Surgery for *Mycobacterium avium* complex lung disease in the clarithromycin era

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Abstract

Objective: Since the introduction of clarithromycin, it has been assumed that pulmonary *Mycobacterium avium* complex (MAC) disease can be treated with medication alone. This study examines whether surgery can still play an important role in the management of MAC lung disease in the current era.

Methods: Between April 1993 and January 2001, 21 patients (11 men and 10 women) underwent a pulmonary resection for MAC infection. The median age of the patients was 56 years (range: 27–67 years). None of the patients were immunocompromised. Regimens employing clarithromycin were initiated preoperatively in all patients. The indications for surgery were failure of drug therapy in 19 patients and discontinuation of chemotherapy because of drug toxicity in two patients. The pulmonary resections (19 right lung, 2 left lung) performed included lobectomy in 16 patients, pneumonectomy in three, bilobectomy in one, and lobectomy plus segmentectomy in one.

Results: All of the patients survived the surgery. Six major postoperative complications occurred in six patients (28.6%) and these included two bronchopleural fistulas after right pneumonectomy, two space problems, one prolonged air leak, and one case of interstitial pneumonia. All postoperative complications were manageable, and four of these were treated surgically. All patients had sputum-negative status after their operation. Relapse occurred in two patients (9.5%) at six months and two years postoperatively, respectively. The first patient, who originally had a right upper lobectomy, underwent a left upper lobectomy during the follow-up period, attaining sputum conversion. The second patient underwent a right pneumonectomy and then died of respiratory failure four years postoperatively. This one late death was the only fatality.

Conclusions: Although it is associated with relatively high morbidity, surgery provides a high sputum conversion rate for patients whose MAC disease responds poorly to drug therapy. Even in the present clarithromycin era, pulmonary resection remains the treatment of choice when MAC lung disease has not been successfully eradicated by drug treatment alone. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: *Mycobacterium avium* complex; Pulmonary resection; Clarithromycin; Postoperative complication

1. Introduction

Pulmonary disease caused by *Mycobacterium avium* complex (MAC) is usually resistant to conventional antituberculous agents. A recent study has demonstrated that pulmonary MAC disease is still difficult to eradicate with regimens containing rifampicin, ethambutol, and isoniazid [1]. Therefore, when feasible, resectional surgery has been advocated to treat this disease in cases where drug regimens have failed to correct the disorder [2–8]. Since the introduction of clarithromycin, there have been greater expectations that pulmonary MAC disease can be treated with medication alone. Clinical trials have demonstrated that clarithromycin produces significant benefits for patients with pulmonary disease caused by this stubborn pathogen [9–12]. However, medical treatment including clarithromycin is not an absolute panacea, and the emergence of clarithromycin-resistant strains remains a significant problem. Therefore, the possibility that surgical treatment still can play an important role in treatment of MAC lung disease remains to be investigated [13].

Most studies of surgery for MAC lung disease were published in the pre-macrolide era [2–6], and only one study has dealt predominantly with patients receiving clarithromycin [8]. Clarithromycin has been used to treat patients infected with MAC at our institution since 1992. To examine whether surgery continues to play an important role in the management of pulmonary MAC disease in the current era, we reviewed our patients who had received surgery for MAC disease during the clarithromycin era.
clarithromycin-containing regimens preoperatively and then underwent a pulmonary resection for MAC infection after 1993.

2. Materials and methods

Between April 1993 and January 2001, 23 patients with pulmonary MAC disease underwent a pulmonary resection at Fukujuji Hospital, Tokyo. Two patients were excluded from the study because they had never received clarithromycin before their operation. Therefore, 21 patients were analyzed in this study. There were 11 men and 10 women, with a median age of 56 years (range: 27–67 years). Of the 21 patients, 18 patients were below their ideal body weight. None of the patients were immunocompromised.

Upon admission, sputums and cultures of sputum or bronchial washing were examined. All patients met the diagnostic criteria recommended by the American Thoracic Society for disease caused by nontuberculous mycobacteria [14]. The standard preoperative work-up included chest roentgenogram, computed tomographic scan, pulmonary function tests, arterial blood gas analysis, and a quantitative perfusion scan. Bronchoscopy was used in some cases to rule out contralateral disease and/or coexisting malignancies.

The most frequent chest radiographic manifestation of a main lesion was observation of a cavity. The other manifestations were bronchiectasis, nodule, and a destroyed lung (Table 1). In 14 patients (67%), disease was localized to one lung (unilateral disease). In the remaining seven (33%), cavitary lesions were found on one side of the lung, and limited lesions ranging from scattered nodular disease \((n = 6)\) to tiny cavity \((n = 1)\) on the other side (bilateral disease).

Multidrug regimens containing clarithromycin (400–900 mg daily) were initiated preoperatively for all patients. Of these patients, ten patients had received at least six months of prior antituberculous therapy (three of which included clarithromycin), and another ten patients had received less than five months of antituberculous therapy (none of which included clarithromycin) awaiting mycobacterial species identification. Companion drugs for clarithromycin included rifampin in 21 patients (100%), ethambutol in 19 (90%), streptomycin in eight (38%), kanamycin in six (29%), isoniazid in two (10%), amikacin in one (5%), ofloxacin in one (5%), and levofloxacin in one (5%). The most frequent combination was clarithromycin, rifampin, ethambutol, and streptomycin or kanamycin. For two of the 21 patients, chemotherapy was discontinued because of adverse effects (anorexia and highly abnormal liver enzymes). The mean duration of preoperative chemotherapy was 11 months (range: 2.2–29.1 months).

Usually after at least three months of chemotherapy, the efficacy of drug therapy was assessed. In 11 of the patients, their sputum cultures remained positive for MAC. In eight patients, their sputum cultures were converted to negative but their chest radiographic findings deteriorated or did not improve. For these 19 patients, medical treatment was thought to fail and surgical treatment was indicated. Surgery was also considered for the remaining two patients who discontinued chemotherapy because they still had positive cultures. Thus, indications for surgery were the failure of drug therapy in 19 of the patients, and discontinuation of chemotherapy in two. At the time of operation, sputum remained positive for MAC in 13 of the patients (62%, Table 1).

Operations were performed under general anesthesia with the use of a double-lumen endobronchial tube. The great majority of pulmonary resections (19/21) were performed on the right side. Lobectomy was performed in 16 patients, pneumonectomy in three, upper and middle lobectomy in one, and middle lobectomy plus superior segmentectomy in one (Table 2). For patients with bilateral disease, the most responsible lesions (cavities) were resected and small lesions in the contralateral lung remained. The mean operative time was 311 min (range: 128–475 minutes). Intraoperative blood loss ranged from 20 to 1300 ml with a mean of 298 ml. In two patients, blood loss exceeded 1000 ml (1245 and 1300 ml, respectively). A latissimus dorsi muscle flap was used to reinforce the bronchial stump in three of the seven patients operated on after June 1999 (Table 2). The technique of constructing muscle flaps was the same as that described by Pairolero and associates [15]. After the operation, all of the patients except two were

### Table 1

<table>
<thead>
<tr>
<th>Radiographic finding</th>
<th>No. of patients</th>
<th>No. of patients with sputum conversion (rate %)</th>
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</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>16</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Nodule</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Destroyed lung</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>8 (38)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Operation</th>
<th>No. of patients</th>
<th>Complication (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right pneumonectomy</td>
<td>1</td>
<td>Bronchopleural fistula (1)</td>
</tr>
<tr>
<td>Right pneumonectomy with latissimus dorsi muscle flap</td>
<td>1</td>
<td>Bronchopleural fistula (1)</td>
</tr>
<tr>
<td>Right upper lobectomy</td>
<td>9</td>
<td>Space problems (1)</td>
</tr>
<tr>
<td>Right upper lobectomy with latissimus dorsi muscle flap</td>
<td>2</td>
<td>Intersitial pneumonia (1)</td>
</tr>
<tr>
<td>Right upper and middle lobectomy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Right middle lobectomy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Right middle lobectomy plus superior segmentectomy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Right lower lobectomy</td>
<td>3</td>
<td>Prolonged air leak (1)</td>
</tr>
<tr>
<td>Left pneumonectomy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Left upper lobectomy</td>
<td>1</td>
<td>Space problems (1)</td>
</tr>
</tbody>
</table>
kept on drugs for 6–12 months. Postoperative regimens were generally the same as preoperative ones. Follow-up was completed on June 30, 2001, with a median follow-up period of 34.8 months (range: 5.6–98.6 months). A relapse-free rate was calculated using the Kaplan–Meier method.

3. Results

All of the patients survived the surgery. Six major postoperative complications occurred in six patients (28.6%) (Table 2). All postoperative complications were manageable, and four of these were treated surgically. Postpneumonec- tomy bronchopleural fistula occurred in two patients undergoing a right pneumonectomy two and three months after the operation, respectively. One of these two patients developed a fistula with the use of a latissimus dorsi muscle flap in combination with a pneumonectomy. Both patients were treated by reclosure of the bronchial stump. Two patients for whom space problems occurred were treated with thoracoplasty. A patient with a prolonged air leak was treated by tube thoracostomy. A patient who developed interstitial pneumonia was treated by mechanical ventilation.

All patients had negative sputum status after their operation. Relapse occurred in two patients (9.5%). The first patient had a relapse six months after a right upper lobectomy. He had had bilateral disease before the operation, and relapse was due to cavitary lesions in the contralateral lung. He underwent a left upper lobectomy during the follow-up period, and then attained sputum conversion. The second patient had a relapse on the left side two years after a right pneumonectomy. This patient could not be on chemotherapy before or after the operation because of adverse effects. MAC disease in the left lung gradually progressed, and finally resulted in death by respiratory failure four years after the operation. The 1-year and 3-year relapse-free rates were 95 and 87%, respectively.

4. Discussion

MAC is typically resistant to conventional antituberculous agents. A recent study conducted by the British Thoracic Society has demonstrated that pulmonary disease caused by MAC is still difficult to treat with the standard regimens of rifampicin, ethambutol, and isoniazid, and of rifampicin and ethambutol [1]. The best outcomes have been achieved for patients who had chemotherapy prior to their operation [2–8]. Following the introduction of newer macrolides (clarithromycin and azithromycin), the formerly somewhat bleak prognosis for treatment of pulmonary MAC disease has improved. Clarithromycin was the first single agent that was shown to be efficacious in the treatment of MAC lung disease in HIV-negative patients [9,10]. Next, combination regimens including clarithromycin, ethambutol, rifampin or rifabutin, and initially streptomycin, were reported to achieve high rates of sputum conversion and low rates of relapse [11]. Similar results were also reported from Japan [12]. Nevertheless, the success rates of these medical treatments have peaked at 72–82% [11,12]. There has been a concurrent 13–15% incidence of acquired resistance to clarithromycin during chemotherapy [10,11]. Hence, not all patients with MAC lung disease can be treated by medication alone, and there are still some patients who require a pulmonary resection.

The role of surgery in the management of MAC lung disease in the current macrolide era, therefore, remains to be investigated. However, most previous studies on surgical treatment of pulmonary MAC disease were reported in the pre-macrolide era [2–6]. Only one study so far has dealt predominantly with patients receiving clarithromycin [8]. Of the 28 patients in that study, 17 patients treated after 1991 received regimens containing clarithromycin and rifabutin. To the best of our knowledge, our report is the first study that includes exclusively patients for whom clarithromycin-containing regimens were initiated prior to their operation.

The characteristics of patients in our study were similar to those described in other studies. As reported previously [6–8], most of our patients were middle-aged. Although a majority of patients in previous reports were either male [8] or female [6], we had an equal distribution of men and women. The majority of our patients were not robust as reported in a previous study [8]. Indications for an operation were generally similar to those previously reported [6,8]. We operated on patients who had persistent positive sputum despite chemotherapy. In fact, 62% of patients had positive sputum at the time of their operation. The rate of sputum conversion before operation in our study was lower than that reported in another study [8] (38 vs. 48%). We used lower doses of clarithromycin (400–900 mg daily) than those used in other studies from the USA and France [9–11], because such higher daily doses (1000 mg daily) cannot usually be tolerated in Japanese patients. Moreover, about half of our patients had received antmycobacterial treatment previously. Lower success rates of clarithromycin-containing regimens with patients who have undergone prior drug therapy have been reported [10–12]. In addition, we used rifampin instead of rifabutin. Rifampin has been reported to reduce the serum levels of clarithromycin more than rifabu- tin [16]. Therefore, the lower dose of clarithromycin, the frequency of previous therapy and the use of rifampin in the present study may have been responsible for the lower sputum conversion rates before the operations. We also operated on patients whose sputum became negative before their operation but whose chest radiographic findings deterio- rated or did not improve. Since these patients usually had cavitary disease or a destroyed lung, they had a substantial chance of suffering a relapse. Therefore, we believed that a prophylactic operation was justified for those patients.

The majority of resections were performed on the right lung, which was consistent with previous reports [5–8].
Also, as in previous reports [5–8], upper lobectomy was the most common procedure among the lobectomies. Operations for pulmonary MAC disease are expected to have a low associated mortality. We attained 0% operative mortality, which was consistent with the 2.4–7.1% mortalities reported elsewhere [6,8]. However, as reported previously [6–8], the incidence of postoperative complications remained high. In our study, two patients had a postpneumonectomy bronchopleural fistula. Both fistulas occurred on the right side. One fistula developed despite the use of muscle flap reinforcement of the bronchial stump. Interestingly, both fistulas occurred more than two months after the operation. A high morbidity rate after right pneumonectomy for MAC lung disease was pointed out by Pomerantz and associates [6]. In their study of the eight bronchopleural fistulas that occurred in 38 patients with mycobacterial infections other than tuberculosis, seven fistulas occurred after right pneumonectomy. Moreover, five of these occurred despite the use of muscle flaps.

Other major complications were space problems and prolonged air leaks, which were seen in three patients in this study. Two patients with space problems were treated by thoracoplasty. Although thoracoplasty was used in other studies [7,8], this procedure should be avoided whenever possible. Since June 1999, to prevent bronchopleural fistula and space problems, we have used a muscle flap to buttress the bronchial stump and to obliterate the pleural space when pneumonectomy is performed and when space problems are expected after lobectomy. Our choice of muscle is the latissimus dorsi, which is similar to that chosen by Pomerantz and associates [6]. Using our procedure, no space problems have been encountered. Although the use of latissimus dorsi muscle flaps cannot completely prevent bronchopleural fistula, the liberal use of muscle flaps is still recommended in pulmonary resection for MAC lung disease.

Despite the fact that more than half of the patients had positive sputum at the time of their operation, we achieved a favorable outcome after pulmonary resection. Our sputum conversion rate after the operations was 100%, which was an improvement over that reported by Nelson and associates [8]. Relapse occurred in only two patients. One of these patients, who had had bilateral disease before the operation, attained sputum conversion after undergoing a contralateral upper lobectomy. This indicates that patients with bilateral disease can be treated with surgery if their disease is localized in up to one lobe on each side, and if they can tolerate bilateral procedures. For the other patient, relapse might have resulted from the fact that no chemotherapeutic drugs were used before or after the operation because of adverse effects. Despite having recurrent MAC disease, this patient survived an additional four years.

Several limitations to this study should be pointed out. First, this is a retrospective single-arm study. Actually, it is impossible to conduct a prospective randomized study that compares the results of medical treatment plus surgery for MAC infection to results of medical treatment only. Second, the number of patients enrolled in this study is relatively small. However, most previous studies included less than 40 patients [5–8]. Third, our patients are a highly selected group. Only patients who have both localized disease and sufficient pulmonary reserve can undergo a pulmonary resection. The bilateral nature of MAC lung disease, the advanced age of many patients, and the frequency of underlying chronic lung disease have limited the number of patients who are good candidates for surgery [14]. Nonetheless, our results demonstrate that surgery continues to play an important role in the management of MAC lung disease.

In conclusion, although associated with a relatively high morbidity, surgery provides a high sputum conversion rate for patients whose MAC disease has responded poorly to drug therapy and for patients who cannot tolerate chemotherapy. Even in the clarithromycin era, pulmonary resection remains the treatment of choice when MAC lung disease has not been successfully eradicated by state-of-the-art drug regimens.

References


