Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis

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Background: Some patients with HIV/tuberculosis (TB) coinfection who are on anti-TB treatment and highly active antiretroviral therapy (HAART) will develop an exacerbation of symptoms, signs or radiological manifestations of TB that are not due to relapse or recurrence of their TB. The aetiology of these immune reconstitution inflammatory syndrome (IRIS) reactions is unknown but it is presumed that they occur, at least in part, as a consequence of HAART-related reconstitution of immunity.

Methods: Patients who were diagnosed with their first episode of definitive or presumed TB between January 2001 and July 2003 were identified from the Chelsea and Westminster TB/HIV database. The patients were classified into those who developed IRIS and those who did not using a set definition of the syndrome. Demographic, clinical and laboratory data relating to both HIV and TB were compared between the two groups.

Results: A total of 55 cases of TB were identified, of which 45 cases were confirmed on culture or gene probe and 10 were presumed cases. Fourteen cases (25.5%) developed IRIS with a median (range) duration of 2.53 (0.53–14.97) months. The median baseline CD4 [interquartile range (IQR)] for the IRIS group was significantly lower at 80 (33–117) cells/mm³ (P=0.05) than the non-IRIS group at 139 (77–284) cells/mm³. A significantly greater proportion of patients in the IRIS group [11/14 (78.6%), P=0.011] had baseline CD4 <100 cells/mm³ compared with the non-IRIS group [16/41 (39.0%)]. There was no significant difference between the two groups when comparing the log₁₀ baseline viral load (VL). Eight (57.0%) patients in the IRIS group had disseminated TB at baseline compared with seven (17.0%) in the non-IRIS group (P=0.006). In those who had a detectable VL at baseline, the median fold change (IQR) in CD4 from baseline to 3 months was significantly higher in the IRIS group patients, 1.5 (0.6–5.6), compared with 0.7 (-0.2 to 1.0) for those in the non-IRIS group (P=0.046).

Conclusions: Patients who develop IRIS are more likely to present with disseminated TB, have a CD4 count <100 cells/mm³ and have a prompt rise in CD4 count in the initial 3 months of HAART.

Introduction

Some patients commencing antituberculosis (TB) treatment will develop an exacerbation of symptoms, signs or radiological manifestations of TB that are not due to relapse or recurrence. These ‘paradoxical’ reactions have been well described in patients without HIV infection but appear to occur more commonly in HIV-positive patients [1–4]. The aetiology of these reactions in HIV-positive patients is unknown but it is presumed that they occur, at least in part, as a consequence of highly active antiviral therapy (HAART)-related reconstitution of immunity, leading to an abnormal immune response to antigens released by dead or dying bacilli. This is termed immune reconstitution inflammatory syndrome (IRIS).

These reactions do not have a widely accepted definition and appear not to bear a relationship to initiation of anti-TB treatment. In the few studies where it has been examined, IRIS is characterized by the worsening or appearance of signs, symptoms or radiographical manifestations of TB that occur after initiation of HAART and are not the direct result of TB treatment failure or another disease process [5–10]. The symptoms and signs are often transient but can last many months. There are some data to suggest that the occurrence of IRIS is associated with the time of commencement of HAART [11,12]. In order to characterize the syndrome more clearly, diagnosis of HIV-related IRIS should only be made in patients taking antiviral therapy. Diagnosis must be one of exclusion as it can be confused with recrudescence of TB due to treatment failure and with drug hypersensitivity. Other infections common among immunocompromised patients should be excluded (see Box 1).

IRIS most often presents with fever and increased or new lymphadenopathy. Commonly, the skin over the
nodes can develop a dusky red inflammation and the nodes can spontaneously rupture. Pleural and pericardial effusions, ascites, psoas abscesses, cutaneous lesions, new or expanding central nervous system tuberculosis and worsening pulmonary lesions are also described [13–16]. The management of patients with IRIS is usually carried out with high doses of corticosteroids to control symptoms.

We have analysed clinical and laboratory factors of HIV/TB-coinfected patients diagnosed with IRIS and compared these with HIV/TB-coinfected patients who did not develop IRIS in an attempt to better characterize this enigmatic syndrome.

Methods

Patients who were diagnosed with their first episode of TB between January 2001 and July 2003 were identified from the Chelsea and Westminster TB/HIV clinical and laboratory databases. The demographic, clinical and laboratory data including TB diagnoses were verified using the original case records. TB was diagnosed definitively if a culture or genetic probe was positive for *Mycobacterium tuberculosis* (MTB). A presumptive diagnosis was made if a culture or probe were negative but if positive acid-alcohol fast bacilli (AAFB) smears were seen and/or an early response (less than 2 weeks) to TB treatment occurred. These patients were further classified into those who developed IRIS and those who did not.

Baseline CD4 count and viral load (VL) were defined as the last value recorded up to 3 months prior to commencement of TB therapy.

Statistical methods

Data were analysed using SAS (v8) statistical package (SAS Institute, Inc, Cary, NC, USA). Since the study sample was small, all quantitative data were analysed using non-parametric methods. Mann–Whitney U test statistics were used to compare the two study groups. Fisher’s Exact test was used to test for differences in proportions between the study groups. The log-rank method was used to compare the time to virological success (<50 copies/ml) between the two study groups. Gradients of CD4 count rise from baseline using time-weighted difference in averages were calculated.

Where appropriate, data were analysed including and excluding patients whose VL at baseline was below the level of detection (BLD group). In total, three steps in the analysis were performed: (i) the whole study sample, (ii) excluding the BLD group and (iii) patients who started HAART after commencing TB therapy. All *P* values presented are 2-tailed.

Results

A total of 55 cases of TB were identified, of which 45 were confirmed on culture or gene probe. The 10 patients with presumed TB were from countries with high rates of MTB – five of them had positive smears or histology with granulomas and/or AAFBs seen and one had clinical and cerebrospinal fluid (CSF) findings consistent with TB meningitis. All 10 responded to anti-TB treatment and none of them developed IRIS.

Analysis of all patients in the study sample

Out of the 55 cases, 14 (25.5%) developed IRIS. The median (range) duration of IRIS was 2.53 (0.53–14.97) months. Ten patients with IRIS had single or multiple lymph node aspirations to prevent spontaneous rupture. None of the patients developed spontaneous rupture or a sinus because of this procedure. AAFBs were seen in aspirates from eight patients. None of the aspirates were culture-positive.

The presenting features of IRIS are shown in Table 1. Of the patients with IRIS, 79% were given steroids at doses of 0.5–1 mg/kg. The median (range) duration of steroid therapy was 8.6 (2.9–47.9) weeks. One patient was treated with interleukin (IL)–2 and granulocyte-macrophage colony-stimulating factor, with resolution of a discharging psoas abscess he had had for 15 months.

The median baseline CD4 [interquartile range (IQR)] for patients in the IRIS group was significantly lower [80 (33–117) cells/mm$^3$, *P* = 0.03] than those in the non-IRIS group [139 (77–284) cells/mm$^3$]. There was no significant difference between the two groups when comparing the log$_{10}$ baseline VL. A significantly greater proportion of patients in the IRIS group [11/14 (78.6%), *P* = 0.011] had baseline CD4 <100 cells/mm$^3$ compared with the non-IRIS group [16/41 (39.0%)]. Of those who had IRIS, eight (57.0%) had disseminated TB.
at baseline compared with seven (17.0%) of those who did not have IRIS (P=0.006). There was no significant difference between the proportion of patients who developed IRIS [9/14 (64.3%)] who had not yet started HAART at the time when TB was diagnosed, and patients without IRIS [25/41 (61.0%), P=0.544] (Table 2A).

Gradients of CD4 count rise from baseline using time-weighted difference in averages for (A) time since starting TB therapy, (B) time since starting HAART and (C) time since diagnosis of IRIS, were calculated. Although a lower CD4 count rise from baseline was consistently observed in the IRIS group compared with the non-IRIS group, no significant differences at different time points were observed. However, these results should be interpreted in light of the small sample size, evident by wide 95% confidence intervals (see Figure 1).

Analysis excluding the patients with baseline VL BLD

Patients already on suppressive antiviral therapy had an undetectable VL and relatively stable CD4 counts. In order to examine whether baseline or changes in VL or CD4 might predict the occurrence of IRIS, the data on those patients who had detectable VLs were analysed separately.

The median (IQR) time to virological success from commencement of HAART for patients with IRIS was 5.7 (4.9–6.2) months compared with patients without IRIS 5.6 (2.3 to not attained), P=0.482 using log rank χ² test statistics. The median fold change (IQR) in CD4 from baseline to 3 months was significantly higher in the IRIS group 1.5 (0.6–5.6), compared to 0.7 (0.2–1.0) for those without IRIS (P=0.046) (Table 2B).

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**Table 1. Major presenting symptoms and signs of IRIS**

<table>
<thead>
<tr>
<th>Presenting features</th>
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<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>12</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
</tr>
<tr>
<td>Sternal skin lesion</td>
<td>2</td>
</tr>
<tr>
<td>Spleen micro abscesses</td>
<td>1</td>
</tr>
<tr>
<td>Gluteal abscess</td>
<td>1</td>
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</tbody>
</table>

IRIS, immune reconstitution inflammatory syndrome.

**Table 2. Baseline features associated with developing IRIS**

<table>
<thead>
<tr>
<th></th>
<th>IRIS group</th>
<th>Non-IRIS group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Including all patients of study sample</td>
<td>n=14</td>
<td>n=41</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>35.2 (5.9)</td>
<td>38.2 (9.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (71.4)</td>
<td>23 (56.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (28.6)</td>
<td>18 (43.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline CD4, cells/mm³, median (IQR)</td>
<td>80 (33–117)</td>
<td>139 (77–284)</td>
<td>0.050</td>
</tr>
<tr>
<td>Baseline viral load, log₁₀, median (IQR)</td>
<td>5 (3.5–5.4)</td>
<td>4.5 (1.7–5.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline CD4 &lt;100 cells/mm³, n (%)</td>
<td>11 (78.6)</td>
<td>16 (39.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Baseline CD4 ≥100 cells/mm³, n (%)</td>
<td>3 (21.4)</td>
<td>25 (61.0)</td>
<td></td>
</tr>
<tr>
<td>Naive at time of TB diagnosis, n (%)</td>
<td>9 (64.3)</td>
<td>25 (61.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Disinated TB, n (%)</td>
<td>8 (57)</td>
<td>7 (17)</td>
<td>0.006</td>
</tr>
<tr>
<td>Duration since start of TB treatment to development of IRIS, months, median (IQR)</td>
<td>1.8 (0.3–19.8)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Duration since start of HAART to development of IRIS, months, median (IQR)</td>
<td>1.9 (0.1–71.3)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>(B) Excluding patients with baseline VL BLD</td>
<td>n=12</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td>Time to virological success, months, median (IQR) [n=10]</td>
<td>5.7 (4.9–6.2)</td>
<td>5.6 (2.3 to not attained)</td>
<td>NS</td>
</tr>
<tr>
<td>Fold change in CD4 count from baseline to 3 months, median (IQR) [n=23]</td>
<td>1.5 (0.6–5.6)</td>
<td>0.7 (0.2–1.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>(C) Patients who started HAART after commencing TB therapy</td>
<td>n=9</td>
<td>n=19</td>
<td></td>
</tr>
<tr>
<td>Duration since TB therapy to start of HAART, months, median (IQR)</td>
<td>0.8 (0.3–1.8)</td>
<td>0.6 (0.1–2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration since start of HAART to development of IRIS, months, median (IQR)</td>
<td>0.6 (0.1–9.1)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

NS, not significant (P>0.05); BLD, below the level of detection; HAART, highly active antiretroviral therapy; IQR, interquartile range; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis; VL, viral load.
Patients who started HAART after commencing TB therapy

It has been argued that IRIS is more common in patients who start HAART at the time of, or shortly after, commencing TB therapy. Of our cases, 28 (51%) patients started HAART after TB therapy, and of this group, nine patients developed IRIS. There was no significant difference between the median time (IQR) from start of TB treatment to start of HAART for patients with IRIS [0.8 (0.3–1.8) months] compared with the non-IRIS group [0.6 (0.1–2.2) months, \( P=0.730 \)] (Table 2C).

Figure 1. (A) Rate of increase in CD4 count relative to baseline since starting TB treatment, IRIS group versus non-IRIS group. (B) Rate of increase in CD4 count relative to baseline since starting HAART, IRIS group versus non-IRIS group. (C) Rate of increase in CD4 count relative to baseline since diagnosis of IRIS.

Error bars are 95% confidence intervals. HAART, highly active antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis.
Discussion

In HIV-seronegative patients, IRIS occurs with a reported incidence of 10% [11]. In our cohort of patients with HIV/TB coinfection, 25.5% developed IRIS. As signs and symptoms of IRIS were not prospectively collected and as there are no agreed diagnostic criteria, its incidence may be underestimated. If only the confirmed cases of TB are included, the rate would be substantially higher. Other studies [17,18] have reported incidences of 36% (12/33) and 32% (6/19), respectively, in HIV patients starting HAART. However, in one study, IRIS was not significantly more common in patients receiving HAART [three out of 28 cases (11%)] when compared with patients not receiving antiretroviral treatment [three out of 44 cases (7%)] [19]. With such small datasets it is difficult to predict who might be at risk of IRIS.

The features significantly more common in our patients who developed IRIS are a lower CD4 count at baseline, presenting with disseminated TB and, in those with a detectable viral load at baseline, a rise in CD4 count in the initial 3 months of HAART. An increase in CD4 cell percentage and the ratio of CD4 to CD8 cells after starting HAART has also been associated with IRIS [20].

Our study showed that IRIS was more common in those patients with a CD4 count <100 cells/mm³. This is important as there is debate as to when HAART should be initiated in patients with HIV/TB coinfection [19,21]. In patients with a low CD4 count at presentation, a clinical decision has to be made to balance the risks of further HIV progression and development of IRIS. There are no definitive data to answer this, but Dean et al.’s study suggests that the risk of HIV progression in those patients with CD4 counts <100 cells/mm³ is substantial and consequently treatment with HAART should probably not be delayed [19].

IRIS might occur if subclinical, active TB is present when HAART is started and a subsequent inflammatory reaction is induced against the pathogens. If this was a frequent problem then there should be greater numbers of patients starting HAART who develop active TB without IRIS, yet this is uncommon. There are no data to suggest that latent TB results in IRIS, probably because the mycobacterial burden is extremely low. HAART started within the first 2 months of TB treatment has been associated with an increased risk of IRIS [11] but our analysis demonstrates no such relationship. In fact, many of our patients were already on HAART at the time TB was diagnosed and then developed IRIS. Furthermore, IRIS does not appear to be associated with any particular antiretroviral regimen or drug class.

The aetiology of IRIS may be related to the mycobacterial load and this, in turn, may be related to the severity of CD4 suppression. We suggest that patients with a higher mycobacterial burden and low CD4 count effectively kill but do not seem to be able to eliminate the mycobacteria, in spite of a pronounced rise in CD4 count early after HAART is started. We believe that this is fundamental to the pathophysiology of this syndrome. This theory is supported by the fact that most of the patients whose lymph nodes are aspirated during IRIS are AAFB positive but culture negative. There are data to suggest that, after HAART, certain T-cell clones, which are specific for elimination of mycobacteria, do not expand and anergic abnormal T-cell clones proliferate [22,23]. This may then lead to inadequate, abnormal antigen responses and cell signalling and consequently to the persistence of mycobacterial antigens. These patients may respond to cytokine treatment. There is also evidence of an abnormal humoral immune response, especially in the elaboration of proinflammatory cytokines, including a delay in interferon-γ and IL-12 production and increased levels of IL-6 [24–26]. The development of IRIS may also have a genetic predisposition. French and colleagues have shown that distinct cytokine-mediated mechanisms contribute to IRIS – patients with mycobacterial disease and IRIS never carried the polymorphism in the cytokine gene tumour necrosis factor A308*2 [27].

These studies suggest that the cause of IRIS is complex, involving CD4 cells, cytokine regulation and expression, abnormal antigen responses and cell signalling. Further data need to be gathered on the pathophysiology and immunology of this syndrome.

References


