Familial Disseminated Infection Due to Atypical Mycobacteria with Childhood Onset

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We describe two brothers of consanguineous Pakistani parents who lived in Norway and had disseminated infections due to nontuberculous mycobacteria. The first boy developed clinical signs of disseminated BCG infection after vaccination. He was successfully treated with antimycobacterial agents. Two and one-half years later, he developed disseminated *Mycobacterium avium* complex infection and died at 6 years of age. The second boy, born 5 years after the death of his brother, did not receive BCG vaccine. At 2 years of age, he developed disseminated *M. avium* complex infection. Because he responded only partly to specific chemotherapy, empirical interferon γ treatment was added to the antimycobacterial regimen. After 2 years of combined therapy, his condition is stable. Studies of peripheral blood mononuclear cells from the second boy demonstrated reduced surface expression of the ligand binding chain of interferon γ receptor 1. This defect explains the increased susceptibility to mycobacterial disease in the two brothers.

Atypical mycobacteria are ubiquitous, and disseminated infections caused by these microorganisms are most commonly seen secondary to immunosuppressive therapy, in children with HIV infection, or in individuals with severe malnutrition [1, 2]. However, patients with disseminated infections due to atypical mycobacteria and no demonstrable defect of immunity have been repeatedly described over the years [1, 2]. In only a few of these idiopathic cases has susceptibility to mycobacterial infections been explained [3–8]. Recently, studies of children and adults from some of these families have allowed for the characterization of genetic defects of cellular immunity that predispose to disseminated mycobacterial infections [9, 10].

In the present report, we describe disseminated *Mycobacterium avium* complex (MAC) infection in two brothers of Pakistani descent who lived in Norway. The first boy died of his infection, whereas the younger brother is presently doing well and is receiving combined therapy with antimycobacterial drugs and IFN-γ. In vitro studies of peripheral blood mononuclear cells from the second boy demonstrated absent lymphocyte surface expression of IFN-γ receptor 1 (IFNγR1), a defect likely to be responsible for the increased susceptibility to mycobacterial disease in the two brothers.

Case Reports

We describe two boys with disseminated infections due to atypical mycobacteria. The parents are third cousins from Pakistan. The parents and two other siblings are healthy, whereas one girl has cerebral palsy and one girl was stillborn.

Case 1

This boy was born in Pakistan in 1979 and came to Norway at 5 months of age. He was admitted to the hospital in Kristiansand at 2 years of age, 6 weeks after BCG vaccination, because of fever, a generalized rash consisting of crops of vesicles and crusts, left axillary adenopathy, and hepatomegaly. The hemoglobin concentration was 6.1 g/dL, the leukocyte count was 29.0 × 10^9/L, and the erythrocyte sedimentation rate was 152 mm/h. A chest roentgenogram revealed no abnormalities, and routine cultures of blood and urine yielded no bacteria. Analysis of bone marrow was unremarkable. Histological examination of a biopsy specimen from the enlarged lymph node was inconclusive.

The patient was treated with antibiotics, but his clinical condition did not improve. After 4 weeks, he was still febrile. He had lost weight, his skin eruption persisted, and a fistula had developed in the left axilla. At this time, disseminated BCG infection was suspected. Therefore, the boy was treated with rifampin and isoniazid, and the enlarged lymph node was removed surgically. The clinical response was excellent. After 10 months, he was well and antimycobacterial therapy was stopped.

At 4.5 years of age, the boy stayed in Pakistan for 9 months. He experienced colitis-like symptoms, and *Entamoeba histolytica* was identified in his stools. He was treated with metronidazole, salazopyrin, and prednisone. In spite of eradication of *E. histolytica* from the stools, his condition deteriorated rapidly.

At 5 years of age, he was readmitted to the hospital in Kristiansand because of fever, paleness, and dehydration as...
well as weight loss, anemia, generalized lymphadenopathy, and hepatosplenomegaly. Laboratory investigations showed a hemoglobin concentration of 5.8 g/dL, the leukocyte count was 21.0 × 10^9/L, and the erythrocyte sedimentation rate was 154 mm/h. The serum albumin level was 15.8 g/L, whereas the serum sodium, potassium, chloride, creatinine, alanine aminotransferase, aspartate aminotransferase, and bilirubin levels were normal. Routine bacterial cultures of urine and blood were negative. *Campylobacter jejuni* was isolated from a stool specimen, and this organism was successfully treated with oral erythromycin for 10 days. A Mantoux skin test for mycobacteria was positive (induration, >4 mm). Serological tests for HIV were negative, as were examinations for enlarged lymph nodes. Examination of biopsy specimens from *Salmonella* species, and leishmaniasis.

The serum concentrations of IgG, IgM, IgA, C3, and C4 as well as complement-mediated total hemolytic activity were normal. The patient had normal differential and absolute counts of T and B lymphocytes. In addition, the patient’s mitogenic responses of peripheral blood mononuclear cells and granulocyte killing of staphylococci in vitro were normal. A chest roentgenogram showed pulmonary infiltrates in both lungs. Examination of mediastinal and inguinal lymph node biopsy specimens as well as a laryngeal biopsy specimen showed macrophages laden with numerous acid-fast bacilli. Cultures of gastric aspirate fluid, the above-mentioned biopsy specimens, and stool yielded MAC. The microorganism was resistant to rifampin, streptomycin, ethionamide, cycloserine, and capreomycin but was susceptible to ethambutol.

Despite several months of antimycobacterial therapy (isoniazid, rifampin, pyrazinamide, and ethambutol), antibiotics, multiple blood transfusions, and parenteral nutrition, the child died at 6 years of age of his disseminated *M. avium* complex infection and multiorgan failure. Permission for an autopsy was not granted.

**Case 2**

This boy was born in Norway 6 years after the death of his brother. He did not receive BCG vaccine and was healthy until 2 years of age, when he was admitted to the hospital in Kristiansand because of recurrent fever, weight loss, and hepatosplenomegaly. At the time of admission, he was pale and his liver and spleen were enlarged; there was no lymphadenopathy. The body temperature was 38.3°C. Laboratory tests showed a hemoglobin level of 8.1 g/dL, whereas the total leukocyte count was 46.0 × 10^9/L and the platelet count was 474 × 10^9/L. The differential leukocyte count demonstrated slight granulocytosis. The erythrocyte sedimentation rate was 114 mm/h, and the serum concentration of C-reactive protein was 172 mg/L.

The serum albumin level was 28 g/L, whereas the serum sodium, potassium, chloride, creatinine, alanine aminotransferase, aspartate aminotransferase, and bilirubin levels were normal. No coagulopathy was demonstrated. A Piroquet’s skin test for *Mycobacterium tuberculosis* was negative. Routine bacterial cultures of urine and blood were negative. Serological tests for *Mycoplasma, Chlamydia*, herpesvirus, cytomegalovirus, *Toxoplasma*, and HIV were negative. The serum concentrations of IgG, IgM, and IgA were 17.6 g/L, 7.29 g/L, and 1.99 g/L, respectively. The concentrations of C3 and C4 as well as complement-mediated total hemolytic activity were normal.

The patient’s granulocyte expression of Fcγ receptors I–III and complement receptors was normal, and granulocyte phagocytosis and oxidative burst were similar to controls. A chest roentgenogram showed a pulmonary infiltrate affecting the right upper lobe, and CT of the thorax and abdomen showed enlarged lymph nodes. Examination of biopsy specimens from mediastinal lymph nodes, liver, and bone marrow revealed nonspecific inflammation without signs of malignancy, distinct granulomata, or mycobacteria. Bronchoalveolar lavage fluid was negative for acid-fast bacilli and *Pneumocystis carinii*. The boy was treated with broad-spectrum antibiotics, but his clinical condition did not improve.

Subsequently, atypical mycobacteria were demonstrated in gastric aspirate fluid, and blood cultures yielded MAC. The strain was susceptible to ethambutol, rifabutin, and amikacin. The boy was treated with amikacin (for 5 months), rifabutin, ethambutol, and azithromycin, and his clinical condition improved gradually. However, the pulmonary infiltrate persisted, and during the last 2 years, he has received treatment with IFN-γ in addition to antimycobacterial therapy (rifabutin, ethambutol, and azithromycin). After nearly 5 years of specific treatment, the pulmonary infiltration has not completely subsided. However, the boy is presently doing well, and therapy will be continued.

**Studies of the function of peripheral blood mononuclear cells**. At the time of admission, the boy had normal differential and absolute counts of T lymphocytes (CD4^+^ cell count, 1,337 × 10^6^/L; CD8^+^ cell count, 1,504 × 10^6^/L), B lymphocytes (1,058 × 10^6^/L), and natural killer cells (1,170 × 10^6^/L). The proliferative responses of peripheral blood mononuclear cells to mitogen stimulation (phytohemagglutinin, concanavalin A, or pokeweed mitogen) were in the lower normal range. Flow cytometry of peripheral blood mononuclear cells with use of antibodies to IFN-γR1 (no. 1224-00; Genzyme, Cambridge, MA) showed no IFN-γR1 expression on the patient’s lymphocytes (figure 1).

**Discussion**

Before the AIDS epidemic, disseminated infections due to atypical mycobacteria were rare and usually described in severely malnourished or immunocompromised patients [1, 2]. However, infections have been described in children and adults with no demonstrable defect of immunity [1, 2], and our cases of familial disseminated infections due to atypical mycobacteria add new data to the few earlier reports on familial clustering of these infections [3–8]. The first boy of our family had
was born 6 years after his brother’s death, making the possibility of a common-source outbreak with a particularly virulent mycobacterial strain less likely and suggesting a common genetic host defense defect.

The mechanisms that lead to a protective immune response and away from progressive mycobacterial disease are still poorly understood. Familial clustering, racial differences in incidence, and twin studies suggest that genetic factors play a role in susceptibility [10]. Some studies of sporadic cases of idiopathic disseminated infections due to atypical mycobacteria demonstrated monocyte and macrophage dysfunctions, including defective capacity for intracellular killing [8], reduced motility in response to chemotactic stimuli [4], and decreased production of TNF-α [11]. In addition, studies of a familial cluster of disseminated MAC infections showed low IFN-γ production by peripheral blood mononuclear cells and abnormal monocyte regulation of IL-12 production in a boy and his two maternal uncles [5, 9]. Recently, disabling mutations in the IFNγR1 gene that lead to the absence of IFNγR1 on the cell surface were identified in a family with disseminated atypical mycobacterium infection [10]. Other mutations in the same gene, also leading to no detectable expression of IFNγR1, were reported in sporadic cases of disseminated infantile fatal BCG infection [12] and Mycobacterium smegmatis infection [13]. Jouanguy et al. [14] described a protein-positive hypofunctional mutation in IFNγR1 in association with clinical pulmonary tuberculosis.

Macrophages infected by intracellular mycobacteria produce IL-12, which promotes secretion of IFN-γ from T cells and natural killer cells [15]. Even though the final effector mechanisms involved in killing mycobacteria are not well characterized, IFN-γ plays a critical role in this process [15]. Hence, defective IFNγR1 expression deprives the cell of the opportunity to use IFN-γ and leads to an increased susceptibility to MAC infection. This defect in IFN-γ utilization likely accounts for the absence of granuloma formation in our patients as has been previously reported [12].

IFN-γ has been used in the management of chronic granulomatous disease, leprosy, leishmaniasis, and, recently, nontuberculous mycobacterium infections [5, 8]. Our second patient’s condition appeared to clinically improve somewhat after the addition of IFN-γ to the therapeutic regimen. This occurrence is hard to reconcile with the absence of IFNγR1 on his cell surface. However, similar modest improvements have been described for patients with IFNγR1 deficiency [6, 10]. Whether these responses reflect auxiliary pathways for IFN-γ utilization outside of IFNγR remains to be determined.

In conclusion, we identified disseminated infection due to MAC in two brothers of Pakistani descent who lived in Norway. The first boy died of his infection; the younger brother’s condition is stable, and he continues to receive combined therapy with antimycobacterial drugs and IFN-γ. Absent lymphocyte surface expression of IFNγR1 explains the susceptibility to mycobacterial disease in case 2 and is likely the explanation for his clinical improvement after the addition of IFN-γ to the therapeutic regimen.

**Figure 1.** Results of flow cytometry of peripheral blood lymphocytes from a normal individual and a boy with disseminated infection due to atypical mycobacteria (case 2); this analysis was used to determine lymphocyte surface expression of IFN-γ receptor 1 (IFNγR1). Unconjugated antibody to IFNγR1 (no. 1224-00; Genzyme, Cambridge, MA) with fluorescein isothiocyanate–labeled goat antibody to mouse (GAM) was used, and results were read on a FACScan flow cytometer (Becton Dickinson, San Jose, CA). – – – = background staining with isotype control antibody; ——— — = specific staining for IFNγR1; top panel = normal individual’s lymphocytes with an easily discerned IFNγR1 staining population well separated from the isotype control; bottom panel = the patient’s lymphocytes, in which identity of the isotype control and the IFNγR1-stained cells is noted, thus indicating the absence of IFNγR1.
for the disease seen in case 1. These cases confirm the central role of IFN-γR1 in protection against infections due to nontuberculous mycobacteria and highlight the importance of looking for this defect in children with unexplained disseminated mycobacterial infections.

References