

Misdiagnoses of Tuberculosis Resulting from Laboratory Cross-Contamination of *Mycobacterium Tuberculosis* Cultures—New Jersey, 1998

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A diagnosis of tuberculosis (TB) is rarely disputed if *Mycobacterium tuberculosis* is isolated from a clinical specimen; however, specimen contamination may occur (1-3). Identification of TB strain patterns through molecular typing or DNA fingerprinting is a recent advancement in TB laboratory techniques (3-7). CDC's National Tuberculosis Genotyping and Surveillance Network (NTGSN) performs DNA fingerprinting on TB isolates to determine the frequency of clustering among *M. tuberculosis* strains in project surveillance sites. In November 1998, NTGSN detected 11 isolates from previously reported TB cases among persons in New Jersey whose DNA fingerprints matched the avirulent laboratory *M. tuberculosis* control strain H37Ra. H37Ra does not cause active TB in humans, but it has been reported as a source of cross-contamination (8). In collaboration with the New Jersey Department of Health and Senior Services, CDC investigated H37Ra as a possible cause of TB disease and/or TB misdiagnoses caused by laboratory cross-contamination in the 11 case-patients. This report describes findings from two of the 11 cases and summarizes the results of this investigation, which indicate that TB was misdiagnosed and demonstrate the value of DNA fingerprinting to identify occurrences of cross-contamination of patient specimens.

CASE FINDINGS

Case 1. In October 1998, a 44-year-old woman with multiple sclerosis and no known exposure to a person with active TB had TB diagnosed on the basis of a positive culture result. Cerebrospinal fluid revealed no signs of infection, but the culture grew *M. tuberculosis* at 7 weeks. Her chest radiograph was normal, and a tuberculin skin test (TST) was not documented. Anti-TB therapy was not initiated because no development or progression of symptoms consistent with TB occurred. The cerebrospinal fluid was retested in the same laboratory (7 weeks after the original specimen was obtained) and revealed a stain with 1+ acid-fast bacilli (AFB).

The patient was started on anti-TB medications. The culture for the second specimen was negative for TB. This patient had received 4 months of anti-TB treatment at the time of the investigation.

Case 2. A 58-year-old woman with a history of reactive airway disease and angioedema was taken to a local emergency department with shortness of breath and cough. Her chest radiograph was normal, and a TST was not documented. A sputum specimen obtained at that time was AFB smear-negative, but *M. tuberculosis* culture was positive at 6 weeks. Although the patient had recovered after treatment for acute asthma, she was started on anti-TB treatment. Treatment was discontinued after 2 weeks when health-care providers determined her illness was not TB.

SUMMARY FINDINGS

A list of the 11 case-patients with an isolate with a fingerprint matching H37Ra was compiled, and information on the origin of each case-specimen was obtained. Investigators reviewed hospital, clinic, and health department records for each case-patient to establish the clinical events leading to TB diagnosis. Investigators visited the laboratories where the 11 specimens were processed to interview laboratory personnel about specimen processing techniques and to review laboratory logs for mycobacterial specimen testing.

The 11 case-patients had TB diagnosed and reported during 1996-1998. Mean age of patients was 60 years (range: 36-81 years); eight were women, and three were human immunodeficiency virus (HIV)-positive. Eight cases were classified as pulmonary and three as extrapulmonary. Seven patients had abnormal chest radiograph findings, and two had documented positive TSTs. All case-patients received partial or full-course therapy for TB; treatment durations ranged from 2 weeks to 6 months. Seven patients had contact investigations performed; four of the 32 contacts identified were tested and treated for latent TB infection. Each case met at least one criterion for suspected laboratory

cross-contamination with *M. tuberculosis**. In addition, each of the eight pulmonary patients had clinical courses suggestive of an illness other than TB (i.e., bacterial pneumonia [four], reactive airways disease [two], interstitial lung disease [one], and congestive heart failure [one]).

The laboratory investigation revealed that the 11 specimens were processed during February 1996–October 1998 at four laboratories in New Jersey (three hospital laboratories and one commercial laboratory). Each of the laboratories either used the strain H37Ra or participated in laboratory proficiency testing using H37Ra; however, laboratory logs did not include the specific times when H37Ra was handled on the same day as any of the 11 specimens. In addition, personnel at the laboratories could not recall instances when the control strain may have been mishandled. The average number of specimens collected for AFB culture per patient was four (range: two to 12). All culture-positive patient specimens were smear-negative. Mean number of days to *M. tuberculosis* growth for patient specimens was 38 (range: 17–54 days).

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Editorial Note:

These misdiagnosed cases of TB illustrate the need for heightened awareness of laboratory cross-contamination with *M. tuberculosis*. Clinicians and health department personnel did not suspect laboratory cross-contamination in these 11 cases; therefore, this oversight would not have been detected without the use of DNA fingerprinting through NTGSN. The putative source of cross-contamination for the 11 cases, H37Ra, is a laboratory control strain that is used weekly in some laboratories for routine drug susceptibility testing. H37Ra also is distributed to mycobacteriology laboratories as part of a biyearly proficiency testing required by the Clinical Laboratory Improvement Amendments (9). The control strains for proficiency testing often are processed simultaneously with patient specimens, but many laboratories do not document consistently specific times when proficiency testing is conducted. As a result, it is

difficult to prove that the control strain is the source of cross-contamination in a specific case. In addition, several opportunities exist for specimen carryover, spillage, or inadvertent contamination during specimen processing, but these occurrences are difficult to discover retrospectively. Given these obstacles in discovering cross-contamination, NTGSN has established criteria for suspected laboratory cross-contamination of TB (CDC, unpublished data, 1998).

Reliance on clinical judgment and the presence of corroborating clinical signs and symptoms play pivotal roles in interpreting laboratory data. Systemic symptoms of fever, loss of appetite, weight loss, weakness, night sweats, and malaise are common but not specific for TB. Other signs and symptoms vary according to the site involved. In pulmonary TB, prolonged cough with or without sputum production, and ensuing pulmonary inflammation and necrosis are manifest. Chest radiograph findings of adenopathy, lung infiltrates, and pleural reaction are important correlates in the diagnosis, but these findings may be due to illnesses other than TB, particularly in the presence of HIV. These scenarios often create clinical dilemmas when initial laboratory data support a TB diagnosis. A positive TST is evidence for TB, but the positive predictive value depends on the cut-off value used to determine a positive test and the prevalence of TB infection in the population (10). In the appropriate clinical setting, the presence of a positive AFB smear should raise suspicion for TB; however, a positive smear with a concomitant inconsistent clinical history may represent the presence of H37Ra, a nontuberculous organism, such as *Mycobacterium avium complex*, or environmental contamination with a ubiquitous acid-fast species such as *Mycobacterium gordonae*. H37Ra and nontuberculous organisms are indistinguishable from pathogenic strains of *M. tuberculosis* on a laboratory smear.

For some patients, signs, symptoms, and test results are lacking or conflicting, as illustrated by the case-patients described in this report. If discrepancies exist among clinical and laboratory data, and at least one criterion for laboratory cross-contamination is met, an investigation should ensue to determine whether the patient has a potential TB exposure, whether specimens from the laboratory strain or other TB patients were processed simultaneously with the specimen in question, and whether performance of DNA fingerprinting is ap-

appropriate. To identify occurrences and sources of cross-contamination, it also is important for mycobacteriology laboratories to determine the DNA fingerprint pattern of the *M. tuberculosis* control strain used in their respective laboratories.

The patients described in this report received unnecessary treatment for TB and more than half had a contact investigation initiated. Recognition by health-care professionals and laboratorians of the potential for laboratory cross-contamination with *M. tuberculosis* should help avert erroneous TB diagnoses and avoid unnecessary treatment and associated toxicity. In addition, this awareness assists TB-control programs in avoiding unnecessary patient care costs and futile contact investigations and helps maintain accurate TB case reporting.

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*Suspected laboratory cross-contamination with *M. tuberculosis* may include at least one of the following: 1) patient's clinical course is inconsistent with TB; 2) single positive *M. tuberculosis* culture with no AFB seen in any specimen; 3) culture-positive specimen from a different patient processed or handled on the same day has an identical DNA fingerprint, and no epidemiologic connections exist between patients; 4) laboratory control strain has an identical fingerprint; and 5) time to growth detection is >30 days.

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