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Article

Clinical and Radiological Features of Pulmonary Disease Caused by Rapidly Growing Mycobacteria in Cancer Patients

K. Jacobson, R. Garcia, H. Libshitz, E. Whimbey, K. Rolston, D. Abi-Said, I. Raad

Abstract The role of rapidly growing mycobacteria in the pathogenesis of pulmonary disease is being increasingly recognized; however, the clinical significance of these mycobacteria in patients with underlying malignancy has not been well studied. Over a 6-year period, 37 cancer patients with rapidly growing mycobacteria isolated from respiratory specimens were identified at our center. *Mycobacterium chelonae* group was isolated in 24 cases and *Mycobacterium fortuitum* in 13 cases. Of the 24 cases with cultures yielding *Mycobacterium chelonae* group, eight met the study criteria for infection and were determined to be clinically significant, whereas only one of the *Mycobacterium fortuitum* isolates was determined to represent infection. An average of two antimicrobial agents were used for treatment, most commonly clarithromycin, ciprofloxacin, and trimethoprim/sulfamethoxazole. Although the isolation of rapidly growing mycobacteria represents colonization in most cases, these bacteria, especially the *Mycobacterium chelonae* group, may cause pulmonary disease in cancer patients. The clinical and radiological findings are usually non-specific in this population, and patients with respiratory cultures yielding rapidly growing mycobacteria should be assessed carefully to distinguish infection from colonization. Effective therapy can be provided with oral regimens that include at least two antibiotics to which the organism is susceptible.

Introduction

Rapidly growing mycobacteria (RGM) (Runyon Group IV) are emerging pathogens in that, in recent years, their role in human disease has been increasingly accepted and the clinical situations in which they are likely to occur have been more frequently recognized. This group of mycobacteria consists of ubiquitous environmental organisms that exist in water, soil, and dust [1, 2]. Two members of this group, *Mycobacterium chelonae* group and *Mycobacterium fortuitum*, have been identified as causing disease in both healthy and immunocompromised patients. They can cause a variety of infections, including skin and soft tissue abscesses, post-surgical wound infections, osteomyelitis, corneal ulceration, meningitis, peritonitis, prosthetic valve endocarditis, hepatitis, pulmonary infections, lymphadenitis, bacteremia, and venous catheter-related infections, as well as disseminated disease in immunocompetent and immunocompromised patients [3–22].

The role of RGM in pulmonary disease has been unclear. *Mycobacterium fortuitum* and *Mycobacterium chelonae* group, both of which have been cultured from the saliva and sputum of healthy persons, may colonize the respiratory tract. The clinical presentation of infections by RGM in cancer populations has not been well defined. In a small study, antineoplastic chemotherapy and pre-existing pulmonary disease in patients with malignancies were associated with pulmonary infection rather than simply colonization with RGM [23].

RGM are usually resistant to standard anti-tuberculous agents and have varying susceptibility to other antibio-

K. Jacobson (✉), R. Garcia, H. Libshitz, E. Whimbey, K. Rolston, D. Abi-Said, I. Raad
Department of Medical Specialties, Section of Infectious Diseases, Box 47, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA

tics [24–26]. *Mycobacterium chelonae* group infections in particular have traditionally required treatment by parenteral antibiotics such as amikacin, cefoxitin, and imipenem. Rapidly growing mycobacterial isolates are frequently susceptible in vitro to newer macrolide antibiotic agents such as clarithromycin; however, little data exist as to the clinical efficacy of these agents. This study examines the clinical and radiologic features of 37 cancer patients from whom RGM were isolated in respiratory specimens, adding to the previous descriptions of RGM in cancer patients, and reassesses the role of RGM in the cancer population. Response to antibiotic therapy is also evaluated.

Patients and Methods

Patient Population. The University of Texas M.D. Anderson Cancer Center is a 417-bed inpatient facility. Mycobacterial cultures of respiratory specimens (sputum, bronchoscopy, and lung biopsy specimens) from patients hospitalized at this institution from January 1989 through December 1994 were reviewed. The hospital averaged 17,665 admissions per year during this period, with a racial mix of 72.4% white, 9.7% black, 15.5% Hispanic, 0.5% Asian, and 1.8% other. Gender division was 50.6% female and 49.4% male. Information was collected on patients through chart review: demographic information, underlying malignancy, clinical symptoms, results of bronchoscopy, the presence and characteristics of radiographic infiltrates, and results of lung biopsy or autopsy. The length and type of antibiotic therapy was recorded, as well as response to antibiotic therapy and long-term outcome of the patient, including cause of death, where appropriate.

Diagnostic Criteria. The main criteria for the diagnosis of pulmonary infection were as follows: (i) presence of at least one of the following symptoms compatible with pneumonia: fever, cough, sputum production, hemoptysis, dyspnea, pleuritic chest pain, or unexplained weight loss; (ii) evidence of pulmonary infiltrates on a chest radiograph, and (iii) isolation of *Mycobacterium fortuitum* or *Mycobacterium chelonae* group from a respiratory source. Additional criteria included (i) confirmation of atypical mycobacteria infection by biopsy or autopsy; (ii) clinical response to effective antimicrobial agents (according to specific susceptibility pattern); and (iii) pneumonia not explained by other etiologies after an extensive evaluation. The patients were classified as having clinically significant infection if all three main criteria were fulfilled as well as at least one of the additional criteria. Cases were classified as indeterminate if information on any of the main or additional criteria was unavailable. The patients were classified as being colonized with RGM if there was absence of any of the main criteria or all of the additional criteria.

Microbiological Investigations. Organisms were identified in the University of Texas M. D. Anderson Cancer Center microbiology laboratory as belonging to the *Mycobacterium fortuitum* group (*Mycobacterium fortuitum*, *Mycobacterium peregrinum*, and the third biovariant complex of *Mycobacterium fortuitum*) or the *Mycobacterium chelonae* group (*Mycobacterium chelonae* and *Mycobacterium abscessus*) using standard biochemical techniques that included nitrate reduction and iron uptake [27]. Antimicrobial susceptibility testing was performed by the City of Houston Health and Human Services Laboratory using the agar disk elution method. The following antimicrobial agents and minimum inhibitory concentration breakpoints were used: amikacin (≤ 20 μg/ml), kanamycin (≤ 20 μg/ml), tobramycin (≤ 5 μg/ml), doxycycline (≤ 5 μg/ml), cefoxitin (≤ 30 μg/ml), trimethoprim/sulfamethoxazole ($\leq 0.5/9.5$ μg/ml), sulfisoxazole (≤ 50 μg/ml), erythromycin (≤ 5 μg/ml), imipenem/cilastin (≤ 8 μg/ml), and ciprofloxacin (≤ 1 μg/ml). Standard Kirby-Bauer disk susceptibility and microtiter-broth dilution techniques were used. Susceptibility to clarithromycin was tested by the National Jewish Center for Immunology and Respiratory Medicine in Denver, Colorado, using the agar disk elution method.

Results

Patient Population. Overall, 40 patients with RGM isolated from respiratory specimens were identified at our center during the 6-year period; three patients were eliminated from further analysis due to lack of underlying malignancy. RGM had an isolation rate of 37.7/100000 hospital admissions. *Mycobacterium chelonae* was recovered from 24 patients and *Mycobacterium fortuitum* from 13 patients. The patients' ages ranged between 17 and 83 years, with the median age of 61 years. The demographics are shown in Table 1: the patients were characterized by a slight underrepresentation of females and Hispanics relative to the corresponding percentages of hospital admissions. There was a slight predominance of solid organ tumors

Table 1 Characteristics of 37 patients with pulmonary isolates of rapidly growing mycobacteria

Characteristic	No. (%)	
	All cases ($n=37$)	Cases with clinically significant infection ($n=9$)
Race		
white	28 (75.7)	8 (89)
black	5 (13.5)	0
Hispanic	3 (8.1)	0
Asian	0	0
Other	1 (2.7)	1 (11)
Sex		
Male	23 (62.2)	4 (44)
Female	14 (37.8)	5 (56)
Type of cancer		
Lung	4 (10.8)	1 (11)
Other solid tumor	17 (45.9)	5 (56)
Leukemia	11 (29.7)	2 (22)
Lymphoma/myeloma	5 (13.5)	1 (11)
Underlying lung disease[a]		
Cancer involving lung (primary or metastatic)	13 (35.1)	2 (22)
COPD/asthma	8 (21.6)	2 (22)
Bronchiectasis	1 (2.7)	0
Past tuberculosis	3 (8.1)	0
Other[b]	5 (13.5)	1 (11)
Recent chemotherapy[c]	19 (51.3)	5 (56)
Recent steroids[c]	5 (13.5)	2 (22)
Recent neutropenia[c]	14 (37.8)	2 (22)
Bone marrow transplant	1 (2.7)	1 (11)

[a] Some patients had more than one type of pulmonary disease
[b] Tracheal stenosis ($n=2$), radiation fibrosis ($n=1$), chronic bronchitis ($n=1$), and interstitial lung disease ($n=1$)
[c] Within 30 days prior to culture
COPD, chronic obstructive pulmonary disease

Table 2 Symptoms and clinical presentation of the nine patients with pulmonary infection due to rapidly growing mycobacteria

	No. (%) of patients
Fever	4 (44)
Cough	6 (67)
Sputum production	4 (44)
Hemoptysis	4 (44)
Pleuritic chest pain	0
Malaise	2 (22)
Weight loss	1 (11)
Anemia (Hgb<12 g/dl)	6 (67)
Leukocytosis (leukocytes>12000/mm^3)	1 (11)
Tachypnea (RR>18/min)	6 (67)
Abnormal auscultation	7 (78)

Hgb, hemoglobin; RR, respiratory rate

as the underlying malignancy, and approximately half of the patients had underlying lung disease, predominantly asthma, primary or metastatic cancer involving the lung, or chronic obstructive pulmonary disease. Approximately half of the patients had recently received cancer chemotherapy, and 37.8% had recently been neutropenic. A small minority of the patients had recently received steroids or had received a bone marrow transplant.

Of the 24 *Mycobacterium chelonae* isolates recovered, eight (33.3%) were determined to represent true pulmonary infection. In nine cases (37.5%) the presence of the isolates was classified as colonization and in seven cases (29.2%) as indeterminate. Of the 13 *Mycobacterium fortuitum* isolates recovered, only one (7.7%) was determined clinically significant. In nine cases (69.2%) the presence of the isolates was classified as colonization and in three cases (23.1%) as indeterminate. Isolation of *Mycobacterium chelonae* group more frequently represented infection than did isolation of *Mycobacterium fortuitum* (33.3% vs. 7.7%, $P=0.09$).

Clinical Disease. Among the nine patients with clinically significant infection due to RGM, the median age at the time of culture was 72 years. The patients were primarily white, with an underlying non-pulmonary solid tumor as their cancer diagnosis (Table 1). A slight majority of the patients were female. Most patients did not have pre-existing underlying pulmonary disease. Five had received recent chemotherapy, two had received recent corticosteroids, two had had recent neutropenia, and one had received a bone marrow transplant. None of these patients had coexisting infection with other mycobacteria; however, one of the patients with indeterminate infection with *Mycobacterium chelonae* and two of the patients with colonization with *Mycobacterium fortuitum* also had *Mycobacterium gordonae* isolated from sputum.

Selected symptoms and signs are listed in Table 2. The majority of patients with pulmonary infection due to RGM had cough, tachypnea, abnormal auscultation, and anemia. A large minority also had fever, sputum production, and hemoptysis. Malaise, weight loss, and leukocytosis were uncommon, and pleuritic chest pain was not present.

The clinical profiles and chest radiographic findings of the patients with RGM pulmonary infection are listed in Table 3. Among the nine patients, the most common radiographic finding was non-specific multilobar consolidation. There was one each with radiographic findings similar to primary tuberculosis, invasive fungal infection, and the recently described nodular and bronchiectatic changes characteristic of *Mycobacterium avium* complex infection [28]. Representative radiographs are demonstrated in Figures 1 and 2.

Antimicrobial Susceptibility. All isolates obtained from the patients with clinically significant disease due to RGM were uniformly susceptible to amikacin and kanamycin. Susceptibility rates among these isolates for other antimicrobial agents tested were as follows: tobramycin 55.6%, doxycycline 11.1%, cefoxitin 77.8%, trimethoprim/sulfamethoxazole 55.6%, sulfisoxazole 55.6%, erythromycin 44.4%, imipenem/cilastin 77.8%, and ciprofloxacin 77.8%. One of these isolates was also tested against clarithromycin and found to be susceptible.

Therapy and Outcome. Of the nine patients with clinically significant infection due to RGM, eight were treated with antimicrobial agents active against the individual isolates (Table 3). An average of two antimicrobial agents to which the isolate was susceptible were used (range 2 to 3); four patients were treated with oral agents alone. Among the treated patients, five exhibited clinical and radiologic resolution with therapy, and three died of causes related to progression of the underlying cancer before response to the antimicrobial therapy could be measured. One patient elected not to be treated due to progression of his underlying carcinoma, had progression of his pulmonary infiltrates, and died within 5 months. Of the five patients in whom response to therapy could be measured, duration of therapy ranged from 3 to 24 weeks in three patients and was undetermined in two patients. Length of follow-up in these five patients ranged from 4 months to 3 years; none had evidence of clinical or radiographic recurrence.

Discussion

Pulmonary disease caused by RGM is an uncommon but clinically important entity. Over the last 10 years there has been increased awareness of infections due to

Table 3 Clinical features of patients with pulmonary infection caused by rapidly growing mycobacteria

Case no.	Sex/ age	Underlying malignancy	Organism	Underlying lung disease	Radiologic features	Therapy	Outcome
1	F/72	lung cancer	*M. chelonae* group	cancer (resection of LUL)	LLL consolidation and pleural thickening	clarithromycin, TMP/SMX	resolution of infection
2	F/82	adeno-carcinoma, uterine cancer	*M. chelonae* group	COPD	RML/RLL consolidation with bronchiectasis	doxycycline, clarithromycin	resolution of infiltrates and bronchiectasis
3	M/28	CML	*M. chelonae* group	none	bibasilar nodular opacities with cavitation, mediastinal adenopathy	amikacin, clarithromycin, ciprofloxacin	died 2 weeks later from lymphoma, GVH disease, progressive pneumonia
4	F/42	AML	*M. chelonae* group	none	diffuse bilateral interstitial infiltrates	imipenem, erythromycin, TMP/SMX	marked clinical, radiologic improvement (died 3 months later from sepsis & complications of leukemia)
5	M/83	prostate cancer	*M. chelonae* group	none	bilateral infiltrates	ceftazidime, erythromycin	died 3 weeks later from progression of cancer
6	M/72	thyroid cancer	*M. chelonae* group	tracheal stent, lung metastases	RUL infiltrate, bilateral pleural effusions	ciprofloxacin, TMP/SMX	resolution of infection died 5 months later from complications of cancer
7	F/39	lymphoma	*M. chelonae* group	none	bilateral lower lobe infiltrates	cefoxitin, amikacin, TMP/SMX	died 4 weeks later with progressive lymphoma
8	F/72	pancreatic cancer	*M. chelonae* group	none	fibronodular densities, particularly in RUL	none	progression of infiltrates; patient declined treatment, died 5 months later
9	M/65	hepatocellular cancer	*M. fortuitum*	asthma	LLL, RML, RLL infiltrates	erythromycin, TMP/SMX	resolution of infection

AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; COPD, chronic obstructive pulmonary disease; GVH, graft-versus-host; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; TMP/SMX, trimethoprim/sulfamethoxazole

RGM. *Mycobacterium chelonae* group and *Mycobacterium fortuitum* are common environmental saprophytes. In humans, colonization is often transient and must be distinguished from true infection. Until recently, only a small number of cases of pulmonary disease caused by RGM had been described, usually associated with underlying conditions such as achalasia, malignancy, rheumatoid arthritis, cystic fibrosis, chronic obstructive pulmonary disease, lipoid pneumonia, and previous mycobacterial lung disease [23, 29–34]. In the largest series to date, Griffith et al. [35] described 154 patients with pulmonary disease due to RGM and confirmed an association with underlying cystic fibrosis (6% of patients), gastroesophageal disorders with chronic vomiting (6%) and previously treated mycobacterial disease (18%), and also found an association with coexisting *Mycobacterium avium* complex infection (8%). Malignancy does not seem to be a significant predisposing factor for the development of pulmonary disease due to RGM: in that series, although 68% had an associated underlying disease, only 6% had an underlying malignancy [35]. The organisms were identified to the newly organized species level; the majority of the isolates (82%) were *Mycobacterium abscessus* (formerly *Mycobacterium chelonae* subsp. *abscessus*), and another 14% were identified as *Mycobacterium fortuitum*, with these two species together constituting 96% of isolates.

To date, only one study has addressed pulmonary RGM infection in the cancer population: over an 8-year period, RGM were isolated from the respiratory cultures of 45 patients hospitalized at the University of Texas M.D. Anderson Cancer Center [23]. Of these, five patients were considered to have significant pulmonary infection (3 of 8 patients with *Mycobacterium chelonae* isolates, and 2 of 37 patients with *Mycobacterium fortuitum* isolates). We observed a stable number of isolates each year during the 6-year study period; *Mycobacterium chelonae* group represented 64.9% of all RGM specimens, although only a minority of isolates (37.5%) were found to be associated with disease. *Mycobacterium fortuitum* was isolated less frequently (35.1% of all isolates), and, similar to the previous study in cancer patients [23], was more often a colonizer or contaminant than *Mycobacterium chelonae*. This trend, however, should be interpreted with caution, given the small number of patients

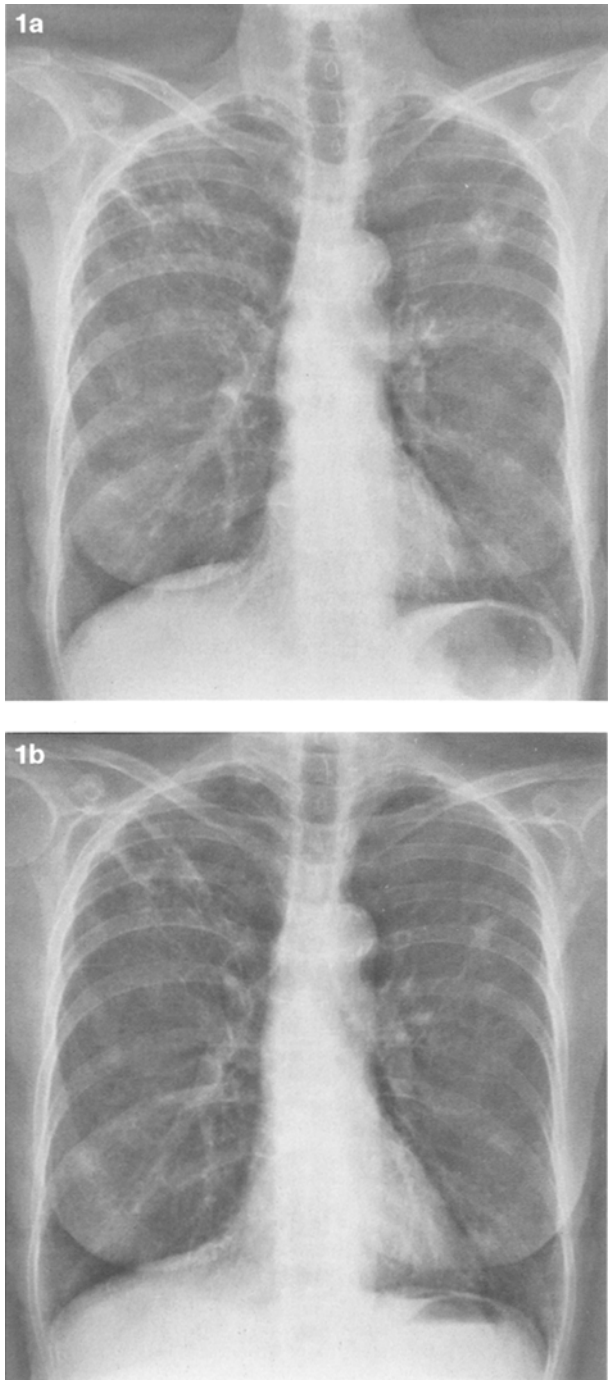

Figure 1 Radiographs of a 72-year-old female with pancreatic cancer and *Mycobacterium chelonae* group isolated from multiple sputum specimens. Fibronodular areas were observed in both lungs, similar to *Mycobacterium tuberculosis* with progression. **1a**: Chest radiograph showing fibronodular changes bilaterally, more marked in the right upper lobe. **1b**: Progression is seen 9 weeks later, prior to initiation of therapy

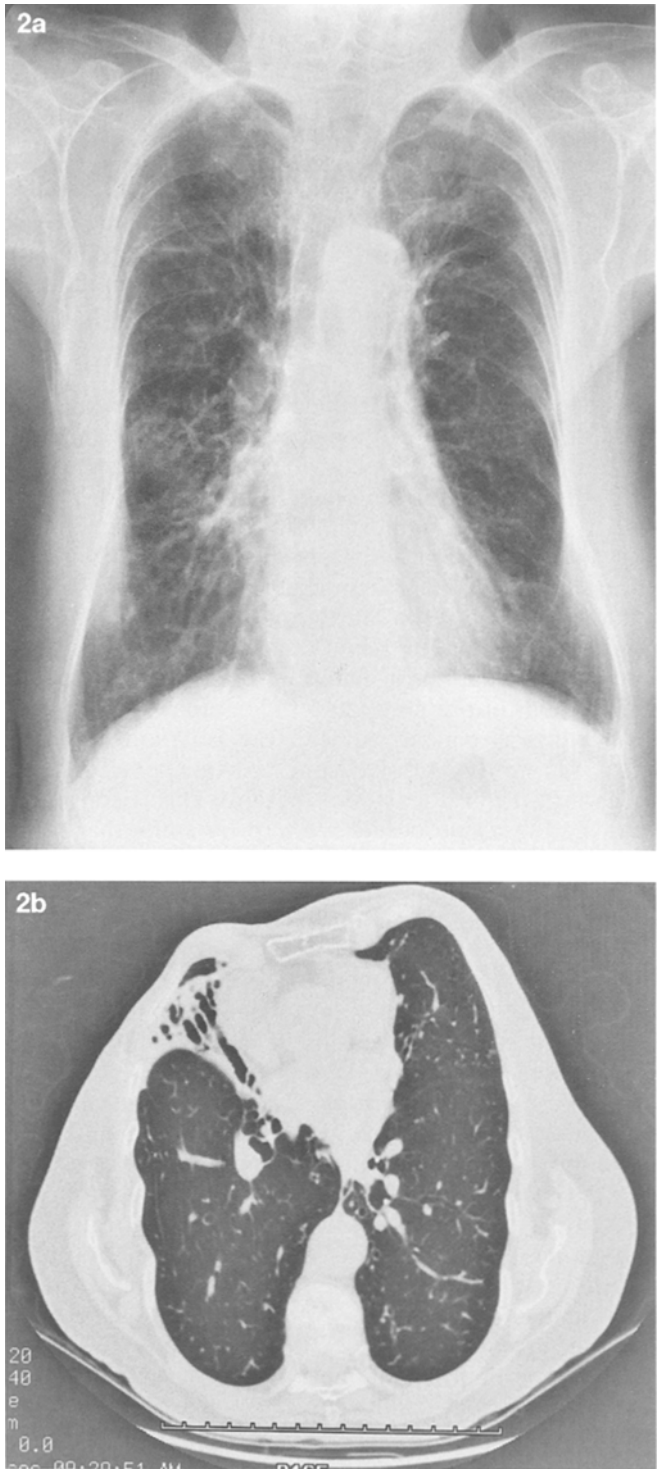

Figure 2 Radiograph and CT scan of an 82-year-old female with uterine cancer and *Mycobacterium chelonae* group isolated from sputum. Bronchiectatic and nodular changes were seen, similar to what has been described with *Mycobacterium avium* complex and, less frequently, with other atypical mycobacteria. **2a**: Chest radiograph showing rounded densities in the lower half of the right lung and prominent bronchi in area of middle lobe. **2b**: Thin-section CT scan showing middle lobe volume loss and bronchiectasis

in our study and the relatively high number of indeterminate cases.

Recent neutropenia, which is an identified risk factor for the development of other bacterial infections in cancer patients, was observed in a minority of the patients with infection due to RGM. However, similar to the prior study of RGM infections in cancer patients, the majority of the patients had received antineoplastic chemotherapy prior to developing their pulmonary infection, and disseminated infection due to RGM was not observed.

Signs and symptoms of RGM pulmonary disease are variable and usually non-specific. As in previous studies [23, 35, 36], the majority of the cancer patients with clinically significant infection due to RGM had cough, tachypnea, abnormal findings on auscultation, and anemia. The patterns on chest radiograph in the patients with clinically significant infection were similar to those reported in a large, prior study [35], with the most frequent finding being that of non-specific multilobar consolidation. Cavitation occurred frequently. One patient in our study had radiographic evidence of bronchiectasis concurrent with the isolation of RGM from sputum that resolved on subsequent radiographs following anti-mycobacterial therapy. This is consistent with the theory proposed by the prior study that some patients develop bronchiectasis as a result of RGM pulmonary infection rather than having primary bronchiectasis followed by colonization or infection.

Mycobacterium fortuitum and *Mycobacterium chelonae* group are uniformly resistant to standard anti-tuberculous agents. These organisms have been shown to be susceptible to a varying degree to oral and parenteral antibiotics. *Mycobacterium fortuitum* is frequently susceptible to the sulfonamides, quinolones, amikacin, tobramycin, imipenem/cilastin, and the cephamycins. The *Mycobacterium chelonae* group is frequently only susceptible in vitro to amikacin, tobramycin, cefoxitin, and imipenem/cilastin [24–26]. In our series of nine patients with pulmonary disease due to RGM, more than half of the isolates (primarily *Mycobacterium chelonae* group) were susceptible to tobramycin, cefoxitin, trimethoprim/sulfamethoxazole, sulfisoxazole, imipenem/cilastin, and ciprofloxacin. Among the patients in whom the response to therapy for RGM pulmonary infection could be judged, clinical and radiologic resolution was achieved in the majority with oral antibiotic therapy, including clarithromycin. The newer oral macrolide agents, including clarithromycin, are currently under evaluation as antibacterial agents against RGM and have been successful in treating disseminated disease due to *Mycobacterium chelonae* [37]. However, reports of the development of resistance to clarithromycin have arisen following monotherapy for disseminated *Mycobacterium chelonae* [37, 38]. Therapy should probably consist of at least two antibiotics to which the organism is susceptible, in order to prevent the emergence of resistance.

Although pulmonary infection caused by RGM in patients with cancer is relatively uncommon, it can be rapidly progressive and fatal in this population if left untreated. While it is an important diagnostic consideration in the presence of pulmonary infiltrates, respiratory isolates, especially *Mycobacterium fortuitum*, are frequently indicative of colonization rather than infection. The clinical and radiographical findings described with RGM pulmonary disease may be difficult to distinguish from those of the underlying malignancy and its associated therapy. The determination of the significance of RGM respiratory isolates is best made on a case-by-case basis; caution should be exercised when a diagnosis is being made on the basis of cultures alone. Although the traditional recommendations for initial therapy of RGM pulmonary infection have involved parental antibiotics or surgical resection, successful therapy of RGM pulmonary infection in the cancer population may be achieved with a combination of oral antibiotics.

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