A Death Associated With Therapy for Nosocomially Acquired Multidrug-Resistant Tuberculosis*

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Treatment of multidrug-resistant tuberculosis is difficult and has been associated rarely with severe side effects. We report the nosocomial transmission of multidrug-resistant tuberculosis to a health-care worker who was seronegative for HIV infection. She died because of liver failure associated with treatment for active multidrug-resistant tuberculosis.

(CHEST 1996; 110:279-281)

Key words: adverse effect; drug resistance; therapy; tuberculosis

Abbreviations: AFB=acid-fast bacilli; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HCW=health-care worker; INH=isoniazid; LFT=liver function test; MDR-TB=multidrug-resistant TB; TB=tuberculosis

Recent reports have documented nosocomial transmission of *Mycobacterium tuberculosis* with subsequent active tuberculosis (TB) disease among health-care workers (HCWs). One of these HCWs died. Treatment of multidrug-resistant TB (MDR-TB) is difficult and has been associated rarely with severe side effects. We report the nosocomial transmission of MDR-TB to a 21-year-old HCW who was seronegative for HIV infection. She died because of liver failure associated with treatment for active MDR-TB.

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materials and methods

Patient, laboratory, and infection-control records on the case-

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The MDR-TB occurred in a 21-year-old previously healthy woman who worked as a nursing assistant in Hospital A. She had no history of family exposure to TB and had had negative results (no specific induration recorded) to a Mantoux tuberculin skin test at a preemployment examination on December 23, 1992.

During April 14 to 21, 1993, while working at Hospital A, she had 5 days of work exposure to an inpatient who had pulmonary TB with sputum smears positive for acid-fast bacilli (AFB) but who was not in respiratory isolation. The hospital conducted a contact investigation of all persons who had been exposed to this patient. The nursing assistant had negative results (no specific induration recorded) to a baseline Mantoux tuberculin skin test on May 21; on August 16, she had a 10-mm induration on repeated testing. Of the 79 employees who were exposed to the source-patient and who were previously Mantoux test negative, the nursing assistant was the only one with a newly reactive Mantoux test 12 weeks after exposure.

The nursing assistant had no signs or symptoms suggestive of TB. Her chest radiograph was normal, and results of baseline liver function tests (LFTs), including transaminases, were within normal limits. On September 29, she began daily oral doses of 300 mg of isoniazid (INH) and 50 mg of pyridoxine. Her medical records did not indicate that the probable source-patient for her skin test conversion had had INH-resistant TB, although the physicians treating the source-patient had made this determination.

No INH-related toxicity was documented in employee health service records during follow-up medical visits, and repeated LFT values were only mildly elevated (alanine and aspartate aminotransferases [ALT and AST]≤72 IU/L) on November 4, November 24, and December 23, 1993, and January 7, 1994. Beginning in mid-November, she told her family that she was fatigued and had lost weight, but these symptoms were not communicated to her medical caregivers. On January 13, 1994, she was admitted to Hospital B with fever, weight loss, menorrhagia, and anemia. The differential diagnoses considered at the time of hospital admission included extrapulmonary TB. She had no respiratory symptoms, and a hospital admission chest radiograph was normal. Sputum smears were negative for AFB on January 30 and 31. On January 30, before culture results were available, the nursing assistant began empiric treatment with INH, rifampin, pyrazinamide, and ethambutol. Serum AST level measured 1 week after starting anti-TB therapy was 34 IU/L.

The nursing assistant was transferred to Hospital C on February.
9, 1994, for further evaluation. Empiric anti-TB therapy continued with no clinical improvement. Mediastinal and hilar adenopathy developed; tissue from a scalene lymph node biopsy specimen and induced sputa were AFB-smear negative. On February 14, physicians at Hospital C learned that the probable source-patient at Hospital A had had TB resistant to numerous first- and second-line drugs (Table 1). The nursing assistant’s therapy was changed to ethionamide, rifabutin, cycloserine, capreomycin, and ofloxacin. Results of LFTs on March 7 were within normal limits (AST, 29 IU/L; ALT, 9 IU/L; alkaline phosphatase, 46 IU/L). She responded clinically to treatment and was discharged from the hospital to her home on March 15, where she continued daily oral doses of 200 mg of ethionamide, 600 mg of rifabutin, 400 mg of ofloxacin, 500 mg of cycloserine, and 50 mg of pyridoxine, and 250 mg of self-administered IM streptomycin.

By May 1994, the nursing assistant’s sputum from Hospital B and lymph node biopsy specimen from Hospital C were reported to be culture positive for M tuberculosis resistant to numerous first- and second-line drugs (Table 1). Restriction fragment-length polymorphism analysis later showed an identical two-band pattern in M tuberculosis isolates obtained from the nursing assistant and from the probable source-patient at Hospital A.

Clinical improvement continued at home. However, on May 2, 1994, the nursing assistant developed nausea, vomiting, and jaundice. Treatment with rifabutin and ethambutol was discontinued. During the next 6 days, symptoms of hepatotoxicity worsened. She was readmitted to Hospital C on May 9. Despite aggressive supportive therapy and plasmapheresis, she developed liver failure with encephalopathy and coagulopathy. Serologic tests for HIV and hepatitis C were negative; she was hepatitis B surface antibody positive and core antibody negative after hepatitis B immunization in early 1993. Treatment for MDR-TB was continued with streptomycin, cycloserine, and ofloxacin on the assumption that ethionamide and/or rifabutin were the most likely causes of the liver failure.

She was transferred on May 25 to Hospital D in Boston. Liver biopsy specimen revealed massive hepatocellular necrosis and no granulomas; AFB smears of liver tissue were negative. An orthotopic liver transplant was performed on May 28. Because of partial donor-liver necrosis, she required further surgery. She subsequently was found to be infected with vancomycin-resistant enterococcus and multidrug-resistant Actinobacter anitratus. She died on June 13, 1994, from sepsis, disseminated intravascular coagulopathy, and liver failure.

### Discussion

This case illustrates several potential difficulties in appropriately managing HCWs exposed to MDR-TB. Reliable date to guide prophylaxis for M tuberculosis resistant to both INH and rifampin are not available. One suggested prophylactic regimen, ofloxacin plus pyrazinamide, has unknown efficacy and has been associated with intolerable side effects in several HCs (and New York State Department of Health, unpublished data, 1994). In the case described herein, M tuberculosis was resistant to INH, rifampin, pyrazinamide, ethambutol, and other drugs. In this situation, some experts would recommend close observation without prophylaxis, especially in HIV-seropositive patients.

Liver failure is rare among young persons receiving TB therapy. Liver failure in the nursing assistant described in this report was related temporally to treatment for active MDR-TB disease. Ethionamide (which is chemically related to INH) and/or rifabutin (which is chemically related to rifampin) were the most likely causes; either drug can rarely cause chemical hepatitis. The other drugs in the nursing assistant’s treatment regimen are less likely to be hepatotoxic, although their contribution to her liver failure cannot be excluded.

Hepatitis associated with INH preventive therapy is a well-described and publicized potential problem. In the treatment of active TB disease, hepatitis associated with multidrug therapy is a rare, and, therefore, acceptable side effect. However, with the expanded use of second-line and experimental drugs to treat MDR-TB, clinicians must be reminded of the potential side effects of these drugs. Monthly monitoring for elevated transaminase levels and clinical liver toxicity is indicated. Also, patients should be educated about early symptoms of hepatitis, so that patients can report immediately such symptoms if they develop.

In the nursing assistant we describe, a noteworthy observation is that complications of therapy for one multidrug-

### Table 1—M tuberculosis Susceptibility Patterns for Source-Patient and Nursing Assistant

<table>
<thead>
<tr>
<th>Source-patient</th>
<th>INH</th>
<th>RIF</th>
<th>PZA</th>
<th>EMB</th>
<th>SM</th>
<th>ETH</th>
<th>CAP</th>
<th>KAN</th>
<th>AK</th>
<th>CIP</th>
<th>CS</th>
<th>RBT</th>
<th>PAS</th>
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<tbody>
<tr>
<td>Sputum, Oct '92</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Sputum, Feb '93</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>—</td>
<td>R1</td>
<td>—</td>
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<tr>
<td>Gastric fluid, March '93</td>
<td>R</td>
<td>R</td>
<td>—</td>
<td>R</td>
<td>S</td>
<td>—</td>
<td>S</td>
<td>R</td>
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<tr>
<td>Lymph node, April '93</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>—</td>
<td>—</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Sputum, April '93</td>
<td>R</td>
<td>R</td>
<td>—</td>
<td>R</td>
<td>R1</td>
<td>—</td>
<td>R</td>
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<tr>
<td>BAL, May '93</td>
<td>R</td>
<td>R</td>
<td>—</td>
<td>R</td>
<td>R1</td>
<td>—</td>
<td>S</td>
<td>—</td>
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</table>

*RIF=rifampin; PZA=pyrazinamide; EMB=ethambutol; SM=streptomycin; ETH=ethionamide; CAP=capreomycin; KAN=kanamycin; AK=amikacin; CIP=ciprofloxacin and ofloxacin; CS=cycloserine; RBT=rifabutin; PAS=para-aminosalicylic acid; R=resistant; S=susceptible; dash=not tested or no result available. If standard drug testing involved two drug concentrations (for example, INH tested at both 0.2 µg/mL and 1.0 µg/mL), susceptibilities in this table refer to both concentrations except as noted below.

1Resistant at 2.0 µg/mL, but susceptible at 10 µg/mL.

2Isolate also resistant to clofazimine at 2.0 µg/mL.

3Reported susceptible to cycloserine at one laboratory, but resistant at another laboratory.
We report an unusual case of bronchioloalveolar carcinoma characterized by production of a large quantity of sputum accompanied by drastic electrolyte and fluid loss. The sputum contained a high level of gastrointestinal cancer-associated antigen (CA19-9) and carcinoembryonic antigen (CEA). An immunohistochemical study of tumor cells showed the specific distribution of gastrointestinal cancer-associated antigen and carcinoma-specific antigen, which were localized in the apical region of tumor cells. (CHEST 1996; 110:281-82)

Key words: bronchioloalveolar carcinoma (BAC); bronchorrhea; carcinoembryonic antigen (CEA) gastrointestinal cancer-associated antigen (CA19-9)

Abbreviations: BAC=bronchioloalveolar cell carcinoma; CEA= carcinoembryonic antigen

A striking feature of bronchioloalveolar carcinoma (BAC) is the production of large quantities of sputum. Recently, biochemical constituents of the sputum have been studied; however, few reports are available concerning the levels of tumor markers. We studied the carcinoembryonic antigen (CEA) and the gastrointestinal cancer-associated antigen (CA19-9) in the sputum produced by a patient with BAC suffering from severe bronchorrhea. The sputum contained significantly higher levels of these tumor markers than the serum.

CASE REPORT

A 49-year-old woman developed a cough accompanied by clear watery sputum of 300 to 400 mL/day. A chest radiograph showed diffuse lesions in both lungs. At bronchoscopy, a large amount of watery fluid was observed in the bronchus of the lower lobe of the left lung. The diagnosis of BAC was made based on the histologic examination of specimens obtained through transbronchial lung biopsy. All sputum expectorated was collected and measured. The analysis of the sputum revealed that CEA and CA19-9 were present at high levels (CEA, 612.7 ng/mL; CA19-9, 33,057 U/mL). Despite these findings, serum levels of these tumor markers were not significantly elevated. CEA, 0.5 mg/mL [normal range, <5 mg/mL]; CA19-9, 91.5 unit/mL [normal range, <35 unit/mL]). Measurement of electrolytes in the sputum were as follows: sodium, 134 mEq/L; chloride, 116 mEq/L; potassium, 7.4 mEq/L.

Corticosteroids, atropine sulfate, and cytotoxic drugs failed to reduce the sputum volume. Several months later, the amount of sputum increased to the maximum of 9 L/day. The patient always had to bend forward to expectorate the sputum. Approximately 10 L fluids were administered daily to restore serum electrolyte levels and water balance. Soon after, her condition deteriorated and she died of severe respiratory failure. The autopsy revealed that the primary site was the lower lobe of the left lung. Both lungs revealed an extensive presence of tumor cells. Microscopic examination showed that the tumor cells were tall and columnar containing periodic acid-Schiff-positive and Alcian blue-negative substances. Immunohistochemical evaluation showed that tumor cells were strongly stained by CEA and CA19-9 antibodies (Fig 1).

DISCUSSION

Production of large amounts of sputum is one of the unique features of BAC. This patient produced an extremely large volume of sputum, much greater than in other cases reported. Because the sputum of the patient contained almost the same concentration of electrolytes as the serum, loss of an