Characterization and Management of Paradoxical Upgrading Reactions in HIV-Uninfected Patients with Lymph Node Tuberculosis

Charlotte R. Hawkey,1 Timothy Yap,2 Janis Pereira,3 David A. J. Moore,1,7 Robert N. Davidson,1 Geoffrey Pasvol,1,3 Onn Min Kon,2 Robert A. Wall,1 and Robert J. Wilkinson1,3,4

1Department of Infection and Tropical Medicine, North West London Hospitals National Health Service Trust, Northwick Park Hospital, Harrow, and 2Chest and Allergy Clinic, St. Mary’s Hospital and 3Wellcome Trust Centre for Research in Clinical Tropical Medicine, Division of Medicine, Wright-Fleming Institute, Imperial College London, London, United Kingdom; and 4Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

In a retrospective analysis, paradoxical deterioration of lymph node tuberculosis in human immunodeficiency virus–uninfected patients was common, occurring in 25 (23%) of 109 patients after treatment had been given for a median of 46 days (interquartile range, 21–139 days) and persisting for a median of 67.5 days (interquartile range, 34–111 days). We found no association between the use of steroids and the duration of reaction.

In leprosy, distinct and well-recognized immunopathological reactions occur during and despite receipt of adequate sterilizing antibacterial therapy. Tuberculosis (TB) can similarly worsen during treatment. This deterioration of TB may be evident in the development of intracranial tuberculomas [1], the expansion of lymph nodes [2], the appearance of worsening findings on chest radiography [3], and other varied presentations. The phenomenon of deterioration of TB has received renewed interest because of the immune reconstitution inflammatory syndrome that can occur in HIV-infected patients with TB when they commence receiving HAART [4]. Deterioration can also occur in HIV-uninfected patients, although, to our knowledge, only 1 substantial case series has been reported [5].

Adjunctive corticosteroid therapy tends to be used in the management of paradoxical upgrading reactions (PURs), although there is no clear evidence of an associated benefit, except in the treatment of disease of the CNS. We therefore undertook a retrospective study to determine the frequency, nature, routine clinical correlates, and outcomes of PUR in patients with lymph node TB. In addition, we examined different treatment modalities to ascertain whether they might have an effect on the outcome of PUR in such patients.

Patients and methods. An unbiased search for patients who were treated for lymph node TB at Northwick Park Hospital (Harrow, United Kingdom) was done by reviewing the microbiological, discharge, and histopathological reports and statutory notifications from 1989 through 2003. Only patients who had culture-confirmed TB, a positive result of testing for acid-fast bacilli, or histological evidence of necrotizing granulomatous lymphadenitis with a positive result of a tuberculin skin test were included in the present study. Patients with serological or clinical evidence of HIV infection were excluded from the study, as were patients who had not completed a standard treatment course.

“PUR” was defined as the worsening of preexisting tuberculous lesions on the basis of clinical or radiological findings or the development of new TB lesions in patients who had received anti-TB treatment for at least 10 days and whose conditions were reported to be improving. “Time to onset of PUR” was defined as the number of days from the start of treatment to the time when the start of deterioration of TB was reported. “Duration of PUR” was defined as the number of days from the onset of PUR to the time when improvement was first recorded (e.g., from the time when the enlargement of a lymph node was first noted to the time when improvement was first recorded). “Baseline blood tests” were defined as blood tests performed closest to the date of initiation of anti-TB chemotherapy. Statistical analysis was performed using SPSS software, version 11.0 (SPSS). Dichotomized data were assessed by contingency analysis. Parametric and nonparametric analyses were performed using Student’s t test and the Mann-Whitney U test, respectively.

Results. A total of 123 sets of patient records became available. Fourteen patients had their records excluded from further analysis; of these 14 patients, 7 had insufficient microbiological or histological evidence of TB, 4 had what appeared to be suboptimal adherence to anti-TB therapy, 2 were transferred out of our care, and 1 who had a PUR was excluded from the study because the infecting organism was resistant to first-line...
therapy (i.e., isoniazid). Therefore, a total of 109 patients (60% of whom were female) underwent further analysis in the present study. Forty-six (42%) of the patients were born on the Indian subcontinent, and 36 (33%) were born in Africa. Of the 39 patients (35%) who underwent HIV testing, all had negative results.

The majority of patients (92 patients [84%]) presented with cervical lymphadenopathy, and 11 patients (10%) presented with axillary lymphadenopathy. Three patients presented with mediastinal, 2 with intra-abdominal, and 1 with inguinal adenopathy. Of the 97 patients who had initial microbiological samples sent for culture, 80% were found to test positive for Mycobacterium tuberculosis. A total of 87% of the isolates that were recovered were fully susceptible to all 4 first-line anti-TB drugs. The analysis included 2 patients who had a PUR and a resistant organism. Both isolates recovered from these patients were resistant to streptomycin only; streptomycin was not used in treatment. The other 8 patients had an uneventful recovery.

Twenty-five patients (23%) experienced a PUR. Two of these 25 patients experienced 2 separate PURs; therefore, there was a total of 27 episodes of PUR. Characteristics of the PURs and the patients who experienced the PURs are shown in table 1.

Three patients experienced a PUR in the year after satisfactory completion of treatment; none had a positive culture result during the time that the PUR occurred. For the majority of patients with a PUR (18 patients [67%]), presentation involved enlargement of lymph nodes; in some patients, this was associated with the development of new nodes or discharging sinus, but, in 1 patient, it was associated with lung consolidation. Two patients developed severe complications: one presented with a pericardial effusion after initially receiving treatment for cervical tuberculous lymphadenitis, and the other had a perforated viscus after M. tuberculosis was isolated from a mesenteric lymph node.

We performed univariate analysis of a number of characteristics and laboratory values noted at baseline, to determine whether any of these factors noted at presentation could be used to predict subsequent development of a PUR (table 2). Most of the factors were not significantly different between patients with or without a PUR. The median peripheral blood monocyte count at baseline was slightly, but significantly, higher in patients who eventually had a PUR: $0.7 \times 10^5$ peripheral blood monocytes/mL versus $0.5 \times 10^5$ peripheral blood monocytes/mL ($P = .02$). Key analytic variables are displayed in table 2. Because no strong predictive variable emerged in the univariate analysis, multivariate analysis was not performed. Microbiological samples were obtained from 6 patients during the PUR and were sent for culture. All but 1 of the samples were found to be sterile. One patient had a negative culture result at the start of treatment, but, for the other 4 patients, culture results were negative after an initial positive culture result had been obtained.

Fourteen episodes of PUR (52%) led to the prescription of prednisolone in various doses (mean dose, 60 mg/day; range, 20–90 mg/day) and for various durations (median duration, 52.5 days; range, 14–169 days). The duration of a PUR was very similar in the groups of patients who did or did not receive steroid treatment (median duration, 64 vs. 68 days; $P = .60$). Intervention in the form of aspiration of pus from the node, incision and drainage, or excision performed during the reaction tended to be associated with a PUR of shorter duration (median duration, 46 vs. 92 days; $P = .10$).

Discussion. In the present study, we have shown that PUR is common in patients with lymph node TB, occurring in almost a quarter of the patients evaluated. A PUR begins most frequently after anti-TB treatment has been given for $\sim 6$ to 7

![Table 1: Demographic and clinical characteristics of 25 patients with lymph node tuberculosis who experienced 27 episodes of paradoxical upgrading reactions (PUR).](cid:200540)
Table 2. Univariate analysis of characteristics or findings at primary presentation that might predict the occurrence of paradoxical upgrading reactions (PURs).

<table>
<thead>
<tr>
<th>Characteristic or finding</th>
<th>Patients with a PUR (n = 25)</th>
<th>Patients without a PUR (n = 84)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>331.6 (2–57)</td>
<td>38.9 (8–66)</td>
<td>.39</td>
</tr>
<tr>
<td>Female sex, no. of patients (%)</td>
<td>16 (64)</td>
<td>49 (58)</td>
<td>.61</td>
</tr>
<tr>
<td>Other symptoms present, median no. (range)</td>
<td>1 (0–5)</td>
<td>1 (0–5)</td>
<td>.62</td>
</tr>
<tr>
<td>Node size, mm (range)</td>
<td>31 (10–100)</td>
<td>30 (5–150)</td>
<td>.74</td>
</tr>
<tr>
<td>Low vitamin D level, (n/N) (%)</td>
<td>11/12 (92)</td>
<td>34/47 (72)</td>
<td>.26</td>
</tr>
<tr>
<td>AFB positive, (n/N) (%)</td>
<td>8/23 (35)</td>
<td>17/80 (21)</td>
<td>.18</td>
</tr>
<tr>
<td>Culture positive, (n/N) (%)</td>
<td>17/24 (71)</td>
<td>61/73 (84)</td>
<td>.17</td>
</tr>
<tr>
<td>Neutrophil count, median no. (\times 10^6/mL) (range)</td>
<td>4.4 (2.2–7.0)</td>
<td>3.7 (1.8–7.8)</td>
<td>.60</td>
</tr>
<tr>
<td>Lymphocyte count, median no. (\times 10^6/mL) (range)</td>
<td>1.5 (1.0–5.4)</td>
<td>1.6 (0.4–1.2)</td>
<td>.74</td>
</tr>
<tr>
<td>Peripheral blood monocyte count, median no. (\times 10^6/mL) (range)</td>
<td>0.7 (0.3–1.3)</td>
<td>0.5 (0.1–3.2)</td>
<td>.02</td>
</tr>
</tbody>
</table>

NOTE. Dichotomized data were assessed by contingency analysis. AFB, acid-fast bacilli.

a The parametric test used was the Mann-Whitney U test.
b Defined as <22 \(\mu\)mol/mL.
c No. of patients with a PUR/total no. of patients for whom the finding was recorded.
d The nonparametric test used was Student’s t test.

weeks, and it lasts for \(\sim 2\) months, although there is wide variability in the duration of both of these periods. Irrespective of the treatment received by the patient, PUR is generally self-limiting and resolves without serious sequelae. The frequency of PUR is very similar to that reported in 1977 as an incidental finding during a therapeutic trial in which 25% of patients with lymph node TB experienced deterioration of their condition [5]. In that study, pyrazinamide was not used, and there was greater reliance on therapeutic node excision. Despite these differences in the management of TB, it is interesting that the rate of PUR in the therapeutic trial was so comparable to the rate of PUR noted in the present study.

Providing advance warning of the possibility that a PUR might occur might improve patient satisfaction and, perhaps, enhance adherence to a prolonged course of anti-TB therapy. Only a higher peripheral blood monocyte count at baseline was associated with the risk of a subsequent PUR, but there was too much overlap between patient groups for this finding to be clinically useful. It was interesting to note the trend toward an association between the presence of acid-fast bacilli on the initial diagnostic smear specimen and subsequent development of PUR (table 2). It may be that a higher bacillary load also predisposes patients to develop a PUR. Because only 1 patient who had a PUR was found to have culture results that were persistently positive, we favor the hypothesis that this phenomenon is caused by hypersensitivity to persistent antigen. That reactions can occur even after prolonged therapy suggests that the antigenic stimulus may be poorly cleared from disease sites. M. tuberculosis has a number of insoluble lipid-rich antigens in its cell wall that potently stimulate the response of mononuclear phagocytes, and it may be that these components are responsible for the phenomenon of deterioration of TB.

The use of corticosteroids in the adjunctive management of PUR is common. Some case reports have described rapid recovery after initiation of corticosteroid therapy [1, 6, 7]. However, in other case reports, continued deterioration has been reported despite steroid treatment [8]. Furthermore, PURs have occurred in patients who were given steroids from the outset of their anti-TB treatment [9, 10], and another report has provided details about PURs that resolved without steroid treatment [2]. The advantage of corticosteroid therapy in reducing edema around enlarging intracranial tuberculomas is apparent, but the advantage associated with the use of such therapy for lymph node TB is less clear. That we did not associate a decreased duration of PURs with steroid treatment suggests that steroids may not be advantageous in treating most PURs in patients with lymph node TB. Furthermore, a common side effect of steroid therapy is illustrated by the fact that, while receiving steroid treatment, 1 patient developed diabetes mellitus that persisted after steroid therapy was stopped. However, the present retrospective analysis has a number of potential confounders. For example, patients with more-severe reactions may have been more likely to receive steroid therapy, and the onset of diabetes mellitus may not have been caused by steroid treatment.

In contrast to patients with intracranial upgrading reactions, most patients with lymph node TB who have a PUR recover without developing severe sequelae. In addition, the simpler intervention of aspiration of pus is associated with fewer unwanted side effects than is steroid therapy. The use of aspiration...
has been reported to be a successful therapeutic intervention for suppurative post–bacille Calmette-Guérin adenitis [11], and a report has suggested that aspiration was useful for the treatment of a PUR in a patient with lymph node TB [12]. We believe that the role of corticosteroid therapy can only be defined by a randomized placebo-controlled trial.

Acknowledgments

We thank Dr. Mark Harries (North West London Hospitals National Health Service Trust, Harrow, United Kingdom), some of whose patients are described in the present study. We also thank Dr. Sandra Eldridge (Queen Mary College, London, United Kingdom) for statistical advice.

Financial support. The Wellcome Trust (grants 064261 and 060079) and the North West London Hospitals National Health Service Trust.

Potential conflicts of interest. All authors: no conflicts.

References