Case Report

NECK MASSES AS A MANIFESTATION OF MYCOBACTERIAL IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED CHILDREN

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Abstract We described immune reconstitution inflammatory syndrome (IRIS) associated with mycobacterial infection in 2 HIV-infected male children. Both cases had severe immune suppression at the initiation of antiretroviral therapy (ART), with a known risk of IRIS. They presented with neck masses that were enlarged and inflamed lymph nodes, which represented an enhanced immune response after 6 weeks of the initiation of an effective ART. The first boy had an unmasking type of M. scrofulaceum IRIS, and the second a worsening type or paradoxical exacerbation of tuberculosis after switching to second line protease inhibitor-based ART. Although both children survived, management was complicated, due to interaction between anti-tuberculous and antiretroviral drugs.

Keywords: HIV, children, immune reconstitution inflammatory syndrome, mycobacterium, lymphadenitis

Immune reconstitution inflammatory syndrome (IRIS) is a complication that usually occurs during the first 3-6 months of antiretroviral treatment (ART). It is caused by an exaggerated immune response to antigens that are usually associated with infectious microorganisms.(1,2) IRIS 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 or paradoxical exacerbation of disease in a patient already treated or being treated for ongoing opportunistic infection (“worsening type”). The risk factors for developing IRIS include a low baseline CD4 cell count and significant decline in plasma HIV RNA level at the time of IRIS.(2,3)

The number of reported mycobacterial IRIS cases in children is limited.(3-6) Although cutaneous, subcutaneous nodules/abscesses have been reported in HIV-infected children with mycobacterial IRIS; localized cervical lymphadenitis/abscesses have not been described.(3-5) In this communication, we report 2 boys who developed neck masses 6 weeks after effective ART initiation (Table 1).

Case reports

Case 1
A 14-year-old Thai boy, presenting at Lamphun Provincial Hospital, complained of having
**Table 1.** Immune reconstitution inflammatory syndrome associated with mycobacterial infection in HIV-infected children while receiving antiretroviral therapy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>CD4 cell count, % (cell/μL)</th>
<th>Prior to effective ART</th>
<th>Nearest to IRIS</th>
<th>HIV RNA level, copies/mL (log10)</th>
<th>Duration between effective ART initiation and onset of IRIS (week)</th>
<th>Types of IRIS</th>
<th>Clinical manifestations (Previous diagnosis)</th>
<th>Investigations</th>
<th>Microbiology</th>
<th>Management (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>M, 14</td>
<td>14</td>
<td>1% (11) ART initiation</td>
<td>3% (118)</td>
<td>NA</td>
<td>8 wk after occurrence of neck mass, 14 wk after ART initiation</td>
<td>6 Unmasking: Neck masses</td>
<td>Chest radiography: normal</td>
<td>HC: no growth</td>
<td>Pus: M. scrofulaceum</td>
<td>INRZEC +5EC</td>
<td>alive</td>
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<td></td>
<td></td>
<td>8% (320)</td>
<td>17 wk after occurrence of neck mass, 23 wk after ART initiation</td>
<td>&lt;50 (1.70 log10)</td>
<td>Unmasking: Neck masses</td>
<td>Chest radiography: normal</td>
<td>HC: no growth</td>
<td>Pus: M. scrofulaceum</td>
<td>INRZEC +5EC</td>
<td>alive</td>
</tr>
<tr>
<td>2)</td>
<td>M, 8</td>
<td>8</td>
<td>0% (2) ART initiation</td>
<td>11% (120)</td>
<td>9 wk after occurrence of neck mass, 15 wk after PI-based regimen</td>
<td>318156 (5.50 log10) ART initiation</td>
<td>9 wk after occurrence of neck mass, 15 wk after PI-based regimen</td>
<td>6 Unmasking: Neck masses, Fever, Pulmonary infiltration (Pulmonary tuberculosis)</td>
<td>Chest radiography: worsening of previously healed pulmonary infiltration</td>
<td>HC: no growth</td>
<td>LN biopsy culture: no growth</td>
<td>12NZE0</td>
<td>alive</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9% (142)</td>
<td>25 wk after occurrence of neck mass, 31 wk after PI-based regimen</td>
<td>&lt;50 (1.70 log10)</td>
<td>Unmasking: Neck masses</td>
<td>Chest radiography: worsening of previously healed pulmonary infiltration</td>
<td>HC: no growth</td>
<td>LN biopsy culture: no growth</td>
<td>12NZE0</td>
<td>alive</td>
</tr>
</tbody>
</table>

Antimicrobial treatment: C, clarithromycin; E, ethambutol; N, isoniazid; O, ofloxacin; R, rifampin; Z, pyrazinamide. HC, hemoculture, LN, lymph node.
had several masses on the right side of his neck for 9 weeks. Seventeen weeks before this admission, he was diagnosed with perinatal HIV infection after presenting with weight loss and oral thrush. His CD4 cell count was 1%, 11 cells/mm³. He was started on *Pneumocystis jirovaci* prophylaxis with trimethoprim-sulfamethoxazole, and GPO-virS30® (a fixed drug combination of stavudine at 30 mg, lamivudine at 150 mg and nevirapine at 200 mg) at 1 tablet twice daily. Six weeks after starting ART he developed subcutaneous masses on the right side of his neck, without response to oral antibiotics. He had no known exposure to tuberculosis.

**Physical examination**

He was a thin (body weight below the fifth percentile for age), short (height at the fifth percentile for age), and developmentally age-appropriate boy. He was afebrile with normal vital signs. His liver was palpable 2 cm below the right costal margin, with multiple pruritic papular eruptions at all extremities. Several enlarged cervical lymph nodes on the right side were palpable and tender, including a 2x2 cm enlarged and inflamed node, which had eroded the skin (Fig. 1).

**Investigations** (Table 1)

A small amount of purulent fluid was obtained by needle aspiration at an intact fluctuated enlarged lymph node. Gram staining of the fluid revealed moderate white blood cells and no bacteria. Ziehl-Neelsen staining of the fluid demonstrated few acid-fast organisms (AFB) per oil-power field (Fig. 2). A tuberculin skin test revealed 4 mm. of induration approximately 72 hours after placement. A complete blood count recorded Hb 10.5 g/dL, Hct 36%, WBC 7,590 cells/µL (35% neutrophils, 43% lymphocytes, 11% monocytes, 11% eosinophils), and platelets at 343,000 cells/µL. Two blood cultures for mycobacterial organisms were sterile. Three induced spuata were negative for AFB by microscopy. Radiography of the chest was unremarkable. Aspirated fluid grew *Mycobacterium spp* on Lowenstein-Jensen media, which was later identified as *Mycobacterium scrofuracium* by using the polymerase chain reaction and restriction enzyme analysis technique as previously described.\(^7\)

CD4 cell counts were repeated twice at 8 and 17 weeks after the occurrence of neck masses, resulting in 3% (118 cells/mm³) and 8% (320 cells/ mm³), respectively. The patient's plasma HIV RNA level was <50 (<1.70 log 10) copies/mL (Table 1).

**Management and outcome**

The patient was treated with both anti-tuberculous and anti-nontuberculous mycobacterial drugs, including isoniazid, rifampin, pyrazinamide, ethambutol and clarithromycin, during the first month due to the delay in identifying the species of AFB. When the organism was identified, only clarithromycin and ethambutol were continued for a total of 6 months. While receiving rifampin, the patient’s ART was switched to stavudine, lamivudine and efavirenz for fear of nevirapine-rifampin interaction. The masses gradually became smaller and healed in 4 months.

**Case 2**

An 8-year-old HIV-infected Thai boy, presenting at Lamphun Provincial Hospital, complained of having had several masses on his neck and low-grade fever for 6 weeks. Four years before, he was diagnosed as perinatal HIV infected; with a CD4 cell count of 0%, 2 cells/mm³ and plasma HIV RNA level at 318,156 (5.50 log10) copies/mL. He was started on ART, GPO-virS30, at 1/2 tablet twice daily. Two months after ART ini-
tiation, his CD4 count was 8%, 168 cells/mm$^3$ and one month later he started to have fever and cough. At that time, he had been treated for pulmonary tuberculosis for 12 months. His highest CD4 count was 16 %, 487 cells/mm$^3$, but his plasma HIV RNA level remained detectable at 8,989, 23,900 and 48,644 copies/mL. The last test had resulted in 78,727 (4.90 log10) copies/mL 2.5 years before this study. About one year previously, his CD4 cell count gradually decreased to below 200 cells/mm$^3$. Then, his ART regimen was changed to a lopinavir/ritonavir-containing regimen. Six weeks after switching, he developed multiple subcutaneous painless neck masses. He was given several antibiotics at a community hospital, but the lesions deteriorated. He was then transferred to Lamphun Provincial Hospital.

**Physical examination**

He was a thin (body weight below the fifth percentile for age), short (height at the fifth percentile for age), developmentally age-appropriate boy. His body temperature was 37.8 °C and other vital signs were within normal range. His liver was palpable 4 cm below the right costal margin. His liver enzymes were within normal range. A tuberculin skin test showed 15 mm. of induration approximately 72 hours after placement. Radiography of the chest on admission showed increased extension of the pulmonary infiltration with right pleural effusion, compared to his healed pulmonary lesion seen 4 months previously. Scant thick, purulent fluid was obtained by needle aspiration at an intact enlarged lymph node. Gram and Ziehl-Neelsen staining of the fluid revealed multiple white blood cells and no bacteria. Cultures showed no growth, and a blood culture for AFB was sterile. Biopsy of an enlarged lymph node revealed caseous and suppurative granulomatous inflammation without any organism. Several incision and drainage specimens were cultured for bacteria (including mycobacterial organisms) and fungus, with no growth shown. Three gastric aspirations were negative for AFB by microscopy, but one of the three grew *Mycobacterium tuberculosis*.

Nine weeks after the occurrence of neck masses, or 15 weeks after switching to a lopinavir/ritonavir-containing regimen, the patient’s CD4 cell...
Neck masses IRIS in HIV-infected children

The patient’s tuberculosis was treated with rifampin-sparing anti-tuberculous drugs for one year, including isoniazid, pyrazinamide, ethambutol and ofloxacin, due to his need for a protease inhibitor (lopinavir/ritonavir) in his ART regimen. Four months after starting anti-tuberculous drugs, his HIV RNA level was undetectable and CD4 cell count 183 cells/mm³. The lymph node lesions continued to rupture, resulting in purulent discharge, and organisms neither showed nor grew. Incision and drainage procedures were performed several times, and it took 12 months for all the patient’s neck and axillary lesions to heal, leaving multiple scars. The added abnormalities in his chest radiography were resolved.

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Discussion

We described 2 HIV-infected, male children. Both developed localized cervical lymphadenitis; the first one 6 weeks after initiation of ART, and the second 6 weeks after switching to an effective ART. Localized cervical lymphadenitis is extensively treated at the outpatient clinics of several community hospitals with antibiotics commonly used to treat purulent cervical lymphadenitis, without success. By the time our patient’s were referred to Lamphun Provincial Hospital, some enlarged lymph nodes had eroded the skin. The children in this study and their families suffered from the chronic nature of the boy’s neck masses.

Both cases had severe immune suppression at ART initiation, which is known for its risk of IRIS.\cite{2,3} The first boy had the unmasking scenario of M. scrofulaceum IRIS. His CD4 cell count rose from 11 cells/mm³ to 118 cells/mm³ nearest to the time of neck mass occurrence. This finding, together with an undetectable HIV RNA level at 17 or 23 weeks after ART initiation, confirmed his immune recovery. He most likely had occult M. scrofulaceum cervical lymphadenitis before initiation of ART. The disease was unmasked by immune recovery, causing local lymphadenitis, which was followed by erosion through the skin. The “unmasking” type of local lymphadenitis explained the finding that AFB could be easily seen and cultured from the neck mass aspirate, while blood culture did not show any growth. That the patient had a negative tuberculin skin test is not surprising because the causative organism was not M. tuberculosis. Although some cases of non-tuberculous mycobacterial infection in immunocompetent hosts can produce a positive tuberculin skin test, such findings are unlikely in HIV-infected cases. In the second boy, the first episode of “pulmonary tuberculosis”, 4 years before, could have been the “unmasking” type of IRIS, which occurred 12 weeks after first line ART initiation, while his CD4 count rose from 0 to 168 cells/mm³. The second episode was a worsening or paradoxical exacerbation of tuber-

Figure 3. Multiple bilateral cervical, submandibular and submental enlarged lymph nodes, with some fluctuating and others having purulent drainage.
crosis after switching to second line (protease inhibitor-based) ART. The patient had already received anti-tuberculous treatment for his pulmonary disease, with clinical recrudescence 4 years before, and he presented with worsening of that previous pulmonary infiltration, new pleural effusion and multiple cervical lymphadenitis/cold abscesses. Although his CD4 cell count prior to switching to second line ART was not available, it was 120 cells/μL 9 weeks after the occurrence of neck masses, or 15 weeks after the switching. His HIV RNA levels decreased to 3.2 log10 copies/mL. These findings supported his immune recovery at the time of the neck mass episode. The ongoing cervical lymphadenitis gradually became draining abscesses slowly subsided within 9 months. Biopsy of an enlarged lymph node adjacent to an abscess revealed multiple caseating granulomas and no AFB organism. Several gastric aspirates and a neck abscess aspirate revealed no AFB. Only one of 3 gastric aspirate cultures grew *M. tuberculosis*, a mycobacterial blood culture showed no growth, and a tuberculin skin test was positive (15 mm of induration). These findings demonstrated an antigen-driven immune activation, with a robust immune response in the setting of few organisms, which supported the scenario of a worsening or paradoxical exacerbation type of IRIS.({2})

Information about the incidence and spectrum of IRIS in children is limited. We described IRIS in 153 symptomatic HIV-infected Thai children in advanced stages (CD4 lymphocyte count <15%). The incidence of IRIS was 19% with a median onset of 4 weeks (range 2-31 weeks) after ART initiation. Nearly 50% of these (14/32) were associated with mycobacterial organisms.({8}) In another study, in South Africa, 34/162 (21%) infant children developed IRIS at a median of 16 days (range 7-115 days) after ART initiation. Bacillus Calmette-Guérin reaction was the most common occurrence in 24 (71%) of the 34 children.({9})

IRIS occurred in this report 6 weeks after effective ART, which is similar to a previous study of nontuberculous IRIS in Thai HIV-infected children, but the prominent presentation of cervical lymphadenitis/cold abscesses in this report was not described in the previous study.({3}) These cervical lymphadenitis/cold abscesses represented local severe, chronic cervical lymphadenitis that eroded the skin.

Differentiation between *M. tuberculosis* and non-tuberculous *Mycobacterium* takes 4-6 weeks by conventional culture methods. While waiting for identification, both tuberculous and nontuberculous diseases may have to be treated, as in our first case. Effective first-line anti-tuberculous regimen includes isoniazid, rifampin, pyrazinamide and ethambutol. For non-tuberculous *Mycobacterium* diseases, initial empiric therapy should include at least two drugs: clarithromycin or azithromycin plus ethambutol.({10}) Although rifampin is a potent bactericidal drug for *Mycobacterium* organisms, it is a potent inducer of the CYP3A enzyme system that can reduce blood level of non-nucleoside reverse transcriptase inhibitors (nevirapine is more affective than efavirenz). We decided to replace nevirapine with efavirenz in the ART regimen of our first case. Clarithromycin levels can be decreased by efavirenz, but no data are available to recommend dose adjustments for children. Azithromycin has less significant interaction with efavirenz, but its use is limited, due to its high cost. Clarithromycin and ethambutol were continued to complete a 6-month course of treatment. Secondary prophylaxis was not needed in this case, as by the time 6-months therapy was completed, the child’s CD4 cell counts had been >100 cells/μL for more than 3 months.({10})

In contrast to non-nucleoside reverse transcriptase inhibitors, rifampin use is not allowed with all protease inhibitors.({10}) We decided to treat *M. tuberculosis* disease in our second case with a protease inhibitor-based regimen and rifampin-sparing regimen of isoniazid, pyrazinamide, ethambutol and ofloxacin for the first 2 months, followed by a continuation phase of isoniazid, pyrazamide and ethambutol to complete the 12-month course. Without rifampin in the regimen, the duration of treatment generally lasted a minimum of 12-18 months, with the exact length of therapy being based on clinical and radiologic improvement.({10})

In conclusion, we described IRIS associated with mycobacterial infection in 2 HIV-infected male children. Both IRIS events occurred at 6
weeks after the initiation of effective ART. The important risk factor is a low baseline of CD4 cell counts before the initiation of ART. Clinicians should be aware of this syndrome and realize that it represents an enhanced immune response and not treatment failure or adverse drug reactions. When symptoms of suspected mycobacterial IRIS develop, appropriate use of anti-mycobacterial drugs, while maintaining ART, is indicated. Recognizing and properly treating these conditions are essential and should be integrated into the antiretroviral treatment access programs.

References
เด็กติดเชื้อเอชไอวีที่มีภูมิคุ้มกันที่คอเป็นอาการแสดงของโรคภูมิคุ้มกันฟอร์มที่เกิดปฏิกิริยาต่อเชื้อมัยโคแบคทีเรีย

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บทคัดย่อ
รายงานผู้ป่วยเด็กชายติดเชื้อเอชไอวี 2 ราย ที่มีภูมิคุ้มกันที่คอเป็นอาการแสดงของโรคภูมิคุ้มกันฟอร์มที่เกิดปฏิกิริยาต่อเชื้อมัยโคแบคทีเรีย ทั้งสองคนมีภาวะภูมิคุ้มกันที่รุนแรงมากก่อนเริ่มยาต้านไวรัสเอชไอวีซึ่งเป็นปัจจัยเสี่ยงของการเกิดโรคภูมิคุ้มกันฟอร์มที่เกิดปฏิกิริยาต่อเชื้อในสองราย ทั้งคู่แสดงอาการของโรคหนึ่งง่ายได้ด้านไวรัสเอชไอวีที่มีประสิทธิภาพ 6 สัปดาห์ เพื่อค้นพบเจาะอาการชนิด unmasking จากเชื้อ M. scrofulacium จนที่สองแสดงอาการชนิด worsening จากเชื้อ M. tuberculosis ทั้งคู่หายจากโรคดังกล่าวได้ภายในเวลาของการรักษาที่ผ่านมา เพราะต้องให้ยาต้านไวรัสเอชไอวีร่วมกับการใช้ยาต้านวัณโรค ซึ่งอาจส่งผลกับรูปแบบการปฏิกิริยาต่อเชื้อ เซิม้าของวารสาร 2553; 49(2):67-74.

คำสำคัญ: เด็กติดเชื้อเอชไอวี โรคภูมิคุ้มกันที่คอ ต้านไวรัสเอชไอวี โรคภูมิคุ้มกันที่คอ ของยีนแตกต่าง ยาต้านวัณโรค มัยโคแบคทีเรีย