Clinical Spectrum of Paradoxical Deterioration During Antituberculosis Therapy in Non-HIV-Infected Patients

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Abstract. Paradoxical deterioration during antituberculosis therapy, defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves, remains a diagnostic dilemma. Although different clinical presentations of paradoxical response have been described, a systematic analysis of the entity in non-HIV-infected patients is lacking. Reported here are two cases of paradoxical deterioration in which sequential changes in lymphocyte counts and tuberculin skin test results are emphasized. In addition, 120 episodes of paradoxical response after antituberculosis treatment were reviewed. Of the 122 episodes, 101 (82.8%) were associated with extrapulmonary tuberculosis. The median time from commencement of treatment to paradoxical deterioration was 60 days. The median time to onset of central nervous system manifestations (63 days) was longer than the time to onset of manifestations at other sites (56 days) (P=0.02). Development of new lesions in anatomical sites other than those observed at initial presentation was observed in 31 (25.4%) episodes. A surge in the lymphocyte count, accompanied by an exaggerated tuberculin skin reaction, was observed in our patients during the paradoxical deterioration, analogous to the findings in HIV-positive patients. Treatment of the paradoxical response included surgical

intervention (60.7%) and administration of steroids (39.3%). The use of steroids appeared to be safe in this series, as 95% of the *Mycobacterium tuberculosis* isolates were susceptible to first-line antituberculosis therapy.

<heading1>Introduction

Deterioration during antituberculosis therapy remains a clinical challenge to infectious disease and respiratory specialists. Although immunopathological damage has been suggested as a possible explanation for the paradoxical worsening of tuberculosis after initiation of treatment [1], a rapid and reliable diagnostic test is not available to substantiate this clinical diagnosis. In fact, a paradoxical response is generally defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves with antituberculosis therapy. The diagnosis can only be ascertained when other differential diagnoses such as secondary community-acquired or nosocomial infections, inadequate antituberculosis therapy as a result of drug resistance, poor compliance, and side effects of antituberculosis therapy, are excluded. In contrast to the extensive review of paradoxical responses during antituberculosis therapy in HIV-positive patients, there has been no systematic analysis of this situation in HIV-negative patients.

In this article, we report two HIV-negative patients in whom paradoxical deterioration occurred during antituberculosis therapy. A surge in the lymphocyte count, associated with a strongly positive tuberculin skin test result, was observed during the paradoxical response in both patients. A literature review of the clinical spectrum of paradoxical response to antituberculosis therapy in HIV-negative patients is performed (Medline search, 1966--2001). The anatomical sites of involvement, the time to development of the paradoxical response, and the issues of management and clinical outcome are also examined.

<heading1>Materials and Methods

<heading2>Patients

Clinical data of the two patients were collected prospectively. Clinical specimens were collected and handled according to standard protocols [2, 3].

<heading2>Definition of Paradoxical Response

For the purpose of this study, paradoxical response 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 is at least 2 weeks after the initiation of treatment. Patients who presented with progressive tuberculosis without initial clinical improvement, whose compliance to antituberculosis therapy could not be ascertained, or in whom an alternative diagnosis was made were excluded. For neurological manifestations, in particular, only patients with worsening of preexisting symptoms or a new onset of clinical symptoms or signs such as headache, mental confusion, seizure, cranial nerve palsy, or cortical signs after initial improvement were included, while those with expected deterioration were excluded from the study.

<heading2>Time to Development of Paradoxical Response

The time to the 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>Tuberculin Skin Test Result

The absolute value of induration was measured if available; otherwise, the positive or negative result was recorded.

<heading2>Literature Review

The English literature was searched in the Medline database of the National Library of Medicine (1966--2001). The keywords "tuberculosis", "tuberculous", "paradoxical", "worsening", and "deterioration", were used to select the cases in Tables 1--4. All the case reports and clinical studies with full clinical details were included in this study if they matched the above definition of paradoxical response and sufficient clinical information was available in order to rule out complications other than a paradoxical response. The cited bibliographies were also retrieved for further analysis, where appropriate.

<heading2>Statistical Analysis

The chi-squared 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, Hong Kong) was used for all analyses.

<heading1>Results

<heading2>Case Reports

Case 1 was a 56-year-old Chinese who man presented with fever, cough, and abnormal liver function and was diagnosed to have disseminated tuberculosis involving the lungs, right supraclavicular lymph node, and liver. He was treated with standard antituberculosis therapy, including isoniazid 300 mg q.i.d., rifampicin 450 mg q.i.d., pyrazinamide 35 mg/kg, and ethambutol 15 mg/kg, under direct observed therapy. The baseline Mantoux test was done with 2 tuberculin units of purified protein derivative, PPD-RT23. No measurable induration was detected after 48 h. The lymphocyte count was 570 cells/μl. Subsequently the liver biopsy specimen was culture positive for *Mycobacterium tuberculosis*, which was susceptible to isoniazid, rifampicin, streptomycin, and ethambutol. Fever, chest radiograph, and liver dysfunction gradually improved after 3 weeks of antituberculosis therapy.

Three months after treatment, the patient developed a painless lump over the right subscapular area of the back. Computer tomography of the thorax revealed a 6 cm×15 cm subcutaneous abscess. Surgical drainage yielded 100 ml of pus that was sent for microbiological examination. The pus was smear positive but culture negative for acid-fast bacilli (AFB). A second Mantoux test was performed, and an induration of 16 mm was recorded after 48 h. The concomitant lymphocyte count was elevated, at 2,600 cells/μl. Antituberculosis therapy was continued for a total of 1 year. The abscess resolved and the patient recovered without further complications. He was negative for HIV antibody.

Case 2 was a 16-year-old Chinese boy who presented with severe right neck pain and swelling 6 weeks after conventional antituberculosis therapy for culture-documented tuberculous lymphadenitis of the right anterior and lower cervical lymph nodes. The *Mycobacterium tuberculosis* isolate was susceptible to isoniazid, rifampicin, streptomycin, and ethambutol. The pretreatment Mantoux test showed 3 mm of induration, and the lymphocyte count was 1,400 cells/μl. On admission, he had a painful, red, tense, and cystic swelling of 8 cm in diameter over

the lower end of the sternocleidomastoid tendon that extended to the right posterior triangle of the neck, compatible with collar stud abscess. A Mantoux test was performed, and an induration of 23 mm with central necrosis was noted after 48 h. The lymphocyte count was elevated, at 3,100 cells/μl. A diagnosis of paradoxical inflammatory response was made. In view of the tense swelling with impending sinus formation, surgical drainage was performed. The pus was AFB smear positive, but AFB culture negative. Prednisolone 1 mg/kg was given orally and gradually tapered off over 12 weeks. The patient completed a 6-month course of antituberculosis therapy and remained well without further complications.

<heading2>Literature Review

Including the two presented here, a total of 143 episodes of paradoxical response was found in the English literature, of which 122 episodes in 104 patients matched our definition (Table 1) [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54]. The male-to-female ratio was 1.2:1. The ages ranged from 4 months to 80 years, with a median of 28 years. Fifty-seven (46.7%) episodes occurred in Asian patients. Of these episodes, 27 occurred in Indian patients and 18 in Chinese patients, so that these groups together constituted 78.9% of Asian patients.

An initial diagnosis of pulmonary tuberculosis was made in 21 (17.2%) episodes, whereas extrapulmonary tuberculosis, including disseminated tuberculosis (42 episodes), meningitis (26 episodes), intracranial tuberculoma (7 episodes), and tuberculosis with involvement of the pleura (12 episodes), lymph nodes (6 episodes), spinal cord (3 episodes), abdomen (3 episodes), and osteoarticular sites (2 episodes) was diagnosed in the remaining 101 (82.8%) episodes (Table 2). The presence of *Mycobacterium tuberculosis* was confirmed by culture in 49 (40.2%) episodes; in 24 of these, smear results for acid-fast bacilli were positive. Diagnosis was made by histology in 10 episodes in which cultures for *Mycobacterium tuberculosis* were negative.

Forty strains of *Mycobacterium tuberculosis* were fully susceptible to first-line antituberculosis drugs, while two episodes were caused by strains showing resistance to pyrazinamide and ethambutol and streptomycin, respectively. The sensitivity patterns of the remaining strains were not mentioned.

The clinical symptoms and signs of paradoxical deterioration manifested in the initial site of infection in 91 of the 122 (74.6%) episodes, of which 52 occurred in the central nervous system and 34 in the respiratory system. A paradoxical response occurred in an anatomical site other than that of the initial presentation in 31 (25.4%) episodes, of which 8 were initially manifest in the central nervous system and 10 in the respiratory system (Table 2). Overall, the central nervous system was also the most common site of involvement in paradoxical response (60/122 episodes), followed by the respiratory system (44/122 episodes).

The clinical and radiological manifestations of paradoxical deterioration are summarized in Table 3. Clinical features of paradoxical deterioration in the central nervous system included headache, mental confusion, focal seizure, cranial nerve palsy, and cortical signs such as hemiparesis, paraparesis, and hemianesthesia; such features resulted from the enlargement or development of intracranial tuberculoma and hydrocephalus. The most common manifestation in the respiratory system was worsening or development of pleural effusion, either in the ipsilateral or contralateral side, while an increase in pulmonary parenchymal infiltration and an increase in pleurisy were reported in only two and three episodes, respectively. Paradoxical deterioration occurred in cervical, supraclavicular, and mediastinal lymph nodes as enlargement of pre-existing lesions or development of new cold abscesses. Paradoxical manifestations in skin and soft tissue were reported in eight episodes and were characterized by the development of new lesions such as erythematous and purpuric papules, painful swelling of the popliteal fossa and thigh muscles, and abscess formation in the abdominal and chest wall. Magnetic resonance imaging revealed osteomyelitis of the left humerus and tenosynovitis of the flexor tendon of the right palm in a patient with bone and tendon involvement. Both worsening and development of intraabdominal ileocecal masses were also reported. Systemic features such as fever were reported in 16 (13.1%) episodes.

The median time to development of paradoxical response was 60 days for all episodes, 63 days for central nervous system involvement, and 56 days for other sites (Table 1). When the initial site of involvement was analyzed, the median time to paradoxical response was 42 days for pulmonary tuberculosis and 60 days for disseminated tuberculosis (involvement of more than 1 system). Management of paradoxical deterioration included initiation of steroid therapy in 48 (39.3%) episodes. Surgical intervention was employed in 74 (60.7%) episodes, including

insertion of ventriculo-peritoneal shunt, resection of intracranial lesions, percutaneous drainage of pleural effusion, and excision of enlarged lymph nodes and subcutaneous abscesses. The regimen of antituberculosis therapy was changed in 19 (15.6%) episodes. Conservative management with continuation of the original antituberculosis therapy was adopted in 17 (13.9%) episodes. Ninety-five (77.9%) episodes resolved with complete recovery from the paradoxical response.
Baseline tuberculin skin tests were reported in 35 (28.7%) episodes, whereas test results during the paradoxical response were only mentioned in 6 episodes (3.3%). Conversion of tuberculin skin tests from negative to positive was reported in five episodes and the trend of lymphocyte counts in three (Table 4).

<heading1>Discussion

Paradoxical response is not a rare phenomenon. It is identified in 6--30% of patients receiving antituberculosis therapy [38, 55, 56]. The present report shows that paradoxical deterioration requires significant medical attention. In about two-thirds of the 122 episodes being examined, surgical intervention was employed. Modification of antituberculosis regimen was initiated in 15%. Twenty-two percent of all episodes were complicated by residual functional deficits.
Evaluation of the clinical spectrum of paradoxical response showed a high propensity for central nervous system involvement, described in 49% of all cases reported in the literature [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 51, 52, 53, 54]. Because the central nervous system is a highly compact and functionally demanding structure confined within the rigid skull bone, symptomatic neurological deterioration may occur with the enlargement or appearance of intracranial tuberculomas during paradoxical response. This is in contrary to the situation in patients infected with HIV. In a review of 57 episodes of paradoxical response in HIV positive patients, only 2 (3.5%) demonstrated new intracranial tuberculomas [57].
The second most commonly reported manifestation in our series was pleural involvement, the proportion being similar to that seen in HIV-positive patients [57]. In cases in which pleural effusion was massive, respiratory function could be severely compromised [33, 34, 38, 40, 41]. Symptomatic pleurisy may be experienced when an inflammatory reaction in the parietal pleura affects somatic sensory nerve endings [33, 34]. Increasing pulmonary infiltration during

paradoxical response was only reported in two episodes in our series [37, 39]. It may be related to the spacious anatomy and good functional reserve of the lungs. For lesions in superficial sites, such as peripheral lymph nodes [6, 23, 42, 43], skin and soft tissues [44, 45, 46, 47, 48], and bone and tendons [36, 43, 49], the clinical symptoms of paradoxical deterioration are usually obvious. Involvement of lymph nodes during paradoxical deterioration (4%) in our series was significantly less common than that in HIV-positive patients (41%) [57]. The clinical spectrum of paradoxical deterioration may be confounded by functional and anatomical bias. Moreover, the spectrum of diseases that were identified on review of the literature may reflect selection bias, because unusual or severe cases such as those involving the central nervous system are more likely to be reported.

Appearance of new lesions in anatomical sites other than those of the initial presentation should also heighten the alertness of attending physicians. Late occurrence of lesions in the central nervous system (8 episodes) and respiratory system (10 episodes) during paradoxical response was not uncommon in our review [9, 11, 18, 27, 36, 41, 53, 54]. Patients with pulmonary, pleural, miliary, and lymph node tuberculosis could develop intracranial tuberculomas between 2 weeks and 3 months after antituberculosis therapy [9, 11, 18, 27, 53, 54]. Similarly, the appearance of a pleural effusion could occur after 3--19 weeks of antituberculosis therapy for treatment of tuberculous cervical lymphadenitis, meningitis, abdominal lesions, and osteoarticular involvement [36, 41].

The time to onset of paradoxical deterioration occurring in the central nervous system appears to be longer when compared with the time to onset at other sites. This might be explained by the poor drug penetration into the blood-brain barrier of noninflamed meninges after the acute phase of infection. It might take a longer time for mycobacterial killing and recovery of immune function in the immunologically privileged site [29].

Paradoxical response in tuberculosis has been well studied in patients with HIV infection. The two markers, lymphocyte count and tuberculin skin test, were found to correlate with paradoxical deterioration after initiation of highly active antiretroviral therapy. Ten of 11 anergic HIV-positive patients with a paradoxical deterioration demonstrated a strongly delayed hypersensitivity response to the tuberculin skin test. The mean time of tuberculin skin test conversion was 6.5 weeks after antiretroviral therapy [57]. Our review also demonstrated a conversion

of the tuberculin skin test in five HIV-negative patients during paradoxical deterioration [13, 46, 51]. The finding of concomitant increase in ALC and conversion of the tuberculin skin test in our patients (case 1 and 2) during paradoxical deterioration concurred with the observation in a previous report [46]. The clinical severity of paradoxical deterioration is dependent on the exactness and appropriateness of immune recovery [58, 59]. An overwhelming and exaggerated immune recovery may result in excessive immunopathological damage at the tissue level.

The use of systemic steroids in the management of paradoxical deterioration appears to be safe in our series. There were no reports of steroid-related complications. Inhaled steroid as adjunctive therapy in tuberculous pyrexia was reported in nine HIV-negative patients, in four of whom defervescence of fever was achieved between 2 and 5 days [60]. Oxpentifylline was added in a 44-year-old HIV-positive patient for paradoxical enlargement of the mediastinal lymph node and worsening of pulmonary infiltrates that occurred 5 months after of initiation of antituberculosis therapy [61]. In an experimental model, a combination of thalidomide plus antibiotics was shown to protect rabbits from death due to tuberculosis meningitis via the inhibition of tumor necrosis factor [62], indicating that thalidomide might be a potential agent in the treatment of paradoxical deterioration in future.

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Table 1. Summary of cases of paradoxical response (PR) after antituberculosis therapy reported in the English-language literature

	PR within CNS, including spinal cord (*n*=60)	PR in other systems[a] (*n*=62[b])	*P* value
Male: female ratio	1.2: 1	1.2:1	
Median age in years (range)	26 (0.3--75)	32 (14--80)	*P*=0.01
No. in whom baseline TST was performed	20 (33.3%)	15 (24.2%)	*P*=0.8
Median no. of days to onset of PR (range)	63 (14--270)	56 (14--202)	*P*=0.02
No. who received steroid therapy for PR	38 (63.3%)	10 (16.1%)	*P*<0.001
No. who received surgical therapy for PR	21 (35%)	53 (85.5%)	*P*<0.001
No. who recovered from PR	41 (68.3%)	54 (87.1%)	*P*=0.001

CNS, central nervous system; TST, tuberculin skin test

[a]Others sites included pleura (*n*=42), pulmonary system (*n*=2), skin and soft tissue (*n*=8), lymph node (*n*=5), bone and tendon (*n*=3), and abdomen (*n*=2)

[b]Including our two patients

Table 2. Initial site(s) of involvement in 122 patients presenting with paradoxical response during antituberculosis therapy

Sites of paradoxical response	Site(s) of initial involvement	No. of episodes
CNS (*n*=60)	CNS (*n*=52)	
	meninges	23
	meninges plus lungs	3
	meninges plus miliary	5
	meninges plus lungs & miliary	5
	meninges plus lymph node	1
	meninges plus bone	1
	meninges plus IT	7
	IT plus lungs	2
	IT plus pleura	1
	IT plus spinal cord	2
	spinal cord plus testes & epididymis	1
	spinal cord plus lungs & miliary	1
	Other sites (*n*=8)	
	lungs	2
	miliary	4
	lungs & miliary	2
Respiratory system (*n*=44)	Respiratory system (*n*=34)	
	lungs	19
	left pleura	6
	right pleura	4
	bilateral pleura	2
	lungs plus pleura	2
	lungs plus abdomen	1
	Other sites (*n*=10)	
	cervical lymph node	4
	abdomen	2
	meninges	1
	spinal cord	1
	miliary	1

Sites of paradoxical response	Site(s) of initial involvement	No. of episodes
	bone & joint	1
Skin and soft tissue (*n*=8)	Miliary	8
Lymph nodes (*n*=5)	Original lymph node	2
	Lymph node plus meninges	1
	Other site: meninges	2
Bone and tendon (*n*=3)	Bone & joint	1
	Miliary	1
	Lungs & lymph node	1
Abdomen (*n*=2)	Abdomen	1
	Miliary	1

CNS, central nervous system; IT, intracranial tuberculoma

Table 3. Clinical and radiological presentations in 122 episodes of paradoxical response during antituberculosis therapy

Clinical and radiological presentation of paradoxical response by site	No. of episodes
CNS (*n*=60)	
Headache	12
Mental confusion	8
Seizure	16
Focal neurological signs[a]	36
Tuberculoma(s)[b]	46
Hydrocephalus	9
Respiratory system (*n*=44)	
Pleurisy	3
Increasing pulmonary infiltration	2
Worsening of pleural effusion	8
Development of new pleural effusion	30
Contralateral pleural effusion	4
Skin and soft tissue (*n*=8)	
Development of new lesion(s)	8
Lymph node(s) (*n*=5)	

Clinical and radiological presentation of paradoxical response by site	No. of episodes
Inflammation of pre-existing lymph node(s)	2
Development of new lymph node(s)	3
Bone and tendon (*n*=3)	
Development of new lesion(s)	3
Abdomen (*n*=2)	
Inflammation of pre-existing lesion	1
Development of new lesion	1

CNS, central nervous system

[a]Cranial nerve(s) palsy (n=7), motor dysfunction (n=17), sensory dysfunction (n=7), and cerebellar signs (n=5)

[b]Intracranial tuberculoma(s) (n=44), and intramedullary tuberculoma (n=2)

Table 4. Patients with sequential tuberculin skin tests before and after paradoxical response

Reference	Sex/age	Initial site(s) involved	Presentation of PR	Time to onset of PR	Baseline lymphocyte count (cells/μl)	Baseline TST result	Lymphocyte count at PR (cells/μl)	TST result at PR	Tre
6	F/19	miliary, meningitis	left lower limb weakness; intracranial tuberculoma	1 month	NM	negative	NM	positive	steroid
13	M/39	meningitis	headache, left hemianesthesia & hearing loss; intracranial tuberculoma & hydrocephalus	5 weeks	NM	negative	NM	positive (23 mm)	steroid; ins ventriculo-p
Present case 2	M/16	cervical lymph node	painful, red, tense, and cystic swelling of right lower cervical lymph node	6 weeks	1,400	negative (3 mm)	3,100	positive (23 mm)	steroid; exc node
48	M/28	miliary	fever, pain, swelling of left lateral malleolus	8 weeks	378[a]	negative	800[a]	positive	surgical asp
Present case 1	M/56	miliary	new abscess in chest wall	3 months	570	negative (0 mm)	2,600	positive (16 mm)	surgical dra

NM, not mentioned; PR, paradoxical response; TST, tuberculin skin test

[a]CD4+ cell count

Comment [CE1]: Page: 18
The term "miliary" is an adjective and thus cannot be the site of involvement (a noun is required). Would "miliaria" be the correct term to use under the column heading "Initial site(s) involved"? Likewise, "meningitis" indicates inflammation of the meninges rather than the meninges themselves. Would it be acceptable to change "meningitis" in this column to "meninges"?