

Paradoxical Worsening of Tuberculosis Following Antiretroviral Therapy in Patients with AIDS

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Transient worsening of tuberculous symptomatology and lesions following antituberculous therapy (paradoxical response) has previously been described as a rare occurrence. To determine the incidence of paradoxical responses in patients with AIDS and TB who are treated with antituberculous therapy and subsequently with combination antiretroviral therapy (ARV), we conducted a prospective study of 33 HIV-seropositive TB patients treated with anti-TB therapy and antiretroviral therapy (Group 1) compared with 55 HIV-seronegative TB patients treated with anti-TB therapy (Group 2) and 28 HIV-seropositive TB patients treated with anti-TB therapy but not on antiretrovirals (historical control; Group 3). In Group 1 patients, paradoxical responses were temporally more related to the initiation of ARV than to the initiation of anti-TB therapy (mean \pm SD: 15 \pm 11 d versus 109 \pm 72 d [$p < 0.001$]) and occurred much more frequently (12 of 33; 36%) compared with Group 2 (1 of 55; 2%) ($p < 0.001$) or with Group 3 (2 of 28; 7%) ($p = 0.013$). The majority of patients who experienced paradoxical responses and received tuberculin purified protein derivative (PPD) in Group 1 had their tuberculin skin tests convert from negative to strongly positive after ARV. These observations suggest that a paradoxical response associated with enhanced tuberculin skin reactivity may occur after the initiation of ARV in HIV-infected TB patients. Furthermore, the skin test conversion after the initiation of ARV may have important public health implications. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS.

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Transient worsening of tuberculous symptomatology and lesions in response to antituberculous therapy has previously been reported (2-13). Such exacerbations have occurred in various forms of tuberculosis (TB). The development or worsening of lymphadenopathy has been the most commonly reported exacerbation after anti-TB therapy (3-8). Exacerbation of cerebral tuberculomas (11, 12) and adult respiratory distress syndrome (9) have also occurred. Other features of transient exacerbations include recurrent fever, enlargement of existing lesions (e.g., pulmonary foci, endobronchial lesions), and/or the appearance of fresh lesions during administration of appropriate anti-TB therapy (3). These episodes of unexpected exacerbation of the disease while on appropriate therapy have been called "paradoxical responses" by some investigators (3, 9-12, 14). Although such "paradoxical responses" frequently arouse concerns of uncontrolled TB due to drug resistance and/or noncompliance, drug fever, or alternative diagnoses, they are distinct from these and may represent an enhanced antituberculous immune response after the initiation of anti-TB therapy. This is supported by the fact that contin-

ued therapy ultimately results in cure (2-4, 7, 8, 10, 13).

We recently have observed a similar phenomenon of paradoxical TB exacerbation in patients with TB and human immunodeficiency virus (HIV)-induced immunosuppression. However, unlike previous reports where paradoxical TB exacerbations occurred after the initiation of anti-TB therapy, these TB exacerbations were more temporally related to the initiation of potent combination antiretroviral therapy and occurred with greater frequency. Interestingly, many of these previously anergic patients had their tuberculin skin tests convert to strongly positive following the initiation of combination antiretroviral therapy. We hypothesized that "paradoxical responses" would be more frequently encountered in patients with co-infection of TB and HIV because of the marked improvement of immune function following combination antiretroviral therapy. We therefore reviewed the incidence of this phenomenon in patients with TB and HIV, who were started on combination antiretroviral therapy (Group 1), as compared with patients with TB but without HIV infection (Group 2), and with patients with TB and HIV but not on any antiretroviral therapy (historical control; pre-zidovudine [AZT] era) (Group 3).

METHODS

All patients admitted to A. G. Holley State Tuberculosis Hospital with culture-proven TB from February 1, 1996 to January 31, 1997 were prospectively followed for paradoxical responses. Paradoxical responses were defined as (1) new persistent fevers (temperature \geq 101.5° F) which developed after the initiation of antiretroviral therapy and which lasted for more than 1 wk without an identifiable source despite

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an extensive fever workup (e.g., multiple blood cultures, urine and sputa testing, and other procedures when clinically indicated); (2) marked worsening or emergence of intrathoracic lymphadenopathy, pulmonary infiltrates, or pleural effusion determined by agreement of two radiologists who blindly reviewed sequential chest radiographs; or (3) worsening or emergence of cervical adenopathy on serial physical examinations, or worsening of other tuberculous lesions, such as cutaneous or peritoneal.

All patients were tested for HIV serologic status. If HIV serology was positive, the CD4+ percentage (%) of total peripheral blood lymphocyte count, total CD4+ cell count, and CD4+/CD8+ ratio were measured by flow cytometry (SmithKline Beecham Laboratories, Miami, FL) in addition to an HIV RNA quantification by polymerase chain reaction amplification at SmithKline Beecham Clinical Laboratories. These were done on admission, on the day before combination antiretroviral therapy was initiated, then every 2 mo, and whenever a paradoxical response was noted. Combination antiretroviral therapy was initiated at least 2 wk after the initiation of anti-TB therapy in all patients. When rifampin was included in the TB regimen, combination antiretroviral therapy consisted of AZT, lamivudine (3TC), and either zalcitabine (ddC) or didanosine (ddI). When rifampin was not used because of either rifampin-resistant *Mycobacterium tuberculosis*, or due to intolerance to rifampin, combination antiretroviral therapy consisted of AZT, 3TC, and a protease inhibitor (saquinavir). In Group 1, tuberculin purified protein derivative (PPD; Connaught Laboratories, Inc., Swiftwater, PA) skin testing was performed on or shortly before admission and, if the skin test was negative (< 5 mm of induration), it was repeated approximately every 2 wk during hospitalization until a PPD conversion was documented (i.e., induration of greater than 5 mm) or the patient was discharged. Not all patients in Groups 2 and 3 had initial or repeated tuberculin skin tests performed.

A retrospective chart review of patients discharged between January 1, 1986 and December 31, 1987, before AZT was widely used, was conducted to establish a historical control group consisting of HIV-infected TB patients who received TB therapy but no antiretroviral therapy.

Statistical analysis using the Fisher exact test was performed comparing the frequency of paradoxical responses among the groups. Among HIV-infected TB patients treated with antiretroviral therapy, the age of the patients was compared using an unpaired *t* test; CD4+ profile and HIV-RNA viral load were compared using Mann-Whitney rank sum test between the group of patients who developed paradoxical responses and those who did not.

The study was reviewed and approved by the institution's review board.

RESULTS

Ninety-eight patients were admitted to A. G. Holley State Tuberculosis Hospital from February 1, 1996 to January 31, 1997. Ten patients were omitted from the study: three were already taking antiretrovirals at the time of admission, three were ad-

mitted for only a short period of time, three refused antiretroviral therapy, and one did not tolerate antiretrovirals. Although excluded from the study, none of these patients were found to have had a paradoxical response.

Of the 88 study patients, 33 were co-infected with TB and HIV and were given combination antiretroviral therapy during their hospitalization (Group 1). Twelve (36%) of these 33 patients had a paradoxical response. (Two of the 12 patients received combination antiretroviral therapy which included a protease inhibitor since their TB regimen did not include rifampin [rifampin-resistant TB].) Three other patients in Group 1 developed fevers soon after initiating antiretrovirals which were attributed to other causes (i.e., methicillin-resistant *Staphylococcus aureus* bacteremia, *Pneumocystis carinii* pneumonia, and sepsis) and were not considered to have had a paradoxical response.

Fifty-five patients had TB without HIV infection (Group 2) and of these, only one (2%) had a paradoxical response. This was a patient with dermatomyositis and culture-proven cutaneous TB, who developed a paradoxical worsening of tuberculous skin lesions when long-term systemic steroids were tapered. Two patients had persistent fever before anti-TB medications were initiated and thus did not meet the criteria for having had a paradoxical response.

In the historical control group (Group 3), 28 patients were diagnosed with TB and HIV infection and of these two (7%) had paradoxical responses. Two other patients developed fevers that were attributed to other causes (urinary tract infection, and cryptococcal fungemia) and one patient had persistent fevers prior to the initiation of anti-TB medications. Therefore, those three did not meet criteria for having developed a paradoxical response.

Among the TB patients in Group 1, 11 of 27 (41%) had an initial negative PPD reaction. Within this group, 7 of 8 who developed paradoxical responses had an initial PPD of 0 mm (Table 1); 4 of 12 who did not develop paradoxical responses had an initial negative PPD. Among the TB patients in Groups 2 and 3 who received PPD skin testing, 7 of 21 (33%) and 7 of 22 (32%) were PPD-negative, respectively.

Group 1 patients had significantly more frequent paradoxical responses compared with patients in Group 2 ($p < 0.001$) or Group 3 ($p = 0.013$). There was no significant difference between Group 2 and Group 3 ($p = 0.262$) (Table 2). Interestingly, three patients with severe paradoxical responses required systemic steroid therapy to alleviate their symptoms. Two patients (one in Group 1 and one in Group 2) required systemic steroid therapy for paradoxical exacerbation of painful cutaneous tuberculous lesions. One patient in Group 1 re-

TABLE 1
PPD RESULTS AND CD4+ COUNT IN HIV-INFECTED TB PATIENTS ON ANTIRETROVIRALS WHO HAD PARADOXICAL RESPONSES

Patient	PPD before ARV (mm induration)	PPD after ARV (mm induration)	Time to PPD Conversion after ARV (wk)	CD4+ Count before ARV (/mm ³)	CD4+ Count Within a Month of PPD Conversion (/mm ³)
A	0	30	20	12	96
B	0	20	4	80	67
C	0	0	—	27	—
D	15	Not done	—	91	—
E	0	10	2.5	2	32
F	0	67	9	35	350
G	0	20	8	75	30
H	0	7	5	133	110

Definition of abbreviation: ARV = combination antiretroviral therapy.

TABLE 2

INCIDENCE OF PARADOXICAL RESPONSES AMONG TB PATIENTS*

	Group 1 TB, (+)HIV on Antiretrovirals	Group 2 TB, (-)HIV	Group 3 TB, (+)HIV not on Antiretrovirals
Number of patients with "paradoxical responses"	12	1	2
Number of patients without paradoxical responses	18	52	23
Number of patients with transient worsening (nonparadoxical responses) [†]	3	2	3
Total	33	55	28

* Using Fisher exact test, Group 1 patients had significantly more frequent paradoxical responses compared with patients in Group 2 ($p < 0.001$) or Group 3 ($p = 0.013$). There was no significant difference between Group 2 and Group 3 ($p = 0.262$).

[†] These patients had transient clinical worsening from other possible etiologies.

quired steroids for paradoxical exacerbation of marked cervical and intrathoracic lymphadenopathy which caused dysphagia.

Among Group 1 patients who experienced a paradoxical response, the onset was temporally much closer to the initiation of combination antiretroviral therapy (mean \pm SD: 15 \pm 11 d) than to the initiation of anti-TB therapy (109 \pm 72 d) ($p < 0.001$).

Clinical and laboratory findings of all patients who had paradoxical responses are described in Table 3. In Group 1, the

paradoxical responses consisted of hectic fevers (9 patients), intrathoracic lymphadenopathy with or without worsening pulmonary infiltrates (7 patients), cervical lymphadenopathy (5 patients), pleural effusions (2 patients), the appearance of miliary infiltrates (1 patient), worsening cutaneous TB (1 patient), and peritoneal TB (1 patient). The mean of their initial CD4+ cell count was $50.5 \pm 41.3/\text{mm}^3$ (ranging from 2 to $133/\text{mm}^3$) and the mean CD4+ cell count after the onset of paradoxical responses was $92.5 \pm 80.4/\text{mm}^3$ (ranging from 5 to $283/\text{mm}^3$) ($p = 0.18$). The mean of initial HIV viral load [Log (HIV RNA level copies/ml)] was 5.84 ± 0.19 and the mean of HIV viral load [Log (HIV RNA level copies/ml)] after combination antiretroviral therapy around the time of paradoxical responses was 3.43 ± 0.48 ($p < 0.01$).

As seen in Table 4, among Group 1 patients, those who had a paradoxical response tended (though not statistically significant) to have a larger drop in viral load after combination antiretroviral therapy than those who did not ($p = 0.084$). The patients' age, initial CD4+ cell count, initial CD4+%, initial CD4+/CD8+ ratio, increment in CD4+ cell count after combination antiretroviral therapy, or initial HIV viral load were not found to be statistically different between those patients who developed paradoxical response and those who did not.

Of 12 patients on combination antiretroviral therapy who experienced a paradoxical response, eight had an initial PPD skin test. Of these, only one had a positive reaction and seven were initially anergic with a nonreactive PPD. Six of these seven patients had a PPD conversion (median 20 mm indura-

TABLE 3

CLINICAL SUMMARY OF ALL PATIENTS WHO HAD PARADOXICAL RESPONSES

Patient	Time to Symptoms after Anti-TB Therapy Started (wk)	Time to Symptoms after ARV Started (d)	Paradoxical Responses	Total CD4 Count ($/\text{mm}^3$) before ARVs	Total CD4 Count ($/\text{mm}^3$) after Onset of Symptoms	HIV-RNA before ARV (copies/ml)	HIV-RNA after ARV (copies/ml)
A, 1st episode	9	15	Fever \times 11 d,* intrathoracic adenopathies with worsening perihilar infiltrates	12	5	134,615	5,843
A, 2nd episode	15	11	Fever \times 7 d*	5	37	104,882	583
B	40	2	Fever \times 30 d,* intrathoracic and cervical adenopathies	80	67	3,420,595	4,719
C	10	10	Fever \times 12 d*	27	33	907,585	914
D	4.5	4	Fever \times 64 d*	91	116	581,694	4,032
E	10	17	Intrathoracic and cervical adenopathies	2	32	1,319,555	4,516
F	9	5	Fever \times 12 d,* ascites, worsening LLL infiltrates with pleural effusion	35	169	750,000	6,527
G	18	5	Cutaneous TB, pleural effusion	75	30	31,987	< 400
H	10	19	Fever \times 17 d,* intrathoracic and cervical adenopathies	133	110	4,275,175	2,735
I	18	16	Fever \times 17 d,* intrathoracic adenopathies	87	194	Not done	7,890
J	12	12	Fever \times 12 d,* hilar and cervical adenopathies, miliary infiltrates	20	65	271,921	2,061
K	31	40	Cervical adenopathy	73	283	62,727	3,914
L	14	32	Increased paratracheal adenopathy with new RUL infiltrates	17	62	1,831,622	6,072
(Group 2) Non-HIV patient with dermatomyositis	12		Worsening cutaneous TB when systemic steroids for dermatomyositis tapered				
(Group 3) Historical 1	6		Worsening Rt cervical adenopathies after initial improvement	184 (11 d after anti-TB therapy)	53 (49 d after anti-TB therapy)		
(Group 3) Historical 2	3		Febrile on admission but more prominent fever as high as 103°F	381 (10 d after anti-TB therapy)	357 (111 d after anti-TB therapy)		

Definition of abbreviations: LLL = left lower lobe; RUL = right upper lobe; ARV = combination antiretroviral therapy.

* Fever lasted this length of time without more than a 72 h afebrile period.

TABLE 4

CHARACTERISTICS OF HIV-INFECTED TB PATIENTS TREATED WITH COMBINATION ANTIRETROVIRAL THERAPY, WITH AND WITHOUT PARADOXICAL RESPONSES

	(-) Paradoxical Responses* (n = 18)	(+) Paradoxical Responses* (n = 12)	p Value
Age, yr	40.5 ± 8.6	35.8 ± 6.7	0.122
Initial CD4+%	10 (1-36) [†]	6 (1-36) [‡]	0.636
Initial CD4+ cell count, /mm ³	83 (5-820) [†]	54 (2-133)	0.150
Increase in CD4+ cell count after ARVs, /mm ³	32.5 (-228-248) [†]	27.5 (-45-158)	0.763
Initial CD4+/CD8+ ratio	0.12 (0.01-0.67) [†]	0.10 (0.02-0.95) [‡]	0.869
Log (initial HIV RNA level), copies/ml	5.32 (2.79-6.32)	5.88 (4.50-6.63) [‡]	0.121
Drop in Log (HIV RNA level) after ARVs	1.34 (-0.38-3.26)	2.20 (1.20-3.19) [‡]	0.084

* Results are expressed as mean ± SD or median (range).

[†] n = 17.

[‡] n = 11.

tion ranging from 7 to 67 mm) at a median of 6.5 wk (ranging from 2.5 to 20 wk) after the initiation of combination antiretroviral therapy (Table 1). In these six patients, the total CD4+ cell count within a month of conversion was not significantly different from the total CD4+ cell count before combination antiretroviral therapy and in all but one, CD4+ cell count remained $\leq 110/\text{mm}^3$ (Table 1).

In the first patient with a severe paradoxical response (Patient A [Table 3]), all medications including antiretrovirals were temporarily discontinued (4 wk) when the patient developed hectic fever with radiographic worsening. After the medications were resumed, the patient developed similar symptoms; we felt these were immunologically modulated and all the medications were continued. In the other patients with paradoxical responses (Patients B-L [Table 3]) we did not discontinue any anti-TB medications or antiretroviral therapy while investigating and excluding other etiologies.

DISCUSSION

Many of the clinical presentations seen in patients with untreated TB are mediated by the host's immune system. The first treatment reactions based on a possible immune response were reported by Robert Koch in 1890 when he attempted to treat tuberculous patients with injections of large amounts of killed tubercle bacilli (old tuberculin). This resulted in high fevers, ulcerating lesions, and increased morbidity and mortality (15). There have been subsequent observations that TB patients may experience a "paradoxical" worsening of some signs and symptoms of their TB after the initiation of anti-TB therapy (2-13). More recently, such reactions have also been reported in a few HIV-infected TB patients treated with anti-TB drugs (3). Paradoxical reactions have been attributed to immunologic causes such as the strengthening of the host's delayed hypersensitivity response, a decrease in suppressor mechanisms (16), and/or an increased exposure to mycobacterial antigens following bactericidal TB chemotherapy. This is the first report to our knowledge of a similar paradoxical response occurring among HIV-infected TB patients soon after the initiation of combination antiretroviral therapy.

We described patients with TB and immunosuppression from HIV who developed exacerbations of their tuberculous symptomatology and/or lesions soon after the initiation of potent antiretroviral therapy. The reactions included hectic fevers, lymphadenopathy (sometimes severe), a worsening chest

radiographic TB appearance (e.g., miliary infiltrates, pleural effusion) and/or worsening of the original tuberculous lesions (e.g., cutaneous and peritoneal). Patients were generally not toxic and subjectively referred to feeling well. Treatment failure, drug fever, and the development of non-TB HIV-related conditions were considered unlikely since extensive infectious workups were negative and the symptoms and lesions subsided despite continuation of the same TB medications. Furthermore, these events were more temporally related to the initiation of combination antiretroviral therapy (15 ± 11 d afterwards) than to the initiation of anti-TB treatment. Timing of the onset of paradoxical responses after the initiation of combination antiretroviral therapy was similar to that previously reported for TB patients who only received anti-TB therapy (i.e., usually within the first few weeks or months of therapy) (2-5, 9, 10, 13, 14). These events were much more common among HIV-infected TB patients who received TB treatment as well as combination antiretroviral therapy (Group 1), as compared with HIV-noninfected and HIV-infected TB patients who received anti-TB drugs alone. (Control Groups 2 and 3). Patients in Groups 1 and 2 were prospectively studied with a rigorous protocol, whereas those in Group 3 were studied retrospectively. Thus, underascertainment of paradoxical responses is a distinct, though unlikely, possibility.

Phillips and coworkers described the emergence of clinical lymphadenitis and cutaneous lesions secondary to *Mycobacterium avium* complex after initiation of highly active antiretroviral therapy, suggesting that this may have been caused by a possible enhanced immune response (17). Additionally, there was a report of five HIV-infected patients who had low absolute CD4+ counts who then developed cytomegalovirus (CMV) retinitis 4-7 wk after initiation of combination antiretroviral therapy (18). The authors suggested the possibility of subclinical CMV infection which progressed to symptomatic disease accelerated by an improvement in CMV-specific immunity after combination antiretroviral therapy. These likely represent another example of a paradoxical response. As more potent therapies are developed which result in improved immune function in patients with AIDS, it is possible that additional examples of paradoxical reactions will be found.

In Group 1 patients, paradoxical responses corresponded to a concurrent marked drop in HIV viral loads after the initiation of potent combination antiretroviral therapy and, in all but one patient, occurred while peripheral blood CD4+ counts were less than $200/\text{mm}^3$. Nevertheless, despite the relatively low CD4+ cell counts, paradoxical responses were frequently associated with PPD skin test conversions to positive. The post antiretroviral PPD conversions ranged from 7 to 67 mm of induration (mean induration = 25 ± 11 mm). This phenomenon might be attributed to an improvement in CD4+ lymphocyte function as HIV viremia is reduced by antiretroviral therapy. Lederman and coworkers have shown that the short-term administration of highly active antiretroviral therapy enhances CD4 lymphocyte function (e.g., inducing lymphocyte proliferation and increasing naive and memory CD4 cells) as the HIV viral load falls (19). Subsequent to the initiation of our study, highly active antiretroviral regimens that included a protease inhibitor became standard therapy. Therefore, with these newer regimens, one might expect even more frequent and/or severe paradoxical responses and/or PPD skin test conversions.

It is of interest that in our historical (pre-AZT era) control group (i.e., HIV-infected TB patients who were treated for TB but not for HIV), two (7%) of the 28 patients experienced a paradoxical response after anti-TB therapy was initiated. As TB is known to enhance HIV viral replication (20, 21), it is possible that treatment of TB alone may sometimes signifi-

cantly decrease HIV viral load and improve immune function, thereby contributing to a paradoxical response.

Of the seven HIV-infected TB patients who were initially anergic, we observed that six (86%) of seven converted their TB skin tests following triple antiretroviral therapy. French and coworkers have previously observed that HIV-immunosuppressed patients treated with antiretrovirals may regain delayed-type hypersensitivity responses to various skin antigens (22). Restored skin test reactivity may be an indication of enhanced T-cell function independent of CD4+ cell count, CD4+%, or CD4+/CD8+ ratio. Restoration of PPD reactivity in previously anergic HIV-infected patients has major public health and clinical implications. It is recommended that PPD-positive HIV patients receive isoniazid (INH) prophylaxis, in order to prevent the likely progression (8–10%/yr) of tuberculous infection to active TB. Prevention of active TB in an HIV-infected patient may preclude increased HIV replication, accelerated immunosuppression, and more rapid progression to death (23). Some recent studies, however, did not show a benefit of prophylactic therapy in preventing or delaying mortality (24, 25). Prospective studies are needed to determine how frequently potent combination antiretroviral therapy calls forth PPD skin reactivity in previously anergic HIV-infected patients. If restoration of PPD skin reactivity occurs with significant frequency, PPD testing should be routinely recommended for all previously PPD negative or anergic patients after combination antiretroviral therapy.

In summary, a paradoxical exacerbation of tuberculous signs and symptoms may occur not only after TB therapy, but more commonly, soon after the initiation of potent combination antiretroviral therapy in HIV-infected TB patients. This paradoxical reaction may also be associated with an enhanced tuberculin skin reactivity even though the absolute CD4+ cell count remains low. A thorough investigation is necessary to eliminate other etiologies before a diagnosis of paradoxical response can be made. However, it is important that treating clinicians be aware of this phenomenon and realize that this may simply represent an enhanced immune response to *M. tuberculosis* antigens following potent combination antiretroviral therapy and not treatment failure, drug reaction, or other non-TB, HIV-related illnesses. In this case, no change or temporary discontinuation in the anti-TB therapy or antiretroviral therapy is necessary. If the paradoxical lymphadenopathy or other lesions cause significant symptoms, the use of short-term steroids that suppress the enhanced immune response, while maintaining the patient on appropriate anti-TB therapy, may prove to be helpful.

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