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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 kansasii* (1) and *Mycobacterium simiae* (1).

Keywords

human immunodeficiency virus; immune reconstitution syndrome; nontuberculous mycobacterial infection; antiretroviral therapy

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 tuberculous[6–9] and nontuberculous

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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 Thailand, namely the Chiang Mai University Hospital, Lamphun Provincial Hospital and Sanpatong District Hospital.[15] The inclusion criteria were symptomatic HIV infection with severe immunosuppression defined as a baseline CD4 cell percentage of ≤ 15. All patients were observed for at least 12 months after initiation of ART. Patients attended study visits at weeks zero (start of treatment), 2, 4, 8, 12, 18, 24, 32, 40 and 48. During each visit, we reviewed the patient's medical history and did a physical examination. All care-givers were counseled initially and at each visit about adherence to ART, adverse drug events and opportunistic infections. In addition, they were counseled to recognize signs and symptoms indicative of an IRS and to seek appropriate care. These included: 1) persistent fever (defined as temperature > 38.5°C) with symptoms of respiratory tract (eg, dyspnea, cough) or gastrointestinal tract involvement (eg, abdominal pain, diarrhea); or 2) appearance of enlarged lymph nodes or subcutaneous nodules.

Cases of NTM IRS were defined by 1) evidence of a favorable response to antiretroviral therapy, defined as a reduction in HIV RNA load of at least 2 $\log_{10}$ copies/mL or an increase in CD4 lymphocyte percentage of ≥5%, 2) a temporal association between the initiation of antiretroviral therapy and the onset of disease and 3) positive culture for NTM of samples from normally sterile body fluid or from inflammatory lesions. Blood culture was performed by BACTEC 9000MB (Becton Dickinson, MD) using a fluorescence detection system. Cultures from other clinical specimens were performed on Lowenstein-Jensen media. Species identification of *Mycobacterium spp.* was carried out by using the polymerase chain reaction and restriction enzyme analysis technique as previously described.[16] Determination of CD4 cell count and plasma HIV RNA titer was performed at weeks 0, 8, 24 and 48 of ART and whenever clinical syndrome of IRS was noted. CD4 cell counts were performed by a FACSCount apparatus (Becton Dickinson, Mountain View, CA). Plasma HIV RNA level was measured by the Roche Ultrasensitive Amplicor assay, version 1.5 (Roche Diagnostic, NJ). The study was approved by the research ethics committee of Chiang Mai University. Written informed consent was obtained from each child's parent or guardian before enrollment.

Of the 153 HIV-infected children, the mean age at initiation of ART was 7.9 years (standard deviation [SD] 2.8), the mean baseline percentage of CD4 cells was 5.0 (SD 4.7), the mean baseline CD4 cell count was 134 cells/μL (SD 165) and the mean baseline plasma HIV RNA titer was 5.3 $\log_{10}$ copies/mL (SD 0.5). Nine patients were identified as having IRS caused by NTM infection. The clinical characteristics of the patients are shown in Table 1. There were 7 cases of unmasking of previously unrecognized NTM infection and 2 cases of paradoxic worsening of treated NTM infection. The overall incidence rate was 5.9 cases per 100 persons (95% confidence interval = 2.7–10.9). The median time from initiation of ART to the onset of clinical symptoms was 3 weeks (range, 2–26 weeks). The clinical syndrome included fever and dyspnea (2 cases), fever and abdominal pain (3 cases) and subcutaneous nodules or suppurative lymphadenitis (4 cases). The causative species were *Mycobacterium avium* complex (4 cases), *Mycobacterium scrofulaceum* (3 cases), *Mycobacterium kansasii* (one case) and *Mycobacterium simiae* (one case). At the time the diagnosis of IRS was made, NTM could

be cultured from all 7 patients who had the unmasking type of IRS but from none of the 2 patients with the worsening type.

Two patients with severe manifestations (patient nos.1 and 7) were initially treated with 5 antimicrobial agents (isoniazid, rifampin, pyrazinamide, ethambutol and clarithromycin) to cover both *Mycobacterium tuberculosis* and NTM. The treatment regimen was then adjusted after mycobacterial species was identified. Three patients died. Patient no.1 developed chylous ascites secondary to lymphatic obstruction on week 48 of ART while his CD4 cell was 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[15] and adults with IRS.[4,9,12] 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 reaction such as ARDS. Goldsack and coworkers[8] 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 suppurative inflammation. This is similar to what have been reported in adults.[10,11]

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, 2 drugs, usually clarithromycin and ethambutol, were continued to complete a 12-month course of treatment. Secondary prophylaxis was not needed in our cohort, because by the completion of 12-month therapy, the patients' CD4 cell counts were > 100 cells/μL for more than 6 months.[20] Response to therapy in our cohort was slow. This seemed to be related to the nature of the NTM diseases and the severely impaired immune response in these children. Because the unmasking type of NTM IRS is not uncommon, NTM infection should be ruled out or properly treated before the initiation of ART, especially in patients with low baseline CD4 cell counts.

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.

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TABLE 1

Immune Reconstitution Syndrome Associated With Nontuberculous Mycobacterial Infection in 9 HIV-Infected Children After Initiation of Antiretroviral Therapy

Patient No.	Sex, Age (years)	CD4 T Cell (%) (cell/uL)		HIV RNA Level (log_{10} copies/mL)		Time to Onset (weeks)	Clinical Manifestations (previous diagnosis)	Investigations	Microbiology	Management	Outcome
		Baseline	Nearest to IRS	Baseline	Nearest to IRS						
Unmasking type											
1	M, 10	0% (5)	2% (31)	5.02	1.70	2	Fever, abdominal pain	US abdomen: multiple mesenteric lymphadenopathy with mild ascites	HC: *Mycobacterium scrofulaceum*	2 NRZCE + 17 CECi	Dead*
2	M, 11	0% (3)	7% (15)	4.86	ND	2	Fever, abdominal pain	Upper GI scope: duodenal nodules, pathology found granuloma with AFB	HC: *M. scrofulaceum*	CECi	Dead*
3	F, 6	4% (97)	5% (59)	5.56	1.70	2	Fever, supraclavicular lymphadenitis	LN biopsy: granulomatous inflammation with foamy histiocytes contain AFB	HC: *Mycobacterium avium* LN biopsy: *Mycobacterium avium*	2 CECi + 10 CE	Alive
4	M, 8	0% (0)	5% (126)	5.50	2.60	3	Multiple subcutaneous nodules	Aspiration: pus AFB positive	HC: *Mycobacterium kansasii* pus: negative	7 CECi + 5 CE	Alive
5	F, 9	2% (33)	8% (188)	5.40	2.22	3	Multiple subcutaneous nodules	Aspiration: pus AFB positive	HC: negative pus: *M. scrofulaceum*	1 NCECi + 11 NECi	Alive
6	M, 7	1% (31)	9% (100)	ND	4.78	5	Multiple subcutaneous nodules	Aspiration: pus AFB positive	HC: MAC pus: MAC	6 CECi + 6 CE	Alive
7	F, 9	6% (44)	19% (214)	5.57	1.70	26	Fever, pneumonia with acute respiratory distress syndrome	Chest radiograph: bilateral diffused alveolar infiltration BAL: AFB positive	HC: *M. avium* BAL fluid: *M. avium*	NRZCE + prednisolone	Dead*
Worsening type											
8	M, 7	1% (21)	4% (200)	5.47	2.60	10	Fever, abdominal pain (disseminated MAC HC and stool: MAC)	US: multiple mesenteric lymphadenopathy	HC: negative	10 CECi + 2 CE	Alive
9	M, 7	0% (4)	17% (236)	ND	ND	23	High-grade fever, dyspnea (disseminated *Mycobacterium simiae* HC and sputum: *M. simiae)*	Chest x-ray: worsening of previous pulmonary infiltration	Sputum: AFB negative	12 CECi + prednisolone + temporary discontinue of ART	Alive

* 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* septicemia 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; E, ethambutol; N, isoniazid; O, ofloxacin; R, rifampin; Z, pyrazinamide.