Chronic Tuberculous Empyema with Bronchopleural Fistula Resulting in Treatment Failure and Progressive Drug Resistance*

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We treated five patients with a past history of tuberculous pleural infection that led to chronic, quiescent, loculated empyema. Reactivation of TB was associated with formation of BPF and recovery of drug-susceptible Mycobacterium tuberculosis from sputum. All patients had recurrence of positive sputum cultures that yielded tubercle bacilli resistant to drugs they were receiving. The lungs demonstrated gross thickening with calcification of both visceral and parietal pleura. Two patients underwent retreatment chemotherapy followed by decortication-empyemectomy and lung resection surgery; both are now culture-negative for TB. One patient received retreatment chemotherapy but refused surgery; he remains clinically stable with negative sputum cultures. Two other patients' organisms became drug-resistant and they remain sputum-culture positive. We believe that thick, calcified pleural walls limit penetration of drugs into the infected empyema space, resulting in suboptimal drug concentrations and drug resistance. Intensified chemotherapy and surgical intervention should be considered in these cases. (Chest 1991; 100:124-27)

BPF = bronchopleural fistula; NJC = National Jewish Center for Immunology and Respiratory Medicine; TB = tuberculosis

Pleural tuberculosis is most often a manifestation of a primary infection of the lungs caused by Mycobacterium tuberculosis. Inflammation of the pleura generally is associated with the development of delayed-type hypersensitivity against tubercle bacilli located on or near the pleural surface. Usually this is a benign, even a self-limited event: the natural history of tuberculous pleurisy in the pre-chemotherapy era was to undergo spontaneous involution as cell-mediated immunity halted the proliferation and reduced the number of tubercle bacilli in the lungs and pleura. Generally, the pleural effusion receded, leaving a normal chest x-ray film or merely blunting of the costophrenic angle.

However, this primary tuberculous pleural involvement, on rare occasion, proceeded directly to the formation of a chronic, active infection of the pleural space. Another mechanism causing chronic tuberculous pleural disease occurred during the pre-chemotherapy era, when efforts at "collapsing" tuberculosis cavities by introducing air into the pleural space (therapeutic pneumothorax) led to the development of a trapped lung and tuberculous empyema.

Such protracted mycobacterial infections cause thickening, even calcification of the visceral and parietal pleura. Active disease within the pleural space may eventually result in erosion of a tract between the pleural space and the airways, a BPF. In such cases tubercle bacilli from the empyema space may be discharged in the sputum. We report here five patients with chronic pleural tuberculosis and BPF in whom efforts at chemotherapy met with treatment failure and the evolution of drug resistance.

The cases are summarized in Table 1. Illustrative chest radiographs, CT scans and radionuclide lung scans are shown in Figures 1 to 4.

**DISCUSSION**

Exposure of populations of tubercle bacilli to sub-lethal concentrations of a drug is a proven means to select for mutant bacilli resistant to that drug. Modern drugs such as isoniazid or rifampin, taken in appropriate doses, generally result in tissue concentrations sufficiently high to kill strains of drug-susceptible tubercle bacilli. We report here five patients who acquired drug resistance despite receiving appropriate drug regimens, presumably through the mechanism of partial exclusion of the drugs due to thick, fibrotic chronic empyema walls that are relatively impermeable to medications. While we cannot provide absolute proof of compliance with treatment before coming to NJC, all patients claimed to have taken their drugs with reasonable regularity. Patients 1, 2, 4 and 5 failed to convert their cultures while receiving in-patient directly administered therapy at NJC, lending credibility to their claims.

Unlike the usual primary tuberculous pleural effusions that are associated with relatively thin mesothelial membranes, the rare chronic empyema may—

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<table>
<thead>
<tr>
<th>Case, Age (yr), Sex</th>
<th>Prior History</th>
<th>Pleuropulmonary Disease</th>
<th>Acquired Drug Resistance</th>
<th>Management</th>
<th>Current Status</th>
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<tr>
<td>Case 1 62, F</td>
<td>Right effusion in 1947 treated by bed rest; persistent pleural thickening on x-ray; renal disease in 1955; SM and PAS</td>
<td>1984: cough, fever and worsening x-ray film findings; sputum-positive for susceptible <em>M tuberculosis</em>; 1964-1965: 18 months of INH, RIF and EMB; sputum always culture-positive</td>
<td>INH, RIF, EMB</td>
<td>Rifabutine, CSN, PZA, PAS and SM for 4 months; sputum remained positive; decortication and pneumonectomy followed by 18 months of chemotherapy</td>
<td>Culture-negative</td>
</tr>
<tr>
<td>Case 2 64, M</td>
<td>Right effusion in 1948 treated with bed rest and thoracentesis drainage</td>
<td>1984: hemoptysis; sputum-positive for susceptible <em>M tuberculosis</em>; treated with INH and RIF for 9 months and EMB for 2 months; 1985: hemoptysis recurred, culture-positive; retreated with INH, RIF, SM, PZA and EMB but remained culture-positive</td>
<td>INH, RIF, SM, EMB, PZA</td>
<td>CSN, KM, ETA and Cipro for 4 months; culture converted to negative; underwent decortication and right lower lobectomy; surgical specimen yielded heavy growth of <em>M tuberculosis</em> resistant as noted</td>
<td>Culture-negative</td>
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<tr>
<td>Case 3 64, M</td>
<td>Pneumonia with pleurisy in concentration camp in World War II (1945); chest x-ray film persistently abnormal since</td>
<td>1986: onset of cough, fever, sweats and weight loss; sputum positive for susceptible <em>M tuberculosis</em>; received INH and RIF for 9 months; symptoms diminished but chest x-ray film unchanged; 2 months after treatment stopped, productive cough resumed; culture-positive</td>
<td>INH</td>
<td>RIF, EMB (25 mg/kg for 3 months, then 15 mg/kg and PZA (40 mg/kg) for 13 months; surgery encouraged but patient refused</td>
<td>Culture-negative; BPF persists; chronic cough and malaise</td>
</tr>
<tr>
<td>Case 4 55, F</td>
<td>Pulmonary TB in 1943, treated with left, then right pneumothorax; apparent clinical and radiographic improvement</td>
<td>1985: recurrent cough and constitutional symptoms; sputum positive for <em>M tuberculosis</em> reported susceptible; multiple regimens with variety of agents over 4 years; variably culture-positive over this period</td>
<td>INH, RIF, PZA, SM, ETA</td>
<td>PAS, EMB, KM, Cipro and clofazimine; always remained positive; refused resectional surgery or drainage procedure</td>
<td>Culture-positive</td>
</tr>
<tr>
<td>Case 5 67, F</td>
<td>Pulmonary TB in 1939, initial pneumothorax; later, SM and PAS; 1959 relapsed, treated with right subsegmental cavity resection and 6-rib thoracoplasty; complicated by empyema and BPF; 1972, right upper lobectomy; INH for 1 yr</td>
<td>1986: new right chest wall abscess, culture-positive for <em>M tuberculosis</em>, multiply resistant; KM, EMB, ETA, rifabutine and Cipro given with involution of the abscess but persistence of the BPF; surgery not recommended due to respiratory insufficiency</td>
<td>INH, RIF, SM, PZA, CSN</td>
<td>1986: new right chest wall abscess, culture-positive for <em>M tuberculosis</em>, multiply resistant; KM, EMB, ETA, rifabutine and Cipro given with involution of the abscess but persistence of the BPF; surgery not recommended due to respiratory insufficiency</td>
<td>Culture-positive</td>
</tr>
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Abbreviations: INH = isoniazid; SM = streptomycin; PAS = para-aminosalicylate; RIF = rifampin; EMB = ethambutol; PZA = pyrazinamide; ETA = ethionamide; CSN = cycloserine; KM = kanamycin.
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FIGURE 1. Admission posteroanterior chest film from patient 1 demonstrates dense shadows at the lateral base of the right lung with irregular pleural thickening extending superiorly and hazy, amorphous densities in the lower zones of the right lung. Air cannot readily be identified in the right pleural space.

Through continued active infection and inflammation over years—eliciting an extremely thick, fibrocalcific rind that has a relatively deficient blood supply. This defensive fortress, while fairly effective at keeping the infection contained, also may limit the access of antimicrobial agents. In these five patients, a chronic BPF developed that allowed egress of the tubercle bacilli to the respiratory tree and thence to the sputum, making the patients infectious risks to the community.

For patient 1 who had acquired resistance to isoniazid, rifampin and ethambutol, we were unable to effect sputum culture conversion from positive to negative in spite of very aggressive chemotherapy. In patient 2, whose organism had become resistant to isoniazid, rifampin, ethambutol, streptomycin and pyrazinamide, we achieved conversion of culture to negative status but we feared that this might only be transient. In both of these cases, resectional surgery was performed to eliminate the thick-walled fortress that was harboring (and presumably promoting) the infection.

FIGURE 2. A completed tomographic scan from patient 3 demonstrates extraordinary pleural thickening with extensive calcification and an air-fluid level within the empyema space. Also notable is the loss of volume of the left hemithorax associated with longstanding restriction.

FIGURE 3. Ventilation scan from patient 1 demonstrates that 75 percent of the xenon 133 inhaled goes to the left lung.

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FIGURE 4. Perfusion scan from patient 1 demonstrates that 75 percent of the technetium 99-labelled macroaggregated albumen injected intravenously was deposited in the capillary bed of the left lung.
drug-resistant bacilli. For patient 3, who had only lost isoniazid to resistance, we re-treated him with a regimen that included two additional first-line drugs, and he has achieved a negative sputum culture. However, we are anxious about his prospects for recrudescence with increased drug resistance and have encouraged him to undergo surgery. Thus far, he has refused and remains culture-negative 24 months after completing retreatment. In patient 4, extensive bilateral disease was present and respiratory function was compromised. We felt that drainage of the infected space was indicated, but this was refused by the patient. For patient 5, compromised gas exchange and pulmonary function made additional surgical treatment unacceptably hazardous; the patient is receiving chemotherapy but continues to be sputum-positive.

From an uncontrolled series of cases such as this, it is impossible to determine optimal management practices. However, we believe that chronic tuberculous empyema poses a significant risk for the evolution of drug resistance in spite of nominally adequate chemotherapy regimens. We therefore encourage the initial use of aggressive, multiple (three or more) drug treatment plans, employing agents at their maximal tolerated dosages, carefully monitoring response to therapy including serial cultures with drug susceptibility testing, and—when or if failure relapse occurs—prompt consideration of surgical extirpation of the empyema and underlying diseased lung.3

REFERENCES