Long-term Remission for Disseminated *Mycobacterium avium-intracellulare* Complex Associated With Antibody Deficiency

ABSTRACT. ***Mycobacterium avium-intracellulare* (MAI) is a ubiquitous organism with limited virulence in the immunocompetent host. Disseminated disease is associated with a high mortality rate. Except for localized cervical adenitis, MAI disease is rare in immunocompetent children. We report a child with antibody deficiency (dysgammaglobulinemia) and disseminated MAI infection, in whom complete, long-term remission was attained with multiple antimycobacterial therapy.**

The patient presented with progressive cervical lymphadenopathy and hepatomegaly at 7 years of age. A lymph node biopsy showed acid-fast bacilli and granulomas. Despite a transient response to conventional antituberculous therapy, including isoniazid and rifampin, his symptoms progressed. Cultures from blood, bone marrow, spleen, and cervical lymph node tissues revealed an MAI organism. Subsequent treatment using a combination of clarithromycin, amikacin, and ethambutol for 16 months resolved clinical symptoms, and subsequent blood culture results became negative. By the time of this report, the patient has been disease-free for 4 years.

Multiple-drug therapy is promising for the treatment of MAI in children with antibody deficiency; however, the selection of antiinfective drugs should include a member of the newer macrolide family. *Pediatrics* 1999; 103(1). URL: http://www.pediatrics.org/cgi/content/full/103/1/e13; *acquired immunodeficiency syndrome, clarithromycin, dysgammaglobulinemia, Mycobacterium avium-intracellulare, treatment.*

ABBREVIATIONS. MAI, *Mycobacterium avium-intracellulare*; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome. Ig, immunoglobulin.

Mycobacterium avium-intracellulare (MAI) is a ubiquitous organism with limited virulence in the immunocompetent host. Rare before the emergence of human immunodeficiency virus (HIV), MAI became one of the most common opportunistic infections in patients with acquired immunodeficiency syndrome (AIDS) (22%).[1] Except for localized MAI-associated cervical adenitis,[2] MAI disease is rare in children not infected with HIV.[3] Disseminated MAI infection not associated with AIDS has been reported in 13 patients by Horsburgh[4] and in 32 patients by Stone.[5] The majority of the patients studied were immunocompromised. In those series, disseminated MAI infection was fatal if untreated, and showed a poor response to multiple antimycobacterial agents, with an exceedingly high mortality rate. We report a child with antibody deficiency (dysgammaglobulinemia) and disseminated MAI infection in whom complete remission was attained with multiple antimycobacterial agents. To our knowledge, this is the first report of a dysgammaglobulinemia with visceral dissemination of MAI, as well as the first report of long-term survival after multiple-drug therapy for disseminated MAI infection.

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CASE REPORT

A 3½-year-old white boy was referred to the Hospital for Sick Children, Toronto, for sinusitis that had progressed to periorbital cellulitis. Antibiotic therapy was required often because he was prone to recurrent infections of the upper respiratory tract and skin and at 23 months, he had an episode of pneumococcal meningitis, which required hospitalization.

His birth history was unremarkable. The patient was born at 38 weeks' gestation, weighing 4 kg (8 lb, 14 oz). He was intubated briefly for transient tachypnea of the newborn. The infant attained normal developmental milestones and was healthy before 1 year of age.

As a toddler, the patient had chickenpox and handled the viral infection relatively well, although he suffered bacterial superinfection of his skin lesions, which responded to oral antibiotic therapy. His immunization status was up to date at the time of presentation, and he had tolerated the live measles, mumps, and rubella vaccines with no adverse effects. His family history was noncontributory. Results of physical examinations before the present illness had been normal.

Initial laboratory investigations demonstrated a normal complete blood count with no evidence of lymphopenia. Levels of immunoglobulins (Ig), IgG subclasses, and complements were normal. The patient showed, however, an inability to produce isohemagglutinins and to mount an antibody response to the protein antigens of routine childhood immunizations. Lymphocyte markers demonstrated normal numbers of B and T cells. Lymphocyte proliferation studies showed normal intact in vitro function. The patient was HIV antigen- and antibody-negative.

Based on clinical presentation, along with poor specific-antibody responses, diagnosis of antibody deficiency with normal Ig (dysgammaglobulinemia) was made at the age of 6 years, and monthly intravenous Ig-replacement therapy was instituted.

The patient was symptom-free until 7 years of age, when he developed prominent cervical and axillary lymph nodes (1 to 2 cm in diameter and enlarging progressively). This episode was associated with loss

of appetite, a 7-kg (16-lb) weight loss, fatigue, low grade fever, and night sweats. Hepatomegaly also was found during a physical examination. Laboratory investigations showed an elevated erythrocyte sedimentation rate of 102 mm/hour. Cervical lymph-node biopsy demonstrated the presence of acid-fast bacilli and granulomas. Unfortunately, delayed type hypersensitivity testing is not recorded. The patient was started on antituberculous treatment consisting of isoniazid (10 mg/kg per day) and rifampin (10 mg/kg per day) at a community hospital. Despite a finding of acid-fast bacilli, the tissue culture did not grow any organism at this time.

Despite a temporary regression of the lymphadenopathy, the patient's pyrexia, malaise, and weight loss recurred after 4 months of initial therapy. At this time, the acid-fast organism was identified as MAI, and was resistant to rifampin and isoniazid on in vitro drug sensitivity testing. Positive MAI blood culture results were recovered while on antituberculous therapy. A computed tomography scan of the abdomen demonstrated intraabdominal lymphadenopathy, a low-density lesion in the spleen, and a mild thickening of the wall of the small bowel. Histologic examination of the splenic lesion also revealed MAI. Thus, the patient showed evidence of disseminated MAI resistant to routine antituberculous therapy.

After isolation of MAI complex, therapy was initiated with a combination of clofazimine, rifabutin, and ethambutol for 3 months. It was then changed to amikacin (15 mg/kg per day, three times a week), ethambutol (15 mg/kg per day), and clarithromycin (500 mg twice daily) according to final in vitro drug sensitivity results. This triple therapy (ie, amikacin, ethambutol, and clarithromycin) was continued for 16 months. Shortly after the revision outlined above was implemented, the patient began to feel better. His symptoms resolved, and he gained weight. Results of subsequent biannual blood cultures after completion of therapy were negative. Follow-up computed tomography scans of the chest and abdomen also were normal, as were pulmonary and liver function tests. At the time of this report, the patient has been symptom-free, with negative results of microbiologic and imaging studies for >4 years.

DISCUSSION

MAI is a ubiquitous soil and water saprophyte. Initially, *M avium* and *M intracellulare* were differentiated based on their virulence in chicken and rabbits. Today, because the two species are similar, most laboratories, including our reference laboratory, do not distinguish between them and report isolates of both species as MAI complex.[6] Unlike *M tuberculosis*, human-to-human transmission of nontuberculous mycobacteria has not been documented.[6] Both respiratory and gastrointestinal colonization are potential sources of MAI, however, the gastrointestinal tract appears to be a more common portal of entry than does the respiratory tract.[7] Infections caused by nontuberculous mycobacteria have been recognized increasingly through improved culture techniques. Its incidence is inversely related to age, which suggests that MAI infection is acquired rather than reactivated in immunocompromised patients.

During the last decade, the disseminated MAI disease was considered the most common bacterial infection among persons with advanced AIDS, and it was suggested that up to one in four of all AIDS patients will acquire this infection during their lifetime.[8] Later studies suggested that 40% to 50% of patients with AIDS are either colonized or infected with MAI; the fatality rate associated with disseminated MAI in these individuals was reported to be exceedingly high.[9] Although mortality and morbidity in AIDS patients has declined,[10] it is attributed to the use of more intensive antiretroviral therapies rather than to the decrease in the virulence of the MAI complex.[10]

Infection with MAI in patients without predisposing conditions is rare, with poor prognosis. Horsburg and colleagues[4] reported 13 cases and reviewed 24 cases from the literature from 1940 to 1984. All patients have one or more associated condition. Twenty of the 37 patients had compromised host defense to opportunistic pathogens. Thirty-three of the 36 evaluable patients received antimycobacterial chemotherapy. Only 24 patients responded to therapy; however, 4 of these later relapsed and died. Nine patients had progressive disease and died despite all therapeutic efforts; the 3 patients who received no therapy died as well. Prince and associates [11] described 21 adult patients (mean age, 66 years) without predisposing conditions. Eight relapsed when therapy was stopped, and 4 died of progressive pulmonary infection caused by MAI. Stone and coworkers [5] reported disseminated MAI infection not associated with AIDS in 32 pediatric patients ranging from 2 months to 14 years of age. Of the 32 patients reviewed, 34% had MAI with visceral dissemination. Immune defect was reported in only 19% of all reviewed. However, 36% of patients with visceral dissemination of MAI were immunocompromised (ie, Medulloblastoma, acute lymphocytic lymphoma, severe combined immunodeficiency). Of note, immune status was not defined clearly in several case reports.[5] The overall mortality was 41%; however, for MAI with visceral dissemination, the mortality was 82% and for localized pulmonary disease only 20%. Among those patients reported, not 1 had dysgammaglobulinemia.

The relationship between immunopathogenicity of MAI and the immune response to it is not well understood. MAI is an intracellular pathogen that grows primarily in the vesicles of macrophages, where they are shielded from the effects of both antibodies and cytotoxic T cells. T-helper type 1 $CD4^+$ cells activate the macrophages by producing cytokines to eliminate MAI. These include interferon-γ, tumor necrosis factor-α, and interleukin-10.[12] To enhance the cytokine signaling, in combination with conventional antibacterial therapies, interferon-γ has been reported to be effective for some cases of refractory disseminated MAI.[13] A possible role of $\gamma\delta$T cells also has been proposed.[12] Although cellular immunity has a major role in mycobacterial immunity, there also is a possible role for humoral

immunity, because our patient had a deficiency limited to antibody production. Alternatively, it is possible that patients with dysgammaglobulinemia also may have a cellular deficiency that cannot be detected by our routine studies, but that predisposes them to mycobacteria.

Multiple-therapy approaches for resistant diseases are showing promise in children, although because of its rarity, there is very little experience with treatment of MAI. Early (premalignant) studies of the treatment of MAI in patients with AIDS demonstrated the ability of multidrug regimens to lower the burden of mycobacteria in blood and to improve symptoms.[14] However, reports after the introduction of macrolides for treatment of MAI have been promising. Shafran and researchers[15] published a prospective study of a combination-treatment regimen comparing a three-drug combination of rifabutin, ethambutol, and clarithromycin with a four-drug combination of ciprofloxacin, rifampin, ethambutol, and clofazimine. They concluded that their three-drug therapy regimen resolves the bacteremia more frequently than does the four-drug regimen, with better survival rates.[15] Although routine testing of all nontuberculous mycobacteria is discouraged,[16] there are circumstances where susceptibility testing is warranted, including having baseline data available if the patient does not respond to therapy or when relapses occur. Although susceptibility testing to macrolides (clarithromycin, azithromycin, roxithromycin) has proven clinical relevance for MAI, susceptibility testing to amikacin, ciprofloxacin, ethambutol, ethionamide, rifabutin, rifampin, and streptomycin has uncertain clinical relevance.[16]

For our patient, the treatment with standard antituberculous therapy was started in a peripheral hospital, but the MAI remained unresponsive, leading to consideration of other drug combinations. Subsequently, our patient responded to a triple-drug therapy of amikacin, clarithromycin, and ethambutol that was chosen based on in vitro sensitivity testing. Using this combination, the patient showed clinical improvement with negative in vitro cultures. This response has lasted for >4 years. Our patient continued treatment for only 16 months, whereas the current length of therapy recommended is for life.[16]

In conclusion, we report the first patient of dysgammaglobulinemia with disseminated MAI who also is the first patient with long-term remission with antiinfective therapy in the pediatric population. Therefore, we conclude that multiple-drug therapy can be effective in the treatment of MAI with antibody deficiency.

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