vitro to kill intracellular pathogens. However, in patients with advanced AIDS, such cytokine production is usually deficient. Cell-mediated killing of infected macrophages may also be an important mechanism of control of MAC disease [6]; this mechanism is also impaired in these patients. Granuloma formation, a third mechanism for control of mycobacteria in tissues, is also substantially impaired, with failure to form any granulomas in nearly half of patients; those that do form lack normal granulomatous architecture. In addition, growth of MAC can be stimulated by both the high serum levels of triglycerides and the iron overload seen in patients with AIDS [7].

**Dissemination**

Local replication of organisms leads to the formation of local foci that can be visualized endoscopically as 2–4 mm punctate lesions; these are the hallmark of MAC disease in the gut (figure 2). Involvement can be seen in all areas of the gastrointestinal tract but is most common in the duodenum; disease is usually patchy [8]. Unimpeded replication of organisms leads to massive thickening of the gut wall, which can be seen grossly and radiographically [9]. Infection spreads via local lymphatics to involve lymph nodes, where again the bacteria replicate unimpeded in macrophages, eventually breaking outside of these cells and replacing the normal cellular histology with sheets of bacilli. Hematogenous dissemination occurs concurrently, and bacteria are carried throughout the body [10]. In blood, bacteria are largely seen within infected mononuclear cells. In some patients, dissemination may occur after only minimal local proliferation, but usually a local focus can be identified [10, 11]. Bacteria are taken up by phagocytic cells throughout the body.

![Figure 2. Ulcerated colonic lesion due to *Mycobacterium avium* complex with punctate lesions. (Endoscopic photograph courtesy of Mark Sims, Piedmont Hospital, Atlanta.)](image)
and reticuloendothelial organs, such as the liver, spleen, and bone marrow, are the most frequent distant sites. However, MAC have occasionally been recovered from nearly all organs [1].

Entry of MAC into the bloodstream is probably responsible for fever and night sweats, the major symptoms of disseminated disease. Patients with localized disease prior to dissemination have remarkably few symptoms, probably reflecting the minimal response of the immune system. Once bacteremia occurs, serum tumor necrosis factor-α and interleukin-6 levels are elevated and are likely responsible for the predominant symptoms of fever, night sweats, and cachexia [12, 13]. However, these elevated cytokine levels reflect a dysfunctional response by a failing immune system and do not lead to control of the infection.

Anemia is common in patients with disseminated MAC disease, and it is frequently severe. Serum hemoglobin concentrations of <8 mg/dL and hematocrit levels of <26% are common. Despite this, organisms are rarely seen in the marrow; rather, the histologic picture is one of chronic disease, with failure of maturation of red cell precursors. Granulomas are also rare. The mechanism of this anemia is not well understood, as erythropoietin levels can be high, normal, or low, and clinical responses to exogenous erythropoietin are unpredictable [14]. Thus, there may be more than one route by which disseminated MAC interferes with erythropoiesis.

A unique pathophysiologic abnormality seen with MAC disease is marked elevation of serum alkaline phosphatase. About 5% of patients with disseminated MAC manifest this abnormality. The enzyme may reach 20–40 times the normal level with little elevation of transaminases, bilirubin, or other parameters of hepatic function. Nonetheless, fractionation shows it to be of hepatic origin. Patients have little symptomatic discomfort, and the histologic picture does not show marked abnormality. This suggests interference with enzyme metabolism rather than hepatic tissue destruction as the cause of the elevations.

Sequelae

If untreated, the disease progresses to involve the entire gut. This is associated with substantial nausea, and some of the marked weight loss experienced by these patients may be due to decreased caloric intake. Absorptive defects have also been documented in patients with MAC, although other causes of such defects, such as other enteric pathogens or HIV itself, may also have been present [8]. Since host responses are minimal, little tissue damage is seen, and successful treatment restores normal cellular architecture. In many cases, appetite returns and weight loss can be reversed.

Untreated disease is associated with shortened survival. The specific causes of death are usually other infectious processes, and it has become apparent that one way in which MAC shortens survival is by increasing the risk for other opportunistic infections. This likely results from up-regulation of HIV, malnutrition, or both. Up-regulation of HIV infection by MAC is substantial [15]; recent studies have directly demonstrated increased HIV replication in MAC-containing macrophages [16].

Conclusion

Patients with AIDS are uniquely susceptible to MAC disease. The organisms enter through the gut or lung and rapidly disseminate. Host reaction in the tissue is minimal, and little destruction occurs; most signs and symptoms of the disease are the result of interference with normal tissue functions by masses of bacilli and elaboration of cytokines. Antimycobacterial treatment eliminates the organisms and restores functional activity of the tissues. However, foci of infection persist for many months after initiation of therapy [10]. Recently, highly active antiretroviral therapy has been shown to restore immunity to mycobacteria [17]. Patients with MAC disease may have increases in MAC-related symptoms during such therapy, with recurrent fevers and tender swollen lymph nodes. These responses indicate that the immune dysfunction leading to susceptibility to MAC in patients with AIDS may frequently be reversible with effective antiretroviral therapy, and they suggest that MAC may be eliminated from the tissues in such patients.

References


