Surgical Resection Compared to Medical Management in localized Mycobacteria Avium Complex Pulmonary Infections-A Case Control Study

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Abstract

Background

Pulmonary infections associated with *Mycobacterium avium complex* can be challenging to treat medically and the role of surgical lung resection is not well established. We aim to assess safety and microbiologic response in patients with localized *Mycobacterium avium complex* pulmonary infections managed with surgical lung resection compared to medical management alone.

Methods

We present a multi-institutional case series of 16 patients with localized *Mycobacterium avium complex* pulmonary infections managed with surgical lung resection. We highlight the case of a 30 to 40-year-old patient with localized pulmonary disease amenable to surgical resection for illustrative purposes and report on outcomes compared with medically treated patients at the same institution in case-control design.

Results

Of 745 patients meeting microbiologic diagnostic criteria for *Mycobacterium avium complex* pulmonary infections, 98 had localized pulmonary disease and of these 16 underwent surgical resection. Univariate and multivariate analysis results indicated no difference in surgical resection group compared with medical treatment: microbiologic response rate (odds ratio 0.49, 0.1–2.41), 2-year all-cause mortality (odds ratio 0.87, 0.18–4.32), and composite outcome of 2-year mortality and lack of microbiological response (multivariate logistic regression OR = 0.45, 0.09–1.57).

Conclusions

This case series describes patients with localized pulmonary *Mycobacterium avium complex* for whom surgical resection was pursued and shows examples of patients that may benefit from surgery. Though surgery for pulmonary *Mycobacterium avium complex* disease is rarely performed, it appears as safe and at least as effective as medical therapy alone.

Background

*Mycobacterium avium complex* (MAC) pulmonary infections are increasing in prevalence in the US and are associated with high rates of morbidity, mortality and considerable health care cost. Medical treatment is complex and consists of 3–5 antibiotics administered for 12–18 months or longer, yet clinical and microbiological response rates are limited and range as low as 55% or less. As a result, for patients with anatomically appropriate disease, surgical resection has been proposed as adjuvant therapy, but there is limited data on safety and treatment outcomes in intermediate volume centers. There has been one case-control study and several case series describing outcomes of lung resection for Non-tuberculous mycobacterial pulmonary infections (NTMI) that have mostly focused on the more virulent *Mycobacterium abscessus*.

Methods

We conducted a retrospective review using an electronic health record database of all patients treated between 2001–2016 across Partners Healthcare, a multi-institutional health care system located in Boston and its suburbs. We identified all patients with ICD-9 (31.0/31.2) or ICD10 (A31.0/A31.2) diagnostic codes for NTMI, and identified patients with the presence of ≥2 expectorated respiratory samples or a ≥1 bronchioalveolar lavage sample positive for NTM species meeting ATS microbiologic criteria for diagnosis of NTMI. Using natural language processing with regular expressions, we extracted from our electronic health record basic demographics, anthropomorphic data, comorbidities, pulmonary function measurement, radiologic reports, microbiologic data, and surgical reports to build a database of patients. We restricted to patients infected with MAC, had radiographically localized mycobacterial infection, and received medical treatment for MAC during their treatment course. Anatomically limited/localized disease appropriate for surgical resection was defined as radiologic evidence for lesions typical of NTMI (bronchiectasis, nodular opacities, or consolidation) isolated to one lobe or any patient with a cavitary lesion regardless of number of lobes affected. Adequate MAC treatment was defined as a drug regimen containing at least the following drugs: (1) first line: macrolide, ethambutol, and rifampicin or other rifamycin, or (2) second line: first line with substitution of any of the drugs for clofazimine, bedaquiline, or amikacin as these are often used as escalation therapy or in cases of drug intolerance. We assessed the safety and effect of surgical resection on treatment outcomes in patients with MAC pulmonary infections univariate outcomes and a logistic regression model using a composite variable in a case control design comparing patients who underwent surgical resection compared to medical therapy alone.

Outcome measures were defined as microbiologic response and mortality. Microbiological conversion was defined as either of the following criteria met within two years of follow up: (1) ≥2 negative cultures for patients with two or more follow-up cultures available without any recurrent positive culture or (2) one negative culture for patients with only one follow-up culture available. Mortality was defined as 2-year all-cause mortality from the date of first diagnosis. We additionally defined a composite outcome of 2-year mortality and lack of microbiological response, and adjusted
for age and gender using multivariate logistic regression. Approval for this study was obtained from the Partners Health System Institutional Review Board (2017P002469/PHS).

Results

In our database, there were 745 patients meeting ATS criteria for diagnosis of atypical mycobacterial pulmonary infection, of which 554 (74%) were infected with MAC based on available microbiologic data. A total of 98 patients met criteria for radiographically localized MAC infection and received medical treatment. Of these, 16 underwent surgical resection. Table 1 outlines demographics, comorbidities, medical treatment administered, and information regarding surgical resection. Table 2 outlines complications and outcomes for 16 surgically treated patients. Overall, surgical resection was performed rarely: in 16/554 (2.9%) of MAC patients meeting ATS criteria and 16/98 (16%) of the subset with localized disease requiring medical treatment. Of the 16 surgically treated patients, 13 underwent one lung resection. The remaining three patients underwent two resections at separate time intervals for progression of disease. The majority 10/16 (63%) of patients had surgical resection of disease from one lobe and the other six patients had a multi-lobar resection. The indication for surgery was listed as disease refractory to medical therapy in 9/16 (56%) patients and in 6/16 (38%) surgical resection was described as adjunct to medical therapy. For the remaining patient, the indication for surgery was described as hemoptysis with perioperative antimycobacterial administration. Eleven patients had cavitary lesions resected, 4 had bronchiectasis resected, 2 had consolidation resected, and 1 had an abscess resected. Postoperatively there were no bleeding events requiring repeat surgery. Only one of the 16 patients developed a bronchopleural fistula (6%) and another developed a chyle leak (6%).

The baseline characteristics of the surgically treated groups are compared to the medically treated group with disease in Table 2. In univariate analysis on treatment outcome there was no significant difference in microbiologic response rate (odds ratio 0.49, 0.1-2.41) and 2-year all-cause mortality (odds ratio 0.87, 0.18-4.32) between surgical and medical cohorts. The composite outcome of 2-year mortality and lack of microbiological response showed no significant difference between the two groups after adjustment for age and gender (multivariate logistic regression OR=0.45, 0.09-1.57).

Brief Case Presentation

A 30 to 40-year-old patient with a 25 pack-year history of smoking, hypertension, seasonal allergies, and gastroesophageal reflux disease presented with 5-6 months of night sweats, associated weight loss, and chronic productive cough with brown sputum. Prior evaluations for these symptoms about a month prior to presentation were notable for chest radiograph initially visualizing left upper lobe opacities, but interval imaging at the time of presentation showed progression to left upper lobe cavitary lesion. Subsequently, this was confirmed on computed tomography of the chest with revisualization of left upper lobe cavitary lesion, with multiple satellite nodules. Initial induced sputum was notable for abundant 3-4+ acid fast bacilli on two subsequent days. Follow-up bronchoscopy and bronchoalveolar lavage with cultures confirmed a diagnosis of Mycobacterium Avium Complex pulmonary infection. Additional etiologies of cavitary lesions were excluded with negative tuberculin skin testing, negative coccidiosis serum titers, and negative ANCA testing. Susceptibility testing showed MAC susceptibility to clarithromycin.

About a month after initial presentation the decision was made to initiate medical therapy with Azithromycin, Ethambutol, and Rifampin. She tolerated medical therapy well with no hearing problems, no tinnitus, no imbalance, no visual changes, no color vision problems, no nausea, no vomiting, and no diarrhea. About 2 months after initiation of medical therapy surveillance mycobacterial cultures were negative. Initial surveillance chest computed tomography 4 months after therapy initiation showed an interval response to therapy, marked by decrease in the number of satellite nodules and improvement in the cavitary wall thickness and reduced inflammation. Interval imaging 11 months after initiation of therapy, however, showed a persistence of the cavitary lesion. Given persistent unresolved symptoms and the radiographic findings she was referred for surgical evaluation.

With well localized disease, she was deemed a candidate for limited parenchymal surgical resection with curative intent. She underwent a surgical wedge resection of the left upper lobe cavitary 14 months after therapy initiation without any post-operative complications. She received 4 weeks of preoperative and postoperative intravenous amikacin. On pathologic examination, the cavitary lesion was tan-white with a firm wall containing necrotic debris; margins were 0.4 cm and the uninvolved parenchyma was normal without masses. Mycobacterial organisms were visible with Acid fast stain.

In addition to 4 weeks of post-operative intravenous amikacin, a plan was made to continue Azithromycin, Ethambutol, and Rifampin for 1 year post-operatively, but the patient terminated therapy at 6 months for non-medical reasons. Intermittent surveillance cultures were obtained for 16 months after resection remained negative. At the time of follow-up 16 months of after resection she remained asymptomatic without cough, night sweats, or weight loss.

Discussion

We systematically identify a series of surgically treated patients with localized MAC pulmonary disease in an intermediate volume multi-institutional tertiary health care system and present the first case-control study assessing safety and outcomes after surgical lung resection for MAC disease, with prior studies focusing on Mycobacterium abscessus\textsuperscript{7,8}. We find the rate of surgical complications to be low (≤ 6%) suggesting that resection of
localized MAC disease is safe and may be associated with improved clinical and microbiologic response. Though not statistically significant, the measured outcome odds ratios were trending towards favoring surgery across microbiological response and survival.

Our institutional experience is limited by low numbers of patients with MAC that underwent surgical lung resection. Surgical lung resection in patients with NTM at high volume specialty centers is associated with low rates of associated morbidity and mortality. Our case series adds data from an intermediate volume health system and also reports on microbiological clearance and overall outcome compared with medically treated patients.

We highlight the case of a 30 to 40-year-old patient with MAC pulmonary infection localized to the left upper lobe. Her course demonstrates the difficulty in treating MAC pulmonary infection despite long courses of multiple anti-mycobacterial agents. Though, she had negative sputum cultures after initiation of medical therapy, the persistence of symptoms and cavitation raised concerns about a sustained microbiological clearance, with the cavitary lesion acting a reservoir for disease. In particular, her case highlights that patients with well localized disease with few comorbidities may benefit from surgical resection compared to medical therapy alone.

**Conclusions**

Though surgery for pulmonary *Mycobacterium avium complex* disease is rarely performed, it appears as safe and at least as effective as medical-therapy alone in our institutional experience identifying patient localized infections amenable to surgical resection. Future studies should focus on identifying whether surgical resection may offer a mortality benefit or improved microbiologic response rates by analyzing surgical outcomes at high volume surgical centers or utilizing larger registries to better power studies for which we provide deidentified data.

**Abbreviations**

ATS
American Thoracic Society
NTM
non-tuberculous mycobacteria
NTMI
non-tuberculous mycobacteria
MAC
*Mycobacterium avium complex*

**Declarations**

**Ethics approval and consent to participate:**

Approval for this study was obtained from the Partners Health System Institutional Review Board (2017P002469/PHS).

**Consent to publish**

No identifying patient information was included in this case series. This studied was reviewed by Partners Health System Institutional Review Board waiving need to obtain individual patient consent.

**Availability of data and materials**

We provide a de-identified patient database that can be included in future meta-analyses to better assesses treatment outcomes at https://github.com/farhat-lab/Non-tuberculous-Mycobacteria-Chart-Review/blob/master/Deidentified%20MAC%20Patient%20Data.csv

**Competing interest**

None of the authors have competing interests.

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**Authors’ Contributions**

MF and GF are guarantors of the article, taking responsibility for the integrity of the work as a whole, from inception to published article. GF, RD, JW, ML, RH, CR, WO, and MF all contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Tables

Table 1. Case Series of 16 patient with MAC undergoing surgical resection

| Patient | Age | Gender | Comorbidities | Surgical Indication | Treatment Regimen | Duration between initiation of medical treatment and surgery | Antibiotic Duration after Surgery | Location of Disease | Type of Lesion |
|---------|-----|--------|----------------|---------------------|-------------------|-------------------------------------------------------------|----------------------------------|-------------------|---------------|
| 1       | 38  | female | GERD           | Refractory to medical Tx | Rifampin, Azithromycin, Ethambutol, Amikacin<sup>a</sup> | 14 months | 12 months | LUL | Cavitary lesion |
| 2       | 48  | Male   | GERD, History of TB infection | Hemoptysis, Cavity lesion | Rifampin, Azithromycin, Ethambutol | 1 month | 2 months | RUL, RML | Cavitary lesion |
| 3       | 75  | Female | Scoliosis      | Refractory to medical Tx | Amikacin, Moxifloxacin, Ethambutol | 47 months | 1 month | RUL | Cavitary lesion |
| 4       | 58  | Female | GERD, COPD, Breast Cancer, History of TB infection | Refractory to medical Tx | Rifampin, Ethambutol, Azithromycin, Interferonα-1b, Amikacin, Moxifloxacin<sup>a</sup> | 11 years | 17 months | RUL | Bronchiectasis |
| 5       | 45  | Female | GERD, COPD     | Refractory to medical Tx | Rifampin, Amikacin | 1 year | 17 months | LUL, LLL | Cavitary lesion |
| 6       | 75  | Female | None           | Refractory to medical Tx | Clarithromycin, Rifampin, Amikacin, Ethambutol, Rifaxin | Initiated concurrently with surgery | 1 year | LUL | Bronchiectasis |
| 7       | 57  | Male   | GERD, Cystic Fibrosis | Primary adjunct surgery | Clarithromycin, Amikacin, Ethambutol, Rifaxin | 3 months | 1 year | LLL | Consolidation |
| 8       | 47  | Male   | GERD, COPD     | Primary adjunct surgery | Clarithromycin, Rifampin, Amikacin, Ethambutol | 9 months | 17 months | RUL, LUL | Bronchiectasis |
| 9       | 70  | Female | GERD, COPD     | Primary adjunct surgery | Clarithromycin, Rifampin, Amikacin, Ethambutol | 10 months | 12 months | RML | Bronchiectasis |
| 10      | 62  | Male   | GERD, COPD     | Intolerant to medical therapy | Rifampin, Ethambutol, Clofazamine | 2 months | 18 months | RUL | Cavitary lesion |
| 11      | 42  | Female | COPD, History of TB infection | Primary adjunct surgery | Rifampin, Amikacin, Moxifloxacin, Ethambutol | 1 month | 18 months | LUL, LLL | Cavitary lesion |

GERD, Gastroesophageal reflux disease; ABPA, Allergic Bronchopulmonary Aspergillosis; COPD, Chronic Obstructive Pulmonary disease; CF, Cystic Fibrosis; RA, Rheumatoid arthritis; IBD, Inflammatory Bowel Disease; Human Immunodeficiency virus; TB, pulmonary mycobacteria tuberculosis; Tx, treatment; RUL, right upper lobe; RML, right middle lobe, RLL, Right Lower Lobe; LUL, left upper lobe; LLL, left lower lobe;

<sup>a</sup>At time of diagnosis
Treatment given perioperatively

Treatment regimen during recurrence

**Table 2.** Case Series of 16 Patient with MAC undergoing Surgical Resection

| Patient | Type of Surgical Resection | Surgical Complications | Follow-up Time After Procedure | Baseline % Predicted FEV1 | Follow-up % Predicted FEV1 | Microbiologic Conversion | 2-Year Mortality | Radiographic Improvement or Stability | Pulmonary Function Test |
|---------|-----------------------------|-------------------------|--------------------------------|---------------------------|---------------------------|------------------------|----------------|----------------------------------------|-----------------------|
| 1       | Lobectomy                   | None                    | 17 months                      | 111                       | 79                        | Yes                    | No             | Yes                                    | n/a                   |
| 2       | Bilobectomy                 | None                    | 24 months                      | 68                        | 62                        | Yes                    | No             | Worsened                              | Stable FEV1           |
| 3       | Lobectomy                   | None                    | 29 months                      | 7                         | 67                        | Yes                    | No             | n/a                                    | Worsened FEV1         |
| 4       | Lobectomy and subsequent pneumonectomy | Bronchopleural Fistula | 44 months                      | 57                        | 38                        | No                     | No             | Yes                                    | Stable FEV1           |
| 5       | Segmentectomies             | None                    | 17 months                      | n/a                       | n/a                       | Yes                    | Yes            | Worsened                              | n/a                   |
| 6       | Segmentectomy and subsequent lobectomy | Chyle Leak | 28 months                      | 69                        | 69                        | Yes                    | No             | Worsened                              | Stable FEV1           |
| 7       | Lobectomy                   | None                    | 19 months                      | 82                        | n/a                       | n/a                    | No             | n/a                                    | n/a                   |
| 8       | RUL Lobectomy and subsequent LUL segmentectomy | None | 45 months                      | 95                        | 88                        | Yes                    | No             | Worsened                              | Stable FEV1           |
| 9       | Lobectomy                   | None                    | 105 months                     | 90                        | 90                        | Yes                    | No             | Yes                                    | Stable FEV1           |
| 10      | Lobectomy                   | None                    | 28 months                      | n/a                       | 38                        | Yes                    | No             | Yes                                    | n/a                   |
| 11      | Segmentectomies             | None                    | 6 months                       | 113                       | n/a                       | n/a                    | No             | Yes                                    | n/a                   |
| 12      | Lobectomy                   | None                    | 21 months                      | 89                        | n/a                       | Yes                    | No             | n/a                                    | n/a                   |
| 13      | Lobectomy, Segmentectomies  | None                    | 3 months                       | n/a                       | n/a                       | No                     | Yes            | Yes                                    | n/a                   |
| 14      | Lobectomy, Segmentectomies  | None                    | 1 month                        | n/a                       | 95                        | Yes                    | No             | n/a                                    | n/a                   |
| 15      | Segmentectomies             | None                    | 34 months                      | 51                        | 46                        | No                     | No             | n/a                                    | Stable FEV1           |
| 16      | Lobectomy                   | None                    | 182 months                     | 85                        | 99                        | Yes                    | No             | Yes                                    | Yes                   |

FEV1, Forced Expiratory Volume in 1 second; n/a, not available;

**Table 3.** Baseline Characteristics of Patients with MAC Disease, Localized Lesion, and Adequate Medical Treatment
**Demographics**

|               | Overall n=98 | Medical Cohort n=82 | Surgical Cohort n=16 | P-value$^b$ |
|---------------|--------------|---------------------|----------------------|-------------|
| Age$^a$       | 60 (sd=12)   | 61 (sd=12)          | 55 (sd=13)           | 0.1         |
| Female        | 62 (63%)     | 51 (62%)            | 11 (69%)             | 0.8         |
| Non-White Race| 15 (15%)     | 13 (16%)            | 2 (13%)              | 1.0         |
| History of Smoking | n=52       | 20 (32%)            | 17 (32%)             | 0.7         |

**Comorbidities**

|               | Overall n=98 | Medical Cohort n=82 | Surgical Cohort n=16 | P-value$^b$ |
|---------------|--------------|---------------------|----------------------|-------------|
| GERD          | 67 (68%)     | 56 (68%)            | 11 (69%)             | 0.8         |
| ABPA          | 5 (5%)       | 4 (5%)              | 1 (6%)               | 1.0         |
| COPD          | 61 (62%)     | 52 (63%)            | 9 (56%)              | 0.8         |
| CF            | 8 (8%)       | 7 (9%)              | 1 (6%)               | 1.0         |
| HIV           | 12 (12%)     | 11 (13%)            | 1 (6%)               | 0.7         |
| RA            | 9 (9%)       | 9 (11%)             | 0 (0%)               | 0.3         |
| Breast Cancer | 7 (7%)       | 5 (6%)              | 2 (13%)              | 0.3         |
| IBD           | 7 (7%)       | 6 (7%)              | 1 (6%)               | 1.0         |
| Scoliosis     | 8 (8%)       | 6 (7%)              | 2 (13%)              | 0.6         |
| Pectus Excavatum | 0 (0%)   | 0 (0%)              | 0 (0%)               | 1.0         |
| MVP           | 0 (0%)       | 0 (0%)              | 0 (0%)               | 1.0         |

**Disease Severity (Baseline)**

|               | Overall n=98 | Medical Cohort n=82 | Surgical Cohort n=16 | P-value$^b$ |
|---------------|--------------|---------------------|----------------------|-------------|
| Weight        | n=55         | 141 (sd=30)         | 141 (sd=31)          | 136 (sd=22) | 0.6         |
| BMI           | n=56         | 23 (sd=4)           | 23.2 (sd=5)          | 21.7 (sd=3) | 0.2         |
| % Predicted FEV1 | n=58       | 64 (sd=29)          | 64 (sd=29)           | 70 (sd=35)  | 0.5         |
| % Predicted FEV1/FVC | n=56       | 84 (sd=19)          | 84 (sd=20)           | 84 (sd=13)  | 0.9         |
| % Predicted FVC | n=55        | 74 (sd=30)          | 75 (sd=30)           | 77 (sd=42)  | 0.8         |

GERD, Gastroesophageal reflux disease; ABPA, Allergic Bronchopulmonary Aspergillosis; COPD, Chronic Obstructive Pulmonary disease; CF, Cystic Fibrosis; HIV, Human Immunodeficiency virus; RA, Rheumatoid arthritis; IBD, Inflammatory Bowel Disease; MVP, Mitral Valve Prolapse; sd, standard deviation; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity

$^a$At time of diagnosis