

# Chest Radiographic Findings in Patients with Tuberculosis with Recent or Remote Infection

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To determine if chest radiographic findings differ in adult tuberculosis patients with recent and remote infection, we reviewed the chest radiographs of 103 patients with tuberculosis in Los Angeles and performed RFLP analyses of their *Mycobacterium tuberculosis* isolates. Patients whose isolates had identical or closely related RFLP patterns were considered a "cluster." Most patients in large clusters (more than seven patients) had tuberculosis from recent infection, whereas most unclustered patients had tuberculosis from remote infection. Mediastinal adenopathy or pleural effusions were classified as typical of recent infection, and upper lobe infiltrates, cavitation, or fibrosis were classified as characteristic of remote infection. Radiographic patterns were typical of remote infection in 62% of patients and were characteristic of recent infection in 23% of patients. The distribution of these radiographic patterns was similar in clustered and unclustered patients, both with or without human immunodeficiency virus (HIV) coinfection. However, mediastinal adenopathy and pleural effusions were significantly more common in HIV-infected patients. We conclude that: (1) chest radiographic findings in adults with tuberculosis of recent infection are similar to those in patients with remote infection; (2) the distinctive chest radiographic findings in HIV-infected patients with tuberculosis are not due to an increased frequency of recent infection. Jones BE, Ryu R, Yang Z, Cave MD, Pogoda JM, Otaya M, Barnes PF. Chest radiographic findings in patients with tuberculosis with recent or remote infection.

AM J RESPIR CRIT CARE MED 1997;156:1270-1273.

One of the distinctive features of *Mycobacterium tuberculosis* is its capacity to cause disease from weeks to decades after infection. By convention, primary tuberculosis develops within 1 yr after infection, whereas reactivation tuberculosis develops later (1). It is generally assumed that the chest radiographic manifestations differ in primary tuberculosis from recent infection and in reactivation tuberculosis from remote infection. Mediastinal adenopathy and pleural effusions are thought to be characteristic of recent infection, whereas upper lobe infiltrates, cavitation, and fibrosis are considered typical of remote infection. However, the validity of this belief has not been systematically evaluated in adults, as it is difficult to determine if individual patients have tuberculosis caused by recent or remote infection.

The only definitive method to confirm that tuberculosis in an adult is due to recent infection is to document recent tuberculin skin test conversion. Because such data are rarely available, al-

ternative strategies are necessary. One approach is to utilize RFLP analyses of *M. tuberculosis* isolates with the IS6110 and pTBN12 probes. Isolates with identical RFLP patterns are found in patients who were infected from a common source (2-6), whereas isolates with unique RFLP patterns usually represent reactivation of remote infection (7, 8). To determine if the chest roentgenographic findings differ in patients with tuberculosis caused by recent versus remote infection, we reviewed the chest radiographs of a large number of patients with tuberculosis whose isolates had been subjected to RFLP analysis.

## METHODS

### RFLP Analysis

By review of Tuberculosis Control records of Los Angeles County, we identified all 158 patients in whom culture-proved tuberculosis had been diagnosed in central Los Angeles between March 1993 and June 1995. Viable *M. tuberculosis* isolates were available from 153 patients (95%). RFLP analysis with IS6110 was performed on these isolates using standard methods (9). IS6110-based RFLP results are inconclusive if RFLP patterns are identical, but the number of fragments is small (less than six) (7-9) or if RFLP patterns are identical but one isolate has an additional one or two fragments or one or two fragments that differ in size (9). In these situations, secondary RFLP analysis with pTBN12 was performed to enhance discrimination of *M. tuberculosis* strains using standard methods (9, 10). RFLP patterns were compared as described (9) by two of us (ZY and MDC) who had no information about the chest radiographic findings.

(Received in original form September 30, 1996 and in revised form November 26, 1996)

Supported in part by Grants AI-35222 and AI-35265 from the National Institutes of Health, by NIH NCRR CRC Grant M01 RR43 (MCAP), and by the Title I Ryan White Comprehensive AIDS Resources Emergency Act.

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We considered *M. tuberculosis* isolates from different patients to represent the same strain if the IS6110-based RFLP patterns (1) revealed six or more fragments of identical molecular weights; (2) revealed six or more fragments of identical size except that one isolate showed one or two additional fragments, or one or two fragments of different molecular weights, and the pTBN12-based RFLP patterns were indistinguishable; or (3) revealed five or fewer bands of the same molecular weights, and the pTBN12-based RFLP patterns were indistinguishable. A “cluster” was defined as two or more patients infected with the same *M. tuberculosis* strain.

**Interpretation of Chest Radiographs**

The sites serving most patients with tuberculosis in central Los Angeles are the Los Angeles County-University of Southern California Medical Center and two tuberculosis clinics run by the public health department. Of the 153 patients in central Los Angeles for whom RFLP analyses were performed, 130 (85%) were cared for at one of these three locations. Chest radiographs performed at the time of tuberculosis diagnosis were available for 107 (82%) of these 130 patients, and they were reviewed by three of us (BEJ, RR, and PFB). Four of the 107 patients did not have chest radiographic or bacteriologic evidence of pulmonary tuberculosis; the remaining 103 patients constitute the study population.

Chest radiographs were classified as characteristic of recent infection if there was mediastinal adenopathy or a pleural effusion. Chest radiographs were classified as characteristic of remote infection if there was cavitation, predominantly upper lobe infiltrates, or parenchymal or pleural fibrosis with associated volume loss. No radiographs showed features of both recent and remote infection. Chest radiographs that did not show any of the features noted above were classified as indeterminate.

**RESULTS**

**Demographics**

Fifty-seven patients (55%) were African American, 34 (33%) were Latino, six (6%) were non-Latino white, and six (6%) were other races. Seventy-eight patients (76%) were born in the United States, 11 (11%) were born in Mexico, and 14 (14%) were born elsewhere. The mean age was 43.5 ± 1.2 (SE) yr, and 96 patients (93%) were male. Thirty-three patients (33%) were HIV-infected, and 64 patients were HIV-seronegative. Six patients who were not tested for HIV infection were considered HIV-negative. Five of these six were > 54 yr of age and had no HIV risk factors. The sixth patient had a normal ratio of CD4/CD8 cells.

**RFLP Analysis**

Forty patients had *M. tuberculosis* isolates with unique RFLP patterns, suggesting that most of them had tuberculosis caused by remote infection. Fifty patients were in four large clusters, and RFLP patterns of their isolates were shared with isolates from seven to 25 other patients in central Los Angeles. For each cluster, we assumed that one patient developed reactivation tuberculosis from remote infection, whereas the others developed tuberculosis from recent infection. This assumption is reasonable because it is unlikely that more than one patient infected with the same *M. tuberculosis* strain in the distant past would develop reactivation tuberculosis during the relatively brief study period (7, 8). Therefore, four (8%) of these 50 patients had tuberculosis from remote infection, whereas 46 (92%) patients had tuberculosis from recent infection. Thirteen patients had isolates in small clusters, and RFLP patterns were shared with isolates from one to three other patients in central Los Angeles. Because these clusters were small, a significant proportion of these patients probably had tuberculosis caused by remote infection, whereas the remainder had tuberculosis caused by recent infection.

**Interpretation of Chest Radiographs**

Twenty-four chest radiographs (23%) were classified as characteristic of recent infection, including 11 with mediastinal adenopathy, nine with pleural effusions, and four with both findings. Four radiographs had miliary infiltrates in addition. Sixty-four chest radiographs (62%) were classified as typical of remote infection, including 59 with predominantly upper lobe infiltrates, 30 with cavitation, and 39 with parenchymal or pleural fibrosis. Fifteen chest radiographs (15%) were classified as indeterminate, including six with lower lobe infiltrates, four with upper and lower lobe infiltrates, two with solitary nodules and three that were normal. None of the indeterminate radiographs had a miliary pattern.

**Correlation of Chest Radiographic Findings, RFLP Analyses and HIV Infection**

We first compared the chest radiographic patterns in patients who were in large clusters, small clusters, and not in clusters (Table 1). In all three groups, there was no difference in the distribution of chest radiographic patterns, which were typical of remote infection in approximately 60% of cases, and characteristic of recent infection in approximately 25%. Even among the patients in large clusters, most of whom had tuberculosis caused by recent infection, the chest radiograph showed upper lobe infiltrates, cavitation, or fibrosis in most cases. When patients in large clusters, small clusters, and not in clusters were stratified by HIV status, radiographic findings of recent infection in all three groups were significantly more common in HIV-infected than in HIV-negative patients (Table 1). This association remained statistically significant after exclusion of the six patients in whom HIV testing was not performed (data not shown).

To minimize errors in misclassification of chest radiographic patterns, we chose criteria that are generally considered relatively specific for recent or remote infection. One problem with this approach is that a significant proportion of radiographs were classified as indeterminate. Because lower lobe infiltrates without upper lobe disease are sometimes considered to be more typical of recent than of remote infection, we considered these findings to represent recent infection, and we again repeated the correlation of chest radiographic patterns with cluster status and HIV infection. This reclassification did not significantly change the results (data not shown).

TABLE 1  
CHEST RADIOGRAPHIC PATTERNS ACCORDING TO CLUSTER STATUS AND HIV STATUS

Cluster Status	Chest Radiographic Pattern					
	Recent Infection		Remote Infection		Indeterminate	
	(n)	(%)	(n)	(%)	(n)	(%)
Large clusters, n = 50	12	24	31	62	7	14
HIV+, n = 16*	10	63	1	6	5	31
HIV-, n = 34	2	6	30	88	2	6
Small clusters, n = 13	3	23	8	62	2	15
HIV+, n = 5†	3	60	0	0	2	40
HIV-, n = 8	0	0	8	100	0	0
Not clustered, n = 40	9	23	25	63	6	15
HIV+, n = 12*	7	54	1	8	4	33
HIV-, n = 28	2	7	24	89	2	7

\* p < 0.0001, comparing HIV+ and HIV- patients; Fisher's exact test.

† p = 0.008, comparing HIV+ and HIV- patients; Fisher's exact test.

## DISCUSSION

Most cases of tuberculosis arise either from progression of recent infection to disease within 1 yr or from recrudescence of infection acquired in the more distant past (1). Because RFLP analysis can identify clusters of patients infected with the same *M. tuberculosis* strain, it is a powerful tool that allows classification of patients with disease caused by recent or remote infection. Identical or closely related RFLP patterns have been found in patients with tuberculosis who were linked to outbreaks where careful epidemiologic investigations provided evidence of recent transmission in a wide variety of settings, including HIV-infected patients who were infected in a hospital (2), a residential facility (4), and a bar (3), as well as HIV-negative patients who were infected in a hospital (5) or in a neighborhood bar (6). Furthermore, population-based studies in New York and San Francisco demonstrated that patients with tuberculosis in clusters are usually epidemiologically linked, suggesting recent infection in most patients (7, 8). In addition, among patients with tuberculosis in central Los Angeles, epidemiologic links were significantly more common among clustered than among unclustered patients (Peter Barnes, unpublished data). The sum of these data strongly support our underlying assumption for the current study, that most patients in clusters developed tuberculosis from recent infection, whereas most unclustered patients developed tuberculosis from remote infection. We found that chest radiographic findings are similar in clustered and unclustered patients, providing strong evidence that chest radiographic features of recent and remote tuberculosis infection are similar.

In the United States and Europe, most adults have been thought to develop tuberculosis from remote infection, whereas most young children develop disease from recent infection. Because mediastinal adenopathy is common in children with tuberculosis, whereas cavitary upper lobe infiltrates are typical in adults, it is widely believed that mediastinal adenopathy is indicative of recent infection, whereas upper lobe infiltrates and cavities are characteristic of remote infection. This belief is echoed in recent textbooks of internal medicine (11, 12) as well as in recent specialty texts on tuberculosis (13, 14). We believe that this generalization is not justified for three reasons. First, the cell-mediated immune response is less mature in young children than in adults, and the differences in chest radiographic findings between children and adults with tuberculosis may reflect differential efficacy of the immune response rather than differences in the timing of infection. Second, recent studies suggest that a substantial proportion of cases of tuberculosis in adults in the United States are due to recent rather than to remote infection (7, 8). Third, the few studies that have evaluated adults with documented recent infection demonstrated that a substantial proportion of cases have chest radiographic findings considered typical of remote infection (15, 16). Of chest radiographs in 47 adult patients with tuberculosis with recent tuberculin skin test conversion in these studies, 13 (28%) were typical of recent infection, 23 (49%) were typical of remote infection, and 11 (23%) were indeterminate, using our radiographic criteria for classification. These findings support our conclusion that the chest radiographic findings are not clearly associated with the timing of infection.

Our results provide insight into the pathogenesis underlying the distinctive chest radiographic features in HIV-infected patients with tuberculosis. Mediastinal adenopathy and pleural effusions are common in such patients (17, 18), but it has not been clear whether this reflects a higher frequency of recent tuberculosis infection or an ineffective immune response. We found no differences in the frequency of mediastinal aden-

opathy and pleural effusion in clustered and unclustered HIV-infected patients, indicating that these findings are unrelated to the timing of infection, but more likely reflect ineffective immunity. In support of this interpretation, mediastinal adenopathy is typical in HIV-infected patients with tuberculosis with advanced immunodeficiency, whereas cavitation is more common in patients with less advanced HIV infection (19, 20). Studies in laboratory animals also suggest that pulmonary disease is strongly influenced by the integrity of the immune response. When rabbits that are highly susceptible to tuberculosis are infected with *M. tuberculosis*, they develop massive mediastinal lymphadenopathy, diffuse pulmonary infiltrates, and absence of cavitation. In contrast, resistant rabbits develop localized cavitary pulmonary disease without mediastinal lymphadenopathy (21).

In summary, we found that the chest radiographic findings of mediastinal adenopathy and pleural effusion are not reliable indicators of tuberculosis from recent infection, and that upper lobe infiltrates and cavitation are not indicators of remote infection. In HIV-infected patients, the common findings of mediastinal adenopathy and pleural effusions do not result from a higher frequency of recent infection but are more likely to reflect ineffective cell-mediated immunity.

**Acknowledgment:** The writers thank Laura Knowles, Angelita Balanon, and Craig Toyota for assistance in identifying study patients. They also thank Dr. Sydney Harvey, Samuel Chung, Robert Killman, and Diew Nicol for assistance in obtaining *M. tuberculosis* isolates, and Dr. Bruce Ross for providing pTBN12.

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