IMMUNE RECONSTITUTION SYNDROME FROM NONTUBERCULOUS MYCOBACTERIAL INFECTION AFTER INITIATION OF ANTIRETROVIRAL THERAPY IN CHILDREN WITH HIV INFECTION

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Abstract: The immune reconstitution syndrome caused by nontuberculous mycobacterial (NTM) infection is reported in 9 of 153 HIV-infected children 2 to 26 weeks after initiation of antiretroviral therapy. The clinical syndrome included fever and dyspnea (2 children), fever and abdominal pain (3), subcutaneous nodules or suppurative lymphadenitis (4). The causative species were Mycobacterium avium (4), Mycobacterium scrofulaceum (3), Mycobacterium kansasi (1) and Mycobacterium simiae (1).

Keywords: human immunodeficiency virus, immune reconstitution syndrome, nontuberculous mycobacterial infection, antiretroviral therapy

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The advent of antiretroviral therapy (ART) has dramatically changed the prognosis of HIV disease by enabling sustained suppression of HIV replication and recovery of CD4 cells.1,2 Within the first few months of ART, the HIV viral load sharply decreases, whereas the number of CD4 cells rapidly increases.3 This leads to an increased capacity to mount inflammatory reactions against both infectious and noninfectious antigens. The immune reconstitution syndrome (IRS) is an exaggerated immune response to a latent antigen during the immune recovery period usually within 3 months after ART. The majority of antigens causing IRS are those associated with infectious microorganisms.4 IRS associated with infectious agents may arise in 2 different settings: unmasking of disease in a clinically stable patient with previously unrecognized infection (unmasking type) or worsening of disease in a patient being treated for ongoing opportunistic infection (worsening type).5 There were several reports of IRS in HIV-infected adults with mycobacterial infection, both tuberculous5–9 and nontuberculous mycobacterial (NTM) infection.9–12 However, there were few such reports in HIV-infected children.13–15

We report the incidence rate, clinical characteristics and risk factors of IRS caused by NTM infection in HIV-infected children after initiation of ART.

PATIENTS AND METHODS

From May 2002 to April 2004, we prospectively observed all 153 HIV-infected children who started receiving ART in a national program providing access to ART at 3 hospitals in Northern Thai-
### TABLE 1. Immune Reconstitution Syndrome Associated With Nontuberculous Mycobacterial Infection in 9 HIV-Infected Children After Initiation of Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex, Age (years)</th>
<th>CD4 T Cell (%) (cell/μL)</th>
<th>HIV RNA Level (log10 copies/mL)</th>
<th>Time to Onset (weeks)</th>
<th>Clinical Manifestations (previous diagnosis)</th>
<th>Investigations</th>
<th>Microbiology</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Nearest to IRS</td>
<td>Baseline</td>
<td>Nearest to IRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmasking type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F, 10</td>
<td>0% (5) 2% (31)</td>
<td>5.02</td>
<td>1.70</td>
<td>Fever, abdominal pain</td>
<td>US abdomen: multiple mesenteric lymphadenopathy with mild ascites</td>
<td>HC: <em>Mycobacterium scrofulaceum</em></td>
<td>2 NRZCE + 17 CECi</td>
<td>Dead*</td>
</tr>
<tr>
<td>2</td>
<td>M, 11</td>
<td>0% (3) 7% (15)</td>
<td>4.86</td>
<td>ND</td>
<td>Fever, abdominal pain</td>
<td>Upper GI scope: duodenal nodules, pathology found granuloma with AFB</td>
<td>HC: <em>M. scrofulaceum</em></td>
<td>CECi</td>
<td>Dead*</td>
</tr>
<tr>
<td>3</td>
<td>F, 6</td>
<td>4% (97) 5% (59)</td>
<td>5.56</td>
<td>1.70</td>
<td>Fever, supraclavicular lymphadenitis</td>
<td>LC biopsy: granulomatous inflammation with foamy histiocytes contain AFB</td>
<td>HC: <em>Mycobacterium avium</em></td>
<td>2 CECi + 10 CE</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>M, 8</td>
<td>0% (6) 5% (126)</td>
<td>5.50</td>
<td>2.60</td>
<td>Multiple subcutaneous nodules</td>
<td>Aspiration: pus AFB positive</td>
<td>HC: <em>Mycobacterium kansasii</em></td>
<td>7 CECi + 5 CE</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>F, 9</td>
<td>2% (33) 8% (188)</td>
<td>5.40</td>
<td>2.22</td>
<td>Multiple subcutaneous nodules</td>
<td>Aspiration: pus AFB positive</td>
<td>HC: negative pus: <em>M. scrofulaceum</em></td>
<td>1 NCEG + 11 NECi</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>M, 7</td>
<td>1% (31) 9% (100)</td>
<td>ND</td>
<td>4.78</td>
<td>Multiple subcutaneous nodules</td>
<td>Aspiration: pus AFB positive</td>
<td>HC: MAC pus: MAC</td>
<td>6 CECi + 6 CE</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>F, 9</td>
<td>6% (44) 19% (214)</td>
<td>5.57</td>
<td>1.70</td>
<td>Fever, pneumonia with acute respiratory distress syndrome</td>
<td>Chest radiograph: bilateral diffused alveolar infiltration BAL: AFB positive</td>
<td>HC: <em>M. avium</em> BAL fluid: <em>M. avium</em></td>
<td>NRZCE + prednisolone</td>
<td>Dead*</td>
</tr>
<tr>
<td>Worsening type</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M, 7</td>
<td>1% (21) 4% (200)</td>
<td>5.47</td>
<td>2.60</td>
<td>Fever, abdominal pain (disseminated MAC HC and stool: MAC)</td>
<td>US: multiple mesenteric lymphadenopathy</td>
<td>HC: negative</td>
<td>10 CECi + 2 CE</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>M, 7</td>
<td>0% (4) 17% (236)</td>
<td>ND</td>
<td>ND</td>
<td>High-grade fever, dyspnea (disseminated <em>Mycobacterium simiae</em> HC and sputum: <em>M. simiae</em>)</td>
<td>Chest x-ray: worsening of previous pulmonary infiltration</td>
<td>Sputum: AFB negative</td>
<td>12 CECi + prednisolone + temporary discontinue of ART</td>
<td>Alive</td>
</tr>
</tbody>
</table>

*Patient no.1 developed chylous ascites secondary to lymphatic obstruction on 48 weeks after ART initiation and he subsequently died of *Escherichia coli* sepsis at week 74 of ART. Patient no. 2 died from *Pseudomonas aeruginosa* septicaemia 5 weeks after ART initiation. Patient no.7 died from acute respiratory distress syndrome 4 days after diagnosis with IRS.

ND indicates not determined; MAC, *Mycobacterium avium* complex; MAC include *M. avium* complex, *M. intracellulare*, and unclassified MAC; AFB, acid fast bacilli; ART, antiretroviral therapy; BAL, bronchoalveolar lavage; FNA, fine needle aspiration; HC, hemoculture; LN, lymph node; US, ultrasound.

Antimicrobial treatment: C, clarithromycin; Ci, ciprofloxacin; K, ethambutol; N, isoniazid; O, ofloxacin; R, rifampin; Z, pyrazinamide.
119 cells/μL, his plasma HIV RNA was undetectable and his repeated blood cultures for Mycobacterium spp. were negative. He subsequently died of Escherichia coli sepsis at week 74 of ART. Patient no.2 died of Pseudomonas aeruginosa septicemia. He had been receiving ART and antimycobacterial therapy for 5 and 2 weeks, respectively. The death of patient no.7 was attributed to M. avium IRS, which presented as acute respiratory distress syndrome (ARDS) on week 26 of ART. She died 4 days after the diagnosis of IRS was made.

Patients who developed NTM IRS had lower baseline percentage of CD4 cells compared with those who did not (1.6% [SD 2.1] and 5.5% [SD 4.8], P = 0.03). However, the immunologic and virologic responses at weeks 8, 24 and 48 after ART were not statistically different between the 2 groups.

DISCUSSION

We described 9 HIV-infected children who developed an IRS caused by NTM infection after initiation of ART. The common species were M. avium and M. scrofulaceum. The management included anti-NTM therapy, continuation of ART and judicious use of steroid therapy.

NTM has been reported as a major causative agent in both children and adults with IRS.12 There are several factors contributing to this occurrence of NTM IRS in our cohort. First, there is a high prevalence of mycobacterial infections caused by both tuberculosis and NTM organisms in HIV-infected individuals in Thailand.17–19 Second, at the start of ART, the patients were severely immunosuppressed with a mean baseline percentage of CD4 cells of 5% and absolute CD4 cell count of 134 cells/μL. Finally, primary chemoprophylaxis for NTM infection is not routinely prescribed in Thailand.

There were 2 clinical patterns observed in our cohort. All but one of the unmasking types of NTM IRS occurred within the first 5 weeks of ART. The 2 cases with the worsening type of IRS manifested later in the course of ART. The main clinical presentations of NTM IRS were pulmonary disease, intraabdominal disease and subcutaneous nodules or peripheral lymphadenitis, similar to the report in adults.12 The clinical characteristics of NTM IRS were different from that observed in patients not receiving ART. The tissue inflammation and constitutional symptoms were more prominent, which reflected immune reconstitution. Pulmonary symptoms were presented with exaggerated inflammatory reactions such as ARDS. Goldsack and coworkers8 reported ARDS from M. tuberculosis as a severe manifestation of IRS occurring 14 days after the start of ART. In our study, we reported ARDS in a patient who was infected with M. avium complex. Histopathologic study of the biopsied specimens of the lymph nodes and subcutaneous nodules showed prominent granulomatous and/or supplicative inflammation. This is similar to what have been reported in adults.

In our cohort, we managed IRS with the use of appropriate anti-NTM therapy, continued highly active ART to further reconstitute immune function and use of steroid when the patient was at risk for inflammatory damage to major organs (eg, lungs). There are no clear guidelines on when to temporary discontinue ART. In general, discontinuation of ART should be considered if the inflammatory responses are considered life-threatening and not amenable to steroids. With an overlapping clinical syndrome between tuberculosis and NTM infection, it is difficult to differentiate between these entities. In severe cases, antimicrobial agents that cover both organisms are needed while waiting for the culture result. Because of the disseminated pattern of the disease in our immunocompromised children, we used 3 anti-NTM drugs in the initial phase of the treatment. Because rifabutin is not available in Thailand, the drugs used were clarithromycin, ethambutol and ciprofloxacin. After the initial response, we used 3 anti-NTM drugs in the initial phase of the treatment.

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In conclusion, we described IRS associated with NTM infection in 9 HIV-infected children. The majority of events occurred within the first 5 weeks after the initiation of ART. The important risk factor is low baseline CD4 cell counts before initiation of ART. Clinicians should be aware of this syndrome and realize that this represents an enhanced immune response and not treatment failure or adverse drug reactions. When symptoms of suspected NTM IRS develop, appropriate use of anti-NTM drugs while maintaining ART proved to be useful.

REFERENCES


**IMMUNE RECONSTITUTION SYNDROME PRECIPITATED BY BACILLE CALMETTE GUERIN AFTER INITIATION OF ANTIRETROVIRAL THERAPY**

George K. Siberry, MD, MPH,* and Solomon Tessema, MD†

Abstract: Immune reconstitution syndrome resulting from bacille Calmette Guerin (BCG) vaccine occurring 2 weeks to 2 months after institution of antiretroviral therapy (ART) in children has been well documented. We report the earliest onset of BCG-related immune reconstitution syndrome developing 1 week after initiation of ART.

Key Words: bacille Calmette Guerin (BCG), HIV, immune reconstitution syndrome, pediatric

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**CASE REPORT**

A 9-month-old Ethiopian infant was hospitalized because of bacterial pneumonia, severe malnutrition and stunted growth. Detection of HIV antibodies was consistent with previously unrecognized perinatal HIV exposure, and HIV virologic testing confirmed infection in the infant. The infant had received the standard, single-dose of BCG vaccine in the neonatal period. Baseline CD4 lymphocyte values were 9.6% and an absolute count of 582 per mm3, consistent with severe immunosuppression.7 An ART regimen of zidovudine, lamivudine and nevirapine was initiated in the hospital. Baseline viral load testing result was not available, but HIV quantitative RNA obtained 5 days after ART initiation was 122,000 copies per milliliter. While still in the hospital, on day 7 of ART, the BCG site became markedly swollen and erythematous. The infant did not have fever, gastrointestinal symptoms, new pulmonary findings or disseminated lymphadenopathy. Two weeks after ART initiation and 1 week after onset of apparent BCG disease, the absolute CD4 lymphocyte count rose to 716 per mm3 (no percentage available). The inflamed BCG site developed purulent drainage, then

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Age at BCG Vaccination</th>
<th>Age of BCG Disease Onset</th>
<th>BCG Disease Features</th>
<th>Weeks on Antiretroviral Therapy</th>
<th>Baseline CD4 Percent (absolute count)</th>
<th>First CD4 Available After Immune Reconstitution Syndrome Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp³</td>
<td>Australia (Indonesian immigrant)</td>
<td>Birth</td>
<td>8 mo</td>
<td>Fever, suppurative LAN (axillary, supraclavicular)</td>
<td>2</td>
<td>10%</td>
<td>26%</td>
</tr>
<tr>
<td>Hesselings⁴</td>
<td>South Africa</td>
<td>Birth</td>
<td>4 mo</td>
<td>Ipsilateral LAN (axillary); HSM, pulmonary tuberculosis</td>
<td>3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Puthanakit¹</td>
<td>Thailand</td>
<td>Birth</td>
<td>9 yr</td>
<td>Ipsilateral LAN (axillary)</td>
<td>4</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Puthanakit²</td>
<td>Thailand</td>
<td>Birth</td>
<td>8 yr</td>
<td>Abscess, ipsilateral LAN (axillary)</td>
<td>8</td>
<td>13%</td>
<td>24%</td>
</tr>
<tr>
<td>Current case</td>
<td>Ethiopia</td>
<td>Birth</td>
<td>9 mo</td>
<td>Abscess</td>
<td>1</td>
<td>9.6% (582)</td>
<td>— (716)</td>
</tr>
</tbody>
</table>

LAN indicates lymphadenopathy.