Infectious Causes of Right Middle Lobe Syndrome

Aatif Rashid, MD, Sowmya Nanjappa, MBBS, MD, and John N. Greene, MD

Summary: Right middle lobe (RML) syndrome is defined as recurrent or chronic obstruction or infection of the middle lobe of the right lung. Nonobstructive causes of middle lobe syndrome include inflammatory processes and defects in the bronchial anatomy and collateral ventilation. We report on 2 case patients with RML syndrome, one due to infection with Mycobacterium avium complex followed by M asiaticum infection and the other due to allergic bronchopulmonary aspergillosis. A history of atopy, asthma, or chronic obstructive pulmonary disease has been reported in up to one-half of those with RML. The diagnosis can be made by plain radiography, computed tomography, and bronchoscopy. Medical treatment consists of bronchodilators, mucolytics, and antimicrobials. Patients whose disease is unresponsive to treatment and those with obstructive RML syndrome can be offered surgical treatment.

Introduction

The term middle lobe syndrome (MLS) was first used by Graham et al in 1948, and the disease is defined as recurrent or chronic collapse or infection of the middle lobe of the right lung. MLS can present in persons of any age. The syndrome is divided into an obstructive type (demonstrable airway occlusion) and a nonobstructive type (patent right middle lobe [RML] bronchus). Obstructive MLS can be caused either by endobronchial lesions or extrinsic compression of the RML bronchus. Malignancy is the most common cause of the obstructive type followed by an infectious etiology (Tables 1 and 2). Benign tumors (eg, hamartomas) and malignant tumors (eg, primary lung cancer, metastasis) alike can cause obstructive MLS and account for up to 25% of cases. The most common cause of extrinsic compression of the RML bronchus is peribronchial lymphadenopathy due to infection, sarcoidosis, and metastasis. Nonobstructive causes of MLS include inflammatory processes and defects in the bronchial anatomy and collateral ventilation.

We report on 2 cases of RML syndrome, one due to infection with Mycobacterium avium complex (MAC) followed by infection with M asiaticum and the other due to allergic bronchopulmonary aspergillosis (ABPA). MAC is the most common nontuberculous Mycobacteria (NTM) species to infect humans. Pulmonary disease due to MAC infection in immunocompetent individuals can be divided into a primary form, which occurs in healthy persons who do not smoke, monary disease due to MAC infection in immunocompetent individuals can be divided into a primary form, which occurs in healthy persons who do not smoke,
and a secondary form, which occurs in persons with underlying lung disease (eg, chronic obstructive pulmonary disease [COPD], latent tuberculosis, bronchiectasis, cystic fibrosis). In general, the primary form affects elderly women who are otherwise healthy nonsmokers, and it presents with an interstitial/nodular pattern on chest radiography.\(^6\) \textit{Masiaticum} is a slow-growing mycobacterium species first recognized in Australia by Blacklock et al\(^{17}\) in the early 1980s. They surmised that \textit{Masiaticum} was a potential pulmonary pathogen among individuals with an underlying chronic respiratory problem such as COPD.\(^{17}\)

Persons with chronic lung disease are at risk of \textit{Aspergillus} colonization and infection.\(^8\) ABPA occurs as a result of hypersensitivity to colonizing \textit{Aspergillus} species in the airways of persons with asthma, NTM infection, and cystic fibrosis.\(^8\) It affects 2% of those with asthma.\(^9\) MLS caused by ABPA has rarely been documented.\(^9\)

**Case Reports**

**Case 1**

A woman aged 55 years presented with a 10-year history of chronic cough with no prior history of smoking. Serial computed tomography (CT) of the chest was obtained prior to her referral to our center. Bronchoalveolar lavage (BAL) was performed and the culture grew \textit{M. avium} intracellulare (MAI). She was treated with oral azithromycin, ethambutol, and rifampin for 1.5 years. After several years of taking antibiotics, she developed hemoptysis. Repeat BAL was performed and the culture grew methicillin-resistant \textit{Staphylococcus aureus}, so she was treated with oral clindamycin and trimethoprim/sulfamethoxazole for 2 weeks. Following treatment the patient felt better but still had intermittent cough and periodic right lateral chest pain. Following 1 month off antibiotics, BAL was again performed and the culture grew both MAI and methicillin-resistant \textit{S. aureus}.

CT of the chest was obtained and revealed persistent RML bronchiectasis and distal nodularity, with new nodules and bronchiectasis in the superior segment of the right lower lobe. CT results also showed new changes in the left lower lobe, posterior bronchiectasis, and distal nodularity when compared with the results on CT obtained 4 years prior (Fig 1). She was treated with azithromycin and trimethoprim/sulfamethoxazole and advised to undergo surgical removal of the RML.

Six months later she underwent RML resection due to progressive symptoms and severe bronchiectasis predominantly in the RML. Findings on histopathology showed necrotizing granulomatous bronchiolitis. Results from acid-fast bacilli tissue staining were positive with areas of chronic bronchitis and bronchiolitis. She was then treated on azithromycin monotherapy for approximately 5 years with intermittent courses of trimethoprim/sulfamethoxazole.

Five years following resection of the RML, she returned for evaluation with symptoms of hemoptysis, persistent cough, and pleuritic chest pain. Findings on CT demonstrated new areas of nodularity in the anterior medial lingular area with bronchial wall thickening, tree-in-bud nodules in the right posterior lung, and an increase in nodularity in the left medial posterior lung (Fig 2). BAL cultures grew \textit{M. asiaticum} sensitive to amikacin, ciprofloxacin, azithromycin, ethambutol, moxifloxacin, rifabutin, and trimethoprim/sulfamethoxazole.

She was treated with azithromycin and trimethoprim/sulfamethoxazole for 6 months. Her symptoms resolved, and she has remained without any unwanted change in weight or significant pulmonary complaints, except for an occasional nonproductive cough, for 3 years following the discontinuation of the antibiotics.
Case 2
A white woman aged 48 years with a history of rheumatoid arthritis was receiving treatment with methotrexate, adalimumab, and sulfasalazine. She also had a history of asthma requiring therapy with a β-agonist inhaler and intermittent corticosteroids.

Approximately 3 months prior to her presentation, she developed right upper quadrant abdominal pain. Imaging of her abdomen and chest was obtained, the results of which showed a large mass in her RML approximately 6 cm in diameter. Transthoracic needle biopsy was performed that revealed chronic nongranulomatous inflammation with septate hyphae consistent with *Aspergillus* infection. No cultures were sent. Findings from acid-fast bacilli stains were negative. CT and positron emission tomography were performed, and the results showed increasing uptake and a lesion thought to be postobstructive pneumonia (Fig 3). Repeat needle biopsy was performed and demonstrated septate hyphae, also consistent with *Aspergillus* infection. After repeat needle biopsy, she experienced hemoptysis that lasted nearly 2 weeks.

She was referred to our institution to rule out cancer and to consider surgical resection of the RML. At that time, she was having occasional cough and periodic exacerbations of her asthma. We suspected that she had ABPA and chronic necrotizing *Aspergillus* infection complicating her underlying asthma and causing RML syndrome. She was started on twice-daily oral voriconazole 200 mg.

Although her treatment plan consisted of 3 months of therapy, she developed a diffuse rash after taking voriconazole 200 mg for 3 weeks. Thus, voriconazole was discontinued; the rash disappeared approximately 1 week later. She was then started on oral posaconazole, but after several days the drug was discontinued because the patient experienced hematuria. Her cough resolved while in our care, and she felt that her overall condition had improved; thus, she decided to forgo surgical intervention.

Follow-up CT was obtained 1.5 months later, the results of which showed a residual area of bronchiectasis and absence of a mass in the RML. The patient discontinued immunosuppressive therapy for her rheumatoid arthritis. We surmise that the patient had a more rapid resolution of the RML mass because of the 3-week course of voriconazole and short-term corticosteroids she received, thereby suggesting an allergic immune response to the aspergillosis with possible airway obstruction, rather than an invasive infection.

She remains asymptomatic except for occasional bouts of asthma-like symptoms, which are controlled with inhaler therapy.

Discussion
RML syndrome is a phenotype associated with infective and noninfective etiologies (see Tables 1 and 2). In general, the onset of symptoms of RML syndrome is insidious and can include chronic cough, purulent sputum production, unintentional weight loss, fever, lethargy, hemoptysis, chest pain, and night sweats. Many patients with RML syndrome have chronic cough with purulent sputum production as their only symptoms. A history of recurrent or chronic pneumonia may be present. Although RML syndrome occurs in all age groups, its precise incidence rate in children is unknown; however, it may occur twice as often in girls than boys. In adults, it is approximately 1.5 to 3 times more common in women. A history of atopy, asthma, or COPD has been reported in up to 50% of patients.
with RML syndrome.\textsuperscript{2,20} When it is associated with MAC infection, the disease typically occurs in women with a slender build who have thorax or sternum deformities; for example, Pomerantz et al\textsuperscript{21} described most of their patients as slender women with skeletal abnormalities (eg, pectus excavatum, mild scoliosis, straight back syndrome, mitral valve prolapse). It has also been associated with the continuous use of antitussive drugs.\textsuperscript{22} In all cases, treatment is directed at the underlying etiology.

Reich and Johnson\textsuperscript{23} hypothesized that women were more likely to regard expectoration as socially unacceptable behavior, so they may habitually suppress voluntary cough, which leads to an inability to clear secretions (especially from the middle lobe and lingula), resulting in a chronic nidus for inflammation that favors subsequent infection.

Anatomically, the middle lobe and lingula have in common long, narrow-diameter, dependent bronchi (in an upright position) at an acute angle, thus making it more difficult to clear secretions that predispose them to infection. Furthermore, the middle lobe and lingula contain minimal parenchymal bridges due to deep fissures that provide effective barriers to collateral ventilation and isolate these lobes, thereby reducing the likelihood of reinflation once atelectasis has occurred.

Nearly one-half of healthy adults aspirate small amounts of oropharyngeal secretions while asleep.\textsuperscript{24} A low burden of pathogenic bacteria in these secretions — together with forceful coughing, active ciliary transport, and normal immune mechanisms — can result in the clearance of infectious material without sequelae. The risk of aspiration is higher in elderly persons because of increased incidences of dysphagia and gastroesophageal reflux in this population.\textsuperscript{25} Adults with impaired cough or voluntary cough suppression are at risk for developing infection and aspiration pneumonia, particularly in the RML.\textsuperscript{25}

In general, infectious agents associated with RML syndrome in children include \textit{Streptococcus pneumonia} and \textit{Haemophilus influenzae}; by contrast, the causes are more diverse in adults and include MAC and other NTM, and \textit{M tuberculosis}, as well as \textit{Histoplasma}, \textit{Blastosomyces}, and \textit{Aspergillus} species.\textsuperscript{6,12,13} Granulomatous infections, such as tuberculosis, histoplasmosis, and blastomycosis, can cause enlargement of the peribronchial lymph nodes that may lead to RML syndrome.\textsuperscript{13} Chronic infection with \textit{Pseudomonas aeruginosa} commonly occurs in cases of bronchiectasis and is associated with increased symptoms and a decreased quality of life.\textsuperscript{26}

Risk factors for MAC and \textit{M asiaticum} infections are similar to those observed for other NTM species, with COPD and bronchiectasis being the most commonly observed preexisting conditions in pulmonary cases.\textsuperscript{27} \textit{M asiaticum} and MAC infections cause cavitary and nodular diseases. The clinical and radiographical characteristics of this clinical syndrome are initial involvement of the periphery of the lingula or its counterpart, the middle lobe, and the absence of clinically evident predisposing pulmonary disorders, with these features being almost exclusive to older women.\textsuperscript{28}

Pulmonary disease caused by \textit{Afumigatus} infection is classified into 3 groups: aspergilloma, ABPA, and invasive aspergillosis. Diagnosis is based on serology, examination of sputum/BAL fluid, and radiological imaging. The radiological features for \textit{Aspergillus} infection–related lung disease include tree-in-bud nodules and cavities mimicking those of NTM infection. Clinical and serological criteria, including episodic bronchial obstruction (asthma), peripheral blood eosinophilia, and positive \textit{Aspergillus} serology, are used to diagnose ABPA because the radiological features of ABPA (central bronchiectasis and pulmonary infiltrates) are difficult to differentiate in patients with bronchiectasis and NTM infection.\textsuperscript{29} This is important because an association may exist between NTM infection and \textit{Aspergillus} infection–related lung disease. These conditions may be associated with one another because patients with NTM infection receive multiple, broad-spectrum antibiotics that predispose them to \textit{Aspergillus} infection.\textsuperscript{29} In addition, use of steroids or chronic immunosuppression due to chronic lung disorders, such as RML syndrome, may predispose these patients to both NTM infection and \textit{Aspergillus}–related lung disease.\textsuperscript{29}

**Imaging**

Findings on chest roentgenography or CT in patients with RML syndrome often show evidence of infection of the RML or left lingular lobe of the lung. The volume loss resulting from collapse of the RML is seen on chest radiographs as a triangular hyperdensity area between the minor fissure and the lower half of the major fissure, with the apex at the hilum and the base peripherally toward the pleura.\textsuperscript{30} Posterior radiography may also reveal blurring of the right cardiac border called the silhouette sign). Obtaining high-resolution CT may be useful to delineate bronchial patency, any associated bronchiectasis, and other causes of extrinsic compression of the RML airway. Flexible bronchoscopy allows the clinician to evaluate the patency of the RML bronchus and collect specimens for the diagnosis of infectious causes. Endobronchial ultrasonography can help detect extrinsic compressions due to lymph-node enlargement and calcifications. Ultrasonography can also reveal occult lung atelectasis in neonates.\textsuperscript{12,31}

**Nonsurgical Treatment**

Treatment is directed toward the underlying cause. Bronchodilators, mucolytic agents, and antimicrobials...
can be used in cases of nonobstructive MLS. MLS associated with asthma responds to inhaled corticosteroids and bronchodilators. Antimicrobials are based on culture or sensitivity reports from BAL fluid or sputum. Broad-spectrum antimicrobials that cover streptococci, H influenza, Moraxella catarrhalis, and Pseudomonas species can also be used in certain circumstances. Early use of aggressive antibiotic therapy may more successfully eradicate organisms such as Pseudomonas species, and it may also have a beneficial role on subsequent exacerbation rates, because chronic infection with organisms such as P aeruginosa is associated with worse quality of life, increased exacerbation frequency, and rapidly declining lung function.

Consideration must also be given to atypical mycobacteria, fungi, and other unusual infections. Low-dose macrolide therapy may improve quality of life — particularly if bronchiectasis is present — and some have advocated for the long-term rotation of antibiotics (3 weeks on, 1 week off, and then alternate antibiotics).

The success rate of treating MAC-related lung disease with macrolide-containing antibiotic regimens is between 60% and 80%; however, failed treatment responses occur in 20% to 40% of patients, and some whose disease is successfully treated still experience recurrence. Unlike M tuberculosis infection, MAC-related lung disease may be more likely to recur in patients with factors predisposing them to the acquisition of new bacterial strains rather than the persistence of the bacilli. The recurrence rate is also significantly higher in patients with nodular bronchiectatic forms of the disease than in those with a fibrocavitary or unclassifiable type for radiological imaging. Furthermore, many patients with a nodular bronchiectatic pattern have been infected with multiple MAC strains, suggesting polyclonal or recurrent infection with distinct strains. Recurrence and infection by MAC is also associated with inherited interferon γ receptor 1 deficiency. Patients with recurrent complete interferon γ receptor 1 deficiency may have chronic disease that does not resolve on treatment and their disease may rapidly relapse after antibiotic therapy is discontinued. In addition, in this subgroup of patients, Bacillus-Calmette-Guerin vaccination was found to delay the onset of first environmental mycobacterial disease.

Broncholiths and foreign objects can be removed by routine bronchoscopy or rigid bronchoscopy in patients with obstructive MLS. Other nonsurgical bronchoscopy options are balloon dilatation, stent placement, argon plasma coagulation, electrocautery, cryotherapy, and laser therapy to relieve focal nonmalignant obstruction. Chest physical therapy and postural drainage are also important for the management of MLS.

Surgery
Surgical removal of the middle lobe is reserved for persistent, complex cases of MLS unresponsive to therapy and among those whose middle lobe bronchus is obstructed. Recurrent hemoptysis in a patient with MLS for whom interventional radiology techniques have not been successful is also an indication for surgery. Malignancy warrants removal of the middle lobe, together with the surrounding hilar and mediastinal lymph nodes. Surgery may also be considered in patients with MLS who have scarring, fibrosis, and abscess formation. Surgical intervention can be considered in patients with nonobstructive MLS if their symptoms persist and radiological evidence of chronic atelectasis is seen after prolonged medical therapy (~6 months).

Conclusions
Diagnosis of right middle lobe (RML) syndrome may be delayed or go unnoticed unless this unusual pattern is recognized and appropriate diagnostic studies are employed. Oftentimes, patients with RML syndrome will have a history of multiple treatments for recurrent pneumonia or asthma. The middle lobe and lingula are predisposed to inflammation and infection because of their anatomical structures and the absence of collateral ventilation. Most patients with nonobstructive middle lobe syndrome respond to bronchodilators, mucolytics, and broad-spectrum antibiotics. Patients whose disease is unresponsive to medical treatment and those with obstructive RML syndrome may be candidates for resection of the RML or lingula.

References