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Article

Risk Factors for Development of Paradoxical Response During Antituberculosis Therapy in HIV-Negative Patients

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Abstract. The risk factors for development of paradoxical response were studied in a cohort of 104 patients with culture-documented *Mycobacterium tuberculosis* infection. Paradoxical deterioration occurred in 16 (15.4%) patients (case group) during antituberculosis therapy, involving lungs and pleura (*n*=4), spine and paraspinal tissue (*n*=5), intracranium (*n*=3), peritoneum (*n*=2), bone and joint (*n*=1), and lymph node (*n*=1). The median time from commencement of treatment to paradoxical deterioration was 56 days (range, 20– 109 days). Compared with 53 patients without clinical deterioration after antituberculosis therapy (control group), patients with paradoxical response were more likely to have extrapulmonary involvement (62.5% vs. 17.0%; $P<0.05$) at initial diagnosis, to have lower baseline lymphocyte counts (672±315 cells/μl vs. 1,328±467 cells/μl; $P<0.001$), and to exhibit a greater surge in lymphocyte counts (627±465 cells/μl vs. 225±216 cells/μl; $P<0.05$) during paradoxical response. Further studies on lymphocyte subsets and cytokine levels would be useful in understanding the exact immunological mechanisms involved in

immunorestitution.

<heading1>Introduction

Paradoxical response during antituberculosis therapy is a well-known phenomenon in HIV-negative patients [1]. It has been observed in 6– 30% of patients receiving antituberculosis therapy for tuberculous pleural effusion and lymphadenitis [2, 3, 4]. Paradoxical worsening of pre-existing pulmonary and extrapulmonary tuberculosis has been increasingly reported in HIV-positive patients, which produces a diagnostic challenge to caring infectious disease and respiratory physicians [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16]. In recent studies, this condition was found in 11– 36% of patients receiving highly active antiretroviral therapy (HAART) [7, 8, 15]. Although the pathogenesis of paradoxical response has not been clearly elucidated, it appeared more frequently in patients with significant reductions in viral load and increases in CD4+ lymphocyte counts after HAART, especially when HAART was administered within 2 months of antituberculosis therapy [15]. Therefore, appropriate timing of initiation of HAART and antituberculosis therapy may reduce the phenomenon. However, a systematic analysis of the incidence, clinical spectrum and risk factors in this clinical entity in HIV-negative patients is lacking.

In this article, we report a cohort of 104 HIV-negative patients with culture-documented tuberculosis in whom paradoxical deterioration occurred during antituberculosis therapy. Extrapulmonary involvement at initial diagnosis and lower baseline lymphocyte counts were associated with the development of paradoxical response.

<heading1>Materials and Methods

<heading2>Study Design and Patients

All clinical data were collected prospectively over a 24-month period (1 July 2000– 30 June 2002) on patients referred for infectious disease consultation in Queen Mary Hospital, a 1,350-bed tertiary teaching hospital in Hong Kong. Patients who presented with clinical features suggestive of tuberculosis were included in the study.

<heading2>Diagnosis and Treatment of *Mycobacterium tuberculosis* Infection

Investigations for *Mycobacterium tuberculosis*, including culture and examination of smears for acid-fast bacilli, in relevant clinical specimens of all patients with suspected tuberculosis were performed. Polymerase chain reaction to detect *Mycobacterium tuberculosis* (TB-PCR) was performed on pulmonary and extrapulmonary specimens in the following clinical settings: (i) patients with typical radiological changes compatible with pulmonary tuberculosis; (ii) patients with radiological changes due to prior tuberculosis but presenting with new pulmonary infiltrates; (iii) patients with community-acquired pneumonia unresponsive to appropriate antibiotic therapy; (iv) patients undergoing invasive procedures such as image-guided or surgical drainage and biopsy for sterile sites in the work-up for extrapulmonary tuberculosis. Histological examination for *Mycobacterium tuberculosis* was also performed if clinically indicated.

Preliminary diagnosis of *Mycobacterium tuberculosis* was based on positive smear for acid-fast bacilli, TB-PCR, or tissue histology results during the initial work-up. A definitive diagnosis of tuberculosis was made by positive culture results.

Antituberculosis therapy including isoniazid, rifampicin, pyrazinamide, and ethambutol was administered to patients with a preliminary or definitive diagnosis of tuberculosis, or, if clinical suspicion of tuberculosis was high, therapy was administered empirically.

<heading2>Development of Paradoxical Response

Patients were monitored for development of paradoxical deterioration during antituberculosis therapy. The definition of paradoxical response has been described previously [1]. It is defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions not attributable to the normal course of disease in a patient who initially improves with antituberculosis therapy and in whom the onset of paradoxical response occurs at least 2 weeks after the initiation of treatment. Patients who presented with progressive tuberculosis without initial clinical improvement, whose compliance with antituberculosis therapy could not be ascertained, or in whom an alternative diagnosis was made were excluded. The time to development of paradoxical response is defined as the interval between the initiation of antituberculosis therapy and the onset of paradoxical response as defined above.

<heading2>Monitoring of Absolute Lymphocyte Counts

Baseline lymphocyte counts were measured in all patients recruited in this study. Lymphocyte counts were also recorded in patients during paradoxical deterioration and at the end of therapy in those patients who remained uneventful during antituberculosis therapy. Both the absolute values and the serial change in lymphocyte counts from baseline were analysed in

patients with or without paradoxical deterioration.

<heading2>Identification of Immunocompromised Hosts

HIV antibody was checked, after written consent, in patients with a clinical diagnosis of extrapulmonary tuberculosis or if clinically indicated. Patients receiving immunosuppressive therapy (systemic steroids, cytotoxic agents, a combination of steroids and cytotoxic agents, or irradiation) or diagnosed with HIV infection were noted and excluded from the analysis of the change in lymphocyte counts.

<heading2>Statistical Analysis

The characteristics of patients with culture-documented tuberculosis with or without paradoxical deterioration during antituberculosis therapy were compared. The chi-square test was used for categorical variables. Continuous variables were tested by the Student's *t* test. A *P* value of <0.05 was considered significant. A statistical package (SPSS 10.0; SPSS, Hong Kong) was used for all analyses.

<heading1>Results

<heading2>Patients

During the 2-year study period, there were 5,315 inpatient infectious disease consultations from various clinical specialties. One hundred fifty-five patients with clinical symptoms and signs suggestive of tuberculosis were recruited in this study.

<heading2>Diagnosis and Treatment of *Mycobacterium tuberculosis* Infection

A total of 127 of 155 (82%) patients received antituberculosis therapy in this cohort, in which treatment was (i) given

empirically in 10 patients, (ii) based on positive results in initial work-up in 103 patients, and (iii) administered after positive culture results in 14 patients. One hundred eighteen of the 127 (93%) patients had completed the treatment. Nine patients defaulted follow-up after initiation of therapy.

<heading2>Development of Paradoxical Response

Of the 118 patients who completed antituberculosis therapy, 104 with culture documentation of *Mycobacterium tuberculosis* were further analyzed for development of paradoxical deterioration during antituberculosis therapy. Fifty-one of the 104 patients experienced clinical deterioration requiring hospitalization. Culture results for *Mycobacterium tuberculosis* were not yet available at the time of deterioration in 44 (86.3%) patients, among whom TB-PCR was positive in 35 (80%). Thirty-five of the 51 (68.6%) patients were diagnosed to have deterioration due to problems other than paradoxical response: 15 had community-acquired infections, 10 had liver impairment and gouty attack related to antituberculosis drugs, 6 had malignancy, 2 had cerebrovascular accident, and 2 had nonspecific abdominal pain.

Paradoxical response occurred in 16 of 51 (31.4%) patients presenting with clinical deterioration after antituberculosis therapy. There were nine males and seven females, and the mean age was 48.1 years. The median time to onset of paradoxical deterioration was 56 days (range, 20– 109 days) after the initiation of antituberculosis therapy among these 16 patients. Paradoxical response developed in lungs and pleura in four patients, in the spine and paraspinal soft tissue in five patients, in the intracranium in three patients, in the peritoneum in two patients, in the left hip in one patient, and in the right

supraclavicular lymph nodes in one patient (Table 1). Development of new lesions in anatomical sites other than those observed at initial presentation was observed in five (31.2%) patients. Of these 16 patients, results of culture for *Mycobacterium tuberculosis* were not available at the time of worsening of signs and symptoms in 10 (62.5%) patients, but TB-PCR was positive in 6 (60%) of them. The initial *Mycobacterium tuberculosis* isolates in these 16 patients with paradoxical response were tested for susceptibility to isoniazid, rifampicin, ethambutol, and streptomycin. One strain was resistant to streptomycin and sensitive to the other drugs, while all other strains were susceptible to all drugs tested. Smears for acid-fast bacilli and cultures obtained from sputum, pleural fluid, cerebrospinal fluid, and surgical specimens during paradoxical deterioration were all negative. Treatment of the paradoxical response included administration of steroids in 6 (37.5%) patients and surgical intervention in 10 (62.5%). Residual functional deficits occurred in 6 (37.5%) patients.

Compared with 53 patients without clinical deterioration after antituberculosis therapy (control group), there was no difference in age, sex, and underlying comorbidity in patients with paradoxical deterioration (Table 2). There was no HIV-infected patient in either group. Extrapulmonary tuberculosis as an initial manifestation was found in a significantly higher proportion of patients with paradoxical response (81.2%) than in those without clinical deterioration (24.5%). Patients with paradoxical deterioration had a significantly lower lymphocyte count at baseline (672±315 cells/μ l) than those without deterioration (1,328±467 cells/μ l). A surge in absolute lymphocyte counts was observed in patients during paradoxical deterioration, with a mean difference in lymphocyte counts between baseline and

at paradoxical response of 627±465 cells/μ l. Serial lymphocyte counts were also available in the control group, but an increase in absolute lymphocyte counts was not observed. When serial changes in lymphocyte counts were further analysed after exclusion of six hosts with immunosuppressive conditions (autoimmune diseases in 4, bronchogenic carcinoma in 1, and haemoglobin H disease in 1 patient in the control group), a statistically significant result was found.

<heading1>Discussion

Paradoxical response was not an uncommon phenomenon in this study, occurring in 11.1% of patients with a clinical diagnosis of tuberculosis infection, 15.4% of patients with culture documentation of *Mycobacterium tuberculosis*, and 31.4% of patients who deteriorated clinically after receiving antituberculosis therapy. Significant medical and surgical intervention was required in these patients, including use of steroids in one-third of them. Thirty-seven percent of patients were complicated by residual functional deficits.

In the present report, paradoxical response developed more commonly in patients with extrapulmonary tuberculosis, which concurs with the findings in the literature that 101 of 122 (82.8%) episodes of paradoxical deterioration were associated with extrapulmonary tuberculosis in non-HIV-infected patients [1]. The central nervous system remains the most common site of presentation, affected in 50% of the patients with paradoxical deterioration in the present study. In contrast to the recent literature review [1], the present series showed a high propensity for spinal and paraspinal involvement: about one-third of patients had paradoxical response in these areas. The appearance of new lesions in anatomical sites that were

unaffected at initial presentation was observed in 5 (31.2%) patients. This suggests that attending physicians should be alert to this possibility.

Although the clinical spectrum of paradoxical deterioration during antituberculosis therapy in both HIV-negative and HIV-positive patients has recently been described [1, 14], studies on risk factors for development of paradoxical response are scarce and limited exclusively to HIV-positive patients [8, 15]. Of 82 episodes of paradoxical response in 76 HIV-positive patients, paradoxical worsening occurred in 7 (8.5%) episodes. Patients complicated by paradoxical deterioration were more likely to have both pulmonary and extrapulmonary tuberculosis. Those patients with paradoxical response appeared to have a lower median initial CD4+ count (69 cells/μ l) when compared to those without paradoxical deterioration (154 cells/μ l). However, the difference was not statistically significant due to the small number of cases [8].

In our present report, extrapulmonary tuberculosis, with or without pulmonary involvement, and low baseline lymphocyte counts were demonstrated to be significantly associated with subsequent development of paradoxical responses in HIV-negative patients leading to hospital admission. An upsurge in lymphocyte counts was observed in patients during paradoxical deterioration. The mean difference in lymphocyte counts was significantly greater in patients with paradoxical response than those without. Such findings further strengthened our previous observation that a concomitant increase in absolute lymphocyte counts occurred during paradoxical deterioration in both HIV-negative and HIV-positive individuals [1, 17, 18]. However, it must be emphasised that the number of circulating lymphocytes does not always reflect the numbers of lymphocytes in the

involved tissues or their in vivo functional status. For instance, in our previous reported case of a patient with *Pneumocystis carinii* pneumonia undergoing steroid withdrawal, the lymphocyte count surged to a very high level and then dropped to a low level within the same day due to extremely severe immunorestitution, which occurs when the lymphocytes all migrate to the site of restitution to produce severe damage [19]. In cases 2, 10, 14, and 15 (in Table 1), the lymphocyte counts were apparently static or depressed despite paradoxical deterioration, and thus the lack of an upsurge in lymphocyte counts does not exclude the diagnosis.

The clinical severity of paradoxical deterioration is dependent on the exactness and appropriateness of immune recovery. An overwhelming and exaggerated immune recovery may lead to excessive immunopathological damage at the tissue level [19, 20]. Further studies on lymphocyte subsets and cytokine levels would be useful in understanding the exact immunological mechanisms involved in immunorestitution.

Despite gains made in understanding the risk factors for development of paradoxical response, diagnosis of this condition remains difficult in the clinical setting. The diagnosis can be ascertained only when other differential diagnoses or reasons are excluded, such as secondary community-acquired or nosocomial infections, inadequate antituberculosis therapy due to drug resistance, poor compliance, and side-effects of antituberculosis therapy. Since all patients received first-line antituberculosis therapy, including isoniazid, rifampicin, pyrazinamide, and ethambutol as initial therapy, primary or acquired drug resistance should have been excluded before paradoxical deterioration was diagnosed. Although multidrug-resistant *Mycobacterium tuberculosis* has become an emerging

problem in certain parts of the world [21], its overall prevalence remains low (2.1%) in Hong Kong [22]. In our present report, only 1 of 16 strains isolated from patients with paradoxical deterioration was resistant to just a single drug, i.e. streptomycin. However, using the *rpoB* gene sequence, real-time PCR and fluorimetry for rapid detection of mutations associated with rifampicin and isoniazid resistance have been performed in the laboratory setting [23, 24]. The molecular test would be beneficial in regions where the prevalence of multidrug resistance is high.

The clinical spectrum of paradoxical deterioration may be confounded in this study. Since we focused on moderate to severe paradoxical deterioration requiring hospital admission, patients with relatively asymptomatic radiological worsening that does not warrant admission may have been missed. However, it may not be possible to diagnose paradoxical response in an outpatient setting without performing a complete physical examination and investigations to exclude other possibilities. Therefore, further investigation and collaboration with a community chest physician is warranted.

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