Tuberculous (TB) empyema is a chronic, active infection of the pleural space and a rare complication of pleuropulmonary TB (1). Its management may vary depending on the coexistence of spontaneous drainage phenomena (bronchopleural fistula [BPF] or empyema necessitatis) as well as the general and lung health of the patient. As a rule, anti-TB drug treatment alone cannot be relied on for cure. Virtually all cases require some form of external drainage. However, even when spontaneous drainage has occurred via a BPF, anti-TB drug treatment alone has been problematic – orally administered anti-TB drugs have resulted in acquired drug resistance, presumably because of differential penetration of drugs through the thick fibrocalcific wall of the empyema (1-4).

In the past, drainage has been provided using a wide variety of surgical procedures, including decortication to allow re-expansion of the trapped lung and decortication plus pneumonectomy to remove a lung that is predicted to cause ongoing morbidity. However, in the experience of the authors, the performance of these procedures may be lacking. As well, patients may be older or have comorbidities. Nonsurgical drainage may be adequate if it is possible to provide therapeutic drug exposure.

CASE PRESENTATION

In 1954, a 20-year-old man was diagnosed with right-sided TB pleurisy. He was given 12 months of streptomycin and paraaminosalicyllic acid in a sanatorium. In the spring of 2005, during the investigation of a swallowing difficulty and weight loss that ultimately was proven to be due to squamous cell carcinoma of the hypopharynx, he was diagnosed with a right-sided TB empyema (Figure 1). Pleural fluid was opaque and cloudy with a moderate number of lymphocytes and neutrophils. The fluid culture grew Mycobacterium tuberculosis. Antibiotic susceptibility studies revealed multidrug resistance (MDR) with high levels of resistance to isoniazid, rifampin, and ethambutol. Therefore, a multidrug therapy (MDT) regimen was initiated.

The MDT regimen included high-dose isoniazid (10 mg/kg per day), ethambutol (15 mg/kg per day), and levofloxacin (750 mg once daily). Isoniazid was started at a dose of 12 mg/kg per day but increased to 20 mg/kg per day. Ethambutol was started at a dose of 25 mg/kg per day and levofloxacin at 750 mg once daily. The regimen was administered orally and intrapleurally. The intrapleural administration was performed under ultrasonic guidance using a Wonderbag pleural drainage system (Portex, Mailton, ON, Canada). The patient was monitored for 2 months and showed a significant reduction in pleural fluid volume as well as stabilization of weight and swallowing function.

The present case is discussed in the context of the literature on acquired drug resistance in TB empyema. It is argued that high-end doses of oral drugs or combined oral plus intrapleural drugs, along with tube thoracostomy or intermittent thoracentesis, will cure uncomplicated TB empyema without threatening to induce drug resistance or having to resort to surgery.

Key Words: Acquired drug resistance; Tuberculous empyema
Drugs and time to Cmax (Tmax) was increased (Table 1). Pleural concentrations rose to the average maximum concentration (Cmax) at Jewish Medical and Research Center, USA. Serum concentrations were measured using high performance liquid chromatography (for pyrazinamide) or gas chromatography or mass spectrometry (for INH and rifampin) or computed tomography guidance. Baseline and postdose peripheral blood catheter was inserted into the empyema space under computed tomography. All treatment was directly observed.

To assess the adequacy of TB drug exposure, a 10 Fr Navarre catheter was inserted into the pleural space under computed tomography guidance. Baseline and postdose peripheral blood and pleural fluid samples were drawn, and anti-TB drug concentrations were measured using high performance liquid chromatography (for INH and rifampin) or gas chromatography with mass spectrometry (for pyrazinamide) at the National Jewish Medical and Research Center, USA. Serum concentrations rose to the average maximum concentration (Cmax) at 1 h to 2 h postdose, while pleural fluid Cmax was low for all drugs and time to Cmax (Tmax) was increased (Table 1). Pleural fluid Cmax was 30%, 6% and 49% of serum Cmax for INH, rifampin and pyrazinamide, respectively. Repeat postdose concentrations were confirmatory.

To provide external drainage, a 28 Fr chest tube was inserted into the empyema space under computed tomography. To ensure therapeutic drug exposure, a protocol of intrapleural (empyema space) treatment was commenced. It consisted of twice-weekly treatments for six months starting October 5, 2005. On each treatment day, 150 mL of fresh drug-containing solution was prepared. Drugs were chosen on the basis of availability in parenteral formulation, drug susceptibility test results, ability to prevent nonmycobacterial superinfection and cost; INH (20 μg/mL or 3 mg), amikacin (80 μg/mL or 12 mg) and levofloxacin (10 μg/mL or 1.5 mg). Drug concentrations were purposely high-end relative to usual serum concentrations, and a degree of dilution was assumed. The empyema space was first irrigated with 150 mL of nondrug-containing sterile saline (in the Navarre catheter and out the chest tube). The drug-containing solution was then infused; dwell time was two to three days. The duration of intrapleural treatment took into account the time to cure uncomplicated pulmonary TB, but was otherwise empirical. Nonmycobacterial superinfection of the pleural space did not occur despite cancer chemotherapy-induced leukopenia.

Permanent drainage was provided, local tumour was excluded and treatment outcome was confirmed at surgery on May 17, 2006 (5). All tissue and fluid samples were negative for AFB on smear and culture. No local tumour was identified. Unfortunately, the patient died four months later of complications of his hypopharyngeal tumour.

**DISCUSSION**

We describe a patient with classical TB empyema managed in a manner unique to TB empyema but known to chronic abcess. The treatment was designed to provide a timely cure without inducing drug resistance and without resorting to major surgery. It recognized the relatively low morbidity of the lesion despite its remarkable chronicity.

Pharmacokinetic studies confirmed the differential penetration of standard anti-TB drugs into the empyema space and the existence of conditions favourable to the acquisition of resistance. Pleural fluid Tmax was increased and pleural fluid Cmax was 30%, 6% and 49% of serum Cmax for INH, rifampin and pyrazinamide, respectively. In the only other case in which pleural fluid drug concentrations have been compared with serum concentrations, Elliott et al (3) found pleural fluid Tmax matched isolates were not present in the province of Alberta to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs. The fact that DNA fingerprinting was positive for *Mycobacterium tuberculosis* susceptible to all first-line anti-TB drugs.
to be increased and pleural fluid $C_{\text{max}}$ to be 4%, 34% and 48% of serum $C_{\text{max}}$ for rifampin, streptomycin and ofloxacin, respectively. In that case, pleural fluid as well as serum $T_{\text{max}}$ and $C_{\text{max}}$ for ethambutol were virtually identical.

Acquired drug resistance has been reported in eight cases of TB empyema (1-4). All cases were resistant to INH, presumably because it was the only drug that achieved therapeutic concentrations in the pleural space. Using the $C_{\text{max}}$/minimum inhibitory concentration (MIC) ratio – an approximate measure of the potency of INH and rifampin in the pleural space, with a value of greater than four indicating probable effectiveness (6) – INH was effective at 19.2 (0.96/0.05) and rifampin was ineffective at 2.4 (0.48/0.20). The relationship between $C_{\text{max}}$ and MIC is less clear for pyrazinamide. MICs of pyrazinamide for susceptible strains of $M$ tuberculosis, which were determined using radiometric techniques, ranged between 6.2 μg/mL or less and 50 μg/mL when tested at a pH of 5.5 (7). The recommended breakpoint for susceptibility testing is less than 100 μg/mL, while the therapeutic range in vivo is 20 μg/mL to 50 μg/mL. It is probable that the achievable pleural fluid concentrations of pyrazinamide in our patient were therapeutic, especially given that pyrazinamide is only effective in an acidic environment and acidity is a classic feature of TB empyema. However, as a companion drug in the treatment of pulmonary TB, pyrazinamide cannot be relied on to protect against INH resistance (8).

All cases of acquired drug resistance in TB empyema also had a BPF, a complication we speculate contributed to the acquisition of resistance by improving oxygenation, mycobacterial growth and the number of resistant mutants. In the absence of a BPF, Neihart et al (9) cured a patient with TB empyema using a 24-month course of INH and ethambutol (rifampin was also administered but is unlikely to have achieved therapeutic concentrations in the empyema) in combination with intermittent thoracentesis.

Taken together, our own experience and that of Neihart et al (9) and Elliott et al (3) suggest the following:

- it is possible to cure TB empyema, at least one that is uncomplicated by BPF, without resorting to surgical drainage;
- 12 to 18 months of high-end doses of oral INH, pyrazinamide and ethambutol, together with tube thoracostomy or intermittent thoracentesis, are curative without threatening to induce drug resistance; and
- combined oral plus intrapleural anti-TB drugs, along with tube thoracostomy, while offering theoretical advantages (reduced time to cure, reduced likelihood of drug resistance), may not be required in all cases.

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