Surgical treatment to increase the success rate of multidrug-resistant tuberculosis

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Abstract

OBJECTIVE: Mycobacterium tuberculosis infects more than one-third of the world’s population and causes an estimated 2–3 million deaths annually. The medical treatment of multidrug-resistant tuberculosis (MDR-TB) can cure 50–75% of cases. The median prevalence of new MDR-TB cases is 1.1%, while that of previously treated cases is 7%.

METHODS: We carried out a retrospective study on 45 patients with MDR-TB who underwent surgical resection at the Leon Daniello Hospital (Regional Surgery Department) between January 1995 and December 2005. The number of MDR-TB cases has continued to increase despite the implementation of MDR-TB treatment strategies. Drug susceptibility tests showed that all our patients were resistant to at least isoniazid (hydrazide) and rifampicin. Therefore, individual drug regimens including at least five antibiotics were prescribed. Surgery under general anaesthesia (double-lumen endotracheal intubation) was performed by a team of thoracic surgeons. The patients had received anti-tuberculosis (TB) treatment for at least 1 month preoperatively as well as postoperatively.

RESULTS: We collected and analysed patients’ demographic data, clinical characteristics, place of origin, radiological findings, smear and culture status before surgery, TB localization, primary or secondary drug resistance, surgical procedures, complications, bacteriological smear and culture status after surgical treatment. The indications for surgery include medical treatment failure (due to persistent cavitary disease and lung or lobar destruction) and massive haemoptysis. Proper patient selection and the timing of operations are crucial to avoid relapses and to provide a definitive cure. Good cooperation between chest physicians and thoracic surgeons as well as patients’ adherence to pre- and post-chemotherapy can increase the success rate of MDR-TB treatment.

CONCLUSIONS: The absolute indications for the surgical treatment of MDR-TB include failure of medical therapy (due to persistent cavitary disease and lung or lobar destruction) and massive haemoptysis. Proper patient selection and the timing of operations are crucial to avoid relapses and to provide a definitive cure. Good cooperation between chest physicians and thoracic surgeons as well as patients’ adherence to pre- and post-chemotherapy can increase the success rate of MDR-TB treatment.

Keywords: Multidrug-resistant tuberculosis • Surgical treatment • Thoracotomy

INTRODUCTION

Mycobacterium tuberculosis infects more than one-third of the world’s population and causes an estimated 2–3 million deaths annually. Multidrug-resistant tuberculosis (MDR-TB) is defined as the M. tuberculosis strain resistant to at least isoniazid (hydrazide) and rifampicin. The medical treatment for MDR-TB cures <50% of patients (40–50% of these patients succumbing from progressive disease within 10–15 years) [1]. Other studies have reported long-term success rates of up to 75% [2]. The cure rate of non-resistant tuberculosis (TB) was ~95%. In 2005, the World Health Organization (WHO) reported 8.8 million new cases of TB globally, with an incidence of 136/100,000. According to the WHO report in 2000, 3.2% of all new TB cases were MDR. In Estonia and Lithuania, MDR was observed in 14 and 9% of new TB cases [3]. The increase in the Mycobacterium tuberculosis (MTB) infection rates has prompted the WHO to declare MTB a global emergency. In 1995, MTB resulted in more deaths than any other infectious disease [4, 5]. The third round of surveys included new deaths registered between 1990 and 2002 in 77 settings or countries. The median prevalence of new MDR-TB cases was 1.1% (ranging from 0% in 8 countries to 14.2% in Kazakhstan and Israel) [1]. The median prevalence of previously treated cases was 7%. The prevalence of MDR-TB was exceptionally high in almost all the countries from the Former Soviet Union including Estonia, Kazakhstan, Latvia, Lithuania, the Russian Federation or Uzbekistan [6].

Romania is one of the Eastern European countries with limited resources for health care. The number of MDR-TB cases has continued to increase despite the implementation of MDR-TB treatment strategies. Most TB patients can be successfully treated using medical chemotherapy, and only small
populations of patients require surgical treatment (<5%). The indications for surgery include the complications of TB and the management of the drug-resistant form of the disease [1]. Surgery for MDR-TB is generally accepted as an ancillary treatment modality in selected MDR patients. The criteria for selecting the patients who may benefit from the operation remain vague and enigmatic. The gold standard for the surgical management of pulmonary TB is controversial. The surgeon’s expertise plays an important role in determining when and how to operate on an infected lung [7, 8]. Recently, MDR-TB has become a major indication for surgery [8].

METHODS

We carried out a retrospective study on 45 patients with MDR-TB who underwent surgical resection at the Leon Daniello Hospital (Regional Surgery Department) between January 1995 and December 2005. The patients were selected for surgery after being consulted by both a pneumologist and a surgeon.

Patients with recent drug resistance to isoniazid (hydrazide) and rifampicin, HIV-negative patients, patients with sufficient pulmonary reserve for a lateral pulmonary resection, patients without severe comorbidity as well as those who had poor treatment response after 4 months of MDR-TB treatment or presenting with massive haemoptysis underwent surgical resection. Patients with sputum cultures that remained positive after 3 months of medical treatment were considered refractory to medical treatment. Individual drug regimens (including at least five antibiotics) were administered in proper doses for a minimum of 1 month before the time of surgery in patients with massive haemoptysisis, and for a minimum of 4 months in the other patients. Postoperative antituberculosis therapy was continued for a minimum of 18 months (24 months in total). The following preoperative investigations were carried out: electrocardiogram, routine cardiologic consultation, blood analysis, arterial blood gas analysis, standard radiography, computed tomography scanning, spirometry, HIV testing and smear and culture status.

Surgery under general anaesthesia (double-lumen endotracheal intubation) was performed by a team of thoracic surgeons. 3M filter masks were used to protect the surgeons and the surgical team.

We collected and analysed patients’ demographic data, clinical characteristics, place of origin, radiological findings, smear and culture status before surgery, TB localization, primary or secondary drug resistance, surgical procedures, complications, bacteriological smear and culture status after surgical treatment. Acid-fast bacilli smears and drug susceptibility tests were performed in National Reference Laboratories from Cluj-Napoca using standard methods.

All the operations were performed through a posterolateral thoracotomy and the cavities were approached in such a way as to avoid the contamination of the pleural cavity.

Speleoplasty is a surgical procedure in which the pulmonary cavity or cavities are directly accessed through a thoracotomy. After isolating the pulmonary area where the cavernostomy was to be performed, an axial incision was made on the pleural layer of the pulmonary cavity. The incision was extended up to the limit of the pulmonary tissue. The biological product samples were collected from inside the cavern for bacteriological and histopathological examinations. The actual treatment of the cavity consisted of deterging the entire content of the cavity followed by dry dressing. The bronchial stump was closed with interrupted sutures and reinforced with intercostal muscle flaps.

RESULTS

Forty-five cases of culture-confirmed TB with multidrug resistance to at least isoniazid (hydrazide) and rifampicin were reported during the study period. The mean age of the patients was 54.5 years (between 37 and 68 years). As far as gender was concerned; 72% of the patients were male, 74% were from urban areas, 19% had a history of alcohol abuse, 30 patients (70%) were smokers (23 men) and five patients were former smokers. Primary MDR-TB was found in six patients (new cases without previous treatment for TB), while the other patients had secondary MDR due to previously administered treatments or non-compliance to treatment. The number of drugs that patients showed resistance to is presented in Table 1.

The duration of chemotherapy before surgery was 4 months (between 1 and 6 months).

All patients had positive sputum smears at the time of surgery. The smear situation before surgery was as follows: microscopy positive, culture positive (M+C+) in 31 patients (72%); microscopy positive, culture negative (M+C−) in nine patients (21%) and microscopy negative, culture positive (M−C+) in three patients (7%).

All subjects were non-HIV-immunocompromised patients. The other comorbidities are presented in Table 2.

Coughing occurred in 43 patients, while purulent sputum was noticed in 35 patients. Shortness of breath was detected in 31 patients, 31 subjects had haemoptysis, nine presented with thoracic pain and nine experienced fatigue.

Table 1: Drug resistance

<table>
<thead>
<tr>
<th>Drug resistance</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>Hydrazide and rifampicin</td>
<td>14</td>
</tr>
<tr>
<td>Hydrazide, rifampicin and pyrazinamide</td>
<td>2</td>
</tr>
<tr>
<td>Hydrazide, rifampicin and streptomycin</td>
<td>6</td>
</tr>
<tr>
<td>Hydrazide, rifampicin and ethambutol</td>
<td>10</td>
</tr>
<tr>
<td>Hydrazide, rifampicin, pyrazinamide and ethambutol</td>
<td>5</td>
</tr>
<tr>
<td>Hydrazide, rifampicin, streptomycin and ethambutol</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 2: Comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>6</td>
</tr>
<tr>
<td>COPD</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>6</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>5</td>
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COPD: chronic obstructive pulmonary disease.
The following radiographic characteristics were observed: the presence of cavities in 36% of patients, bronchiectasis in 2% of patients, fibrosis and scarring in 20% of patients, lung opacity in 5% of patients and small nodules (microopacity) in 2% of patients. We reported bilateral lesions in 63% of patients; the upper left lobe was affected in 21% of patients, the upper right lobe in 14% of patients and the lower left lobe in 2% of patients. The left lung was mainly affected.

Bronchoscopy was performed in only five cases, and endoscopic findings included ulceration, granulation and stenosis of the affected bronchus. Due to the reduced accessibility to a bronchoscope at the time of the study, bronchoscopy was only performed to determine the type of intervention required. A few patients refused such an invasive investigation, while in other cases the bronchoscopist decided against the investigation due to epidemiological risks.

The indications for surgery were medical treatment failure in 39 patients, persistent cavity lesion with possible relapses in three patients and massive haemoptysis in three patients. Lobectomy was carried out in 30 patients, segmentectomy in four and cavernoplasty (speleoplasty) in 11 patients. Six patients had postoperative complications. However, only minor complications occurred: three wound infections, two minor haemorrhages and one minor pneumothorax. Operative mortality was zero. Four weeks postoperatively, there were 83% smear-negative and 17% smear-positive cultures. Postoperative chemotherapy was continued for a total of 24 months.

**DISCUSSION**

Surgery was one of the main forms of therapy for pulmonary TB until the introduction of effective antibiotics in the 1960s [9]. Before chemotherapy, pulmonary resection for TB had a prohibitive operative mortality rate of 20–40% [10, 11]. With the development of appropriate drug regimens, the types of surgical procedures performed have changed from almost exclusively collapse therapy to practically all resections [12]. The occurrence of MDR-TB with low responsiveness to chemotherapy and the relapse rates of 50% highlight the need for surgery as a therapeutic alternative [13]. The indications for surgical treatment include the complications of TB or sequelae such as bronchial stenosis, aspergillomas, destroyed lung, massive haemoptysis, bronchopleural fistula and empyema. Surgery is also carried out in order to rule out lung cancer or to treat localized diseases unresponsive to chemotherapy (residual foci or complications after resection) [11, 14]. Other studies reported the results of treatment failure in MDR surgery and proposed three surgical indications: (i) when drug resistance is so extensive that there is a high probability of failure; (ii) when the disease is localized and (iii) when there are sufficient drugs to diminish the mycobacterial burden enough to facilitate probable healing [15].

The resection for MDR-TB has two aims: to cure patients and to prevent further spreading of the infection in the community. Surgery was associated with a nearly 5-fold increase in the odds of initial favourable outcomes and higher long-term survival rates [16]. Although surgery reduces TB mortality, it still remains a risky approach [17].

In our study, the low complication rate (lack of bronchopleural fistula, operative mortality or major complications) might be due to the >5 preoperative anti-TB drugs administered for >3 months. The role of routine muscle flap reinforcement in patients with MDR-TB is debatable. In our study, it was used to prevent the postoperative development of bronchopleural fistulae, especially in patients with a positive sputum at the time of the operation. All our patients had positive sputum cultures or smears. Fiberbronchoscopy was performed in only five patients and insufficient information was obtained on the presence of endobronchial TB or the active inflammation of peribronchial lesions adjacent to the bronchial stump. Other authors provide four indications for a muscle flap: (i) positive sputum at the time of surgery, (ii) pre-existing bronchopleural fistula, (iii) polymicrobial contamination of the thoracic cavity and (iv) anticipated space problems after lobectomy [4].

Despite the technical complexity of such resections, the reported mortality rates were low and may vary between 0 and 3% [18]. Recent trends favour early surgery and as much preservation of the lung parenchyma as possible [15]. The literature recommends preoperative anti-TB therapy for a minimum period of 3 months to diminish the positivity of the sputum and hence the risk of complications [17]. Patients whose sputum cultures remained positive after 3 months of medical treatment were considered refractory to medical treatment [4, 19]. According to Pomerantz et al. [4], the optimum time of surgery in patients resistant to almost all antibiotics is within 1–2 months after the initiation of the best available therapy. Patients whose organism is sensitive to antibiotics usually undergo surgery for at least 3 months. Sputum culture conversion occurred in some MDR patients within 2½–3 months of starting treatment [19]. Delayed surgery and prolonged chemotherapy may facilitate the progression of the disease and lead to further drug resistance [20]. The inadequacy of second-line treatment agents has been reflected in the MDR mortality rates of 11–37% [19]. Other authors consider that the success of the procedure depends on the following essential factors: the timing of the operation (after 6–8 months of multidrug Antituberculosis Treatment), the presence of stable functional and biological conditions, anticipated monolateral involvement, the absence of tubercular bronchitis, the absence of radiological improvement of parenchyma sequelae and complicated pulmonary TB (haemoptysis or superimposed infections) [8]. An improved nutritional status can increase the success rate of the treatment [15].

The main subsets of patients with MDR-TB in whom surgery may be indicated include patients who fail to convert despite an adequate drug regimen (with at least four drugs to which the resistant M. tuberculosis strain is sensitive, out of which at least three had not been previously used for >6 months before failure) as well as patients who have already converted to a sputum-negative status, thus preventing a relapse (this indication is still controversial). Unfortunately, the reservoir of resistant bacilli cannot be located. The disease reservoir may lie in residual nodules, bullae, microcavitation or even fibrosis [1].

The main preoperative clinical manifestations included coughing, haemoptysis, expectoration, low-grade fever, chest distress, dyspnoea, night sweats, fatigue, chest pain and emaciation [5]. There is no consensus regarding which patients should undergo resection [15].

At present, the absolute indications for the surgical treatment of MDR-TB are persistent cavitary disease and lung or lobar destruction with treatment failure. Currently, MDR-TB and its associated complications are the primary indications for pulmonary TB surgery. The reasons for resection in patients with cavitary disease are the difficulty of antibiotic penetration and the high number of organisms contained within the cavity, $10^3$–$10^9$ organisms per cavity. For these reasons, it is important to resect...
all cavity disease and destroyed lung, leaving no grossly diseased lung behind [19].

Pomerantz et al. [19] reported left lung destruction in >70% of patients. Similar outcomes were also reported by other authors (possibly due to the anatomic differences between the left and right main stem bronchi). According to a meta-analysis, the treatment success rate of pulmonary resection for patients with MDR-TB was 84%. The rates of failure, relapse, death and default were 6, 3, 5 and 3%, respectively [21]. Another study reported a 93% cure rate in the surgical group associated with this chemotherapy, but this figure cannot be directly compared with the cure rates for the study groups receiving chemotherapy alone. Patients with MDR-TB could have a greater chance of being cured with the use of adjuvant resectional surgery in combination with intensive medical treatment (85% rate even in extensively drug-resistant TB) [21, 22]. With the emergence of extensively drug-resistant TB, adjunctive surgery has become more relevant [23]. In developed countries, there are fewer individuals or centres with the surgical capacity and TB experience while in developing countries, there are large caseloads [23]. Unless countries invest substantially in the management of MDR-TB, the possibility remains that MDR strains could become the dominant form of TB. In 2008, only about 1% of MDR cases were estimated to have received proper treatment according to the standards recommended by the WHO [24].

In conclusion, the surgical management of TB is focused on the biological and anatomical eradication of the disease. Proper patient selection and the timing of the operation are crucial to avoid relapses, provide definite cure and prevent the spread of the disease in the community. Surgery should be incorporated in national and international control programmes to improve the management of MDR-TB patients. Good cooperation between chest physicians and thoracic surgeons as well as the patients’ adherence to pre- and post-chemotherapy can increase the success rate of MDR-TB treatment.

Conflict of interest: None declared.

REFERENCES