Rapidly Growing Mycobacterial Infections : Spectrum of Diseases, Antimicrobial Susceptibility, Pathology and Treatment Outcomes

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Abstract

Objectives : A series of cases infected with rapidly growing mycobacteria were studied to reveal the spectrum of disease, antimicrobial susceptibility, pathology, and treatment outcomes.

Method : The cases identified as rapidly growing mycobacterial infections in Ramathibodi Hospital from January 1993 to June 1999 were retrospectively studied.

Results : There were 20 patients and most of the cases had no underlying disease. Only two cases were HIV-infected patients. The presenting clinical features were lymphadenitis (7), skin and subcutaneous abscess (7), eye infection (4), pulmonary infection (1), and chronic otitis media (1). Four of the seven cases with lymphadenitis had Sweet's syndrome. The organisms were *Mycobacterium chelonae/abscessus* group (17 cases) and *Mycobacterium fortuitum* group (3 cases). The organisms were susceptible to amikacin, netilmicin and imipenem. The *M. fortuitum* group was susceptible to more antibiotics than the *M. chelonae/abscessus* group. Pathology of the infected tissue varied from non-specific findings to suppurative or caseous granuloma. The clinical responses corresponded to the antimicrobial susceptibility. Most of the patients had a good clinical outcome. A combination of two or more drugs was used for the medical treatment. Surgical resection was performed where possible to reduce the load of the organism, especially in cases with very resistant organisms.

Conclusions : Rapidly growing mycobacterial infections can occur in apparently normal hosts. Clinical syndrome is variable. The pathology is non-specific and culture is needed for definite diagnosis. Clinical responses varied but seemed to correlate with the *in vitro* susceptibility result. More studies are needed before one can deal with these infections more effectively.

Key word : *Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium abscessus,* Rapidly Growing Mycobacteria, Susceptibility, Pathology, Lymphadenitis, Sweet's Syndrome, Outcome

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The *Mycobacterium chelonae, Mycobacterium abscessus,* and *Mycobacterium fortuitum* group are the major pathogens of rapidly growing mycobacteria. Infections caused by these organisms are not uncommon and the incidence is increasing. The clinical syndrome is variable[1]. The diseases have involved many tissues and organ systems such as infections of skin and soft tissue[2-4], lymph nodes [5], lung[6-8], joints[9], cornea[10-12], fundi[13], ear and mastoid[14,15], catheter-related site[16,17], prosthesis[18], and disseminated infection[19,20]. Most of the patients have conditions of immunosuppression or antecedent chronic illness[20]. The course of disease is highly variable[1,20]. Treatment is difficult because the organisms do not respond to traditional antituberculous agents and most antibiotics, and relapse of the diseases is common. A clinical trial defining optimal treatment regimen is not available due to a limited number of patients and various clinical syndromes and clinical course. The present study may offer data for taking care of patients with rapidly growing mycobacteria or further research in the future.

MATERIAL AND METHOD

Clinical aspects

Records of cases infected with *M. chelonae/abscessus* group and *M. fortuitum* group in the Division of Infectious Diseases and Microbiology Laboratory, Ramathibodi Hospital, Bangkok, from January 1993 to December 1999 were retrospectively reviewed. Only cases which fulfilled the diagnostic criteria for nontuberculous mycobacterial infection as described by the American Thoracic Society[21] were included. Demographic data and information regarding underlying diseases, clinical features, antimicrobial susceptibility, pathology of the tissues, treatment, and outcome were collected and analysed.

Definition of organ involvement required positive culture from the tissue or clinical specimen. Involvement of the second or third organ needed positive culture or suggestive histological finding. Outcome of treatment was defined as good or poor, depending on general condition, body weight, and resolution of presenting symptoms, physical findings and culture results. A good outcome was defined according to each specific organ involvement as follows: resolution of fever and lymph node decreased in size and inflammation for lymphadenitis; resolution of skin inflammation and abscess for skin and subcutaneous infection; improvement of chest symptoms and resolution of infiltration in chest radiography for lung infection; improvement of abnormal lesions for eye and ear infection. Slight improvement, no improvement, or worsening of the signs and symptoms was categorized as poor outcome.

Microbiological aspects

Acid fast stain of the clinical specimens was done by the carbolfuchsin method (Kinyoun stain). Clinical specimens from various sites were cultured on routine aerobic and mycobacterial media. Identification of rapidly growing mycobacterium was based on the growth on MacConkey agar (crystal violet free) and positive arylsulfatase reaction within 3 days. The *M. fortuitum* group was differentiated from the *M. chelonae/abscessus* group on the basis of the positive iron uptake and nitrate reduction[22]. For the presented set of the biochemical tests, *M. chelonae* was not distinguished from *M. abscessus* and *M. fortuitum* group was not differentiated into the biovar. Susceptibility testing was done by the disk diffusion method. Mueller Hinton agar plate was swabbed with OADC (Oleic acid albumin dextrose catalase) on its surface. The organisms in Mueller Hinton broth with the turbidity of the 0.5 McFarland were swabbed onto the surface. The commercial bacterial antibiotic disks were used and incubated at 37°C for 3-4 days until the signs of growth were tested eminent. The zones of inhibition were measured. The susceptibility were recorded as susceptible or resistant to individual agents according to the suggested susceptibility-zone diameter by Michael H. Cynamon and Sally P. Klemens[23].

RESULTS

There were 22 cases infected by the *M. chelonae/abscessus* group or *M. fortuitum* group in Ramathibodi Hospital from January 1993 to June 1999. Two cases were excluded because the records were not available. There were 20 cases available for study. From 20 cases, 6 were males. The mean age $\pm$ SD of the patients was 40 $\pm$ 12.8 years. Sixteen cases had no underlying diseases. Two cases had HIV infection and one case each had rheumatoid arthritis and systemic lupus erythematosus (SLE). The presenting clinical features were lymphadenitis (7), skin and subcutaneous abscess (7), eye infection (4), pulmonary infection (1), and chronic otitis media (1). The details of all 20 cases are demonstrated in Table 1. Pathologic diagnosis of the tissues or pus from infected tissue is shown in Table 2. Table 3 shows the susceptibility patterns of various antimicrobial agents to the

Table 1. Patients with rapidly growing mycobacterial infections.

Case	Age, Sex	Diagnosis	Organisms	Underlying diseases	Treatment	Outcome
1	57, M	intraabdominal lymphadenitis	*M. fortuitum* group	-	clarithromycin + doxycycline + gentamicin	good
2	39, F	cervical lymphadenitis, parotitis, Sweet's synd.	*M. chelonae/abscessus* group	-	clarithromycin + amikacin + imipenem	good
3	32, F	supraclavicular lymphadenitis	*M. chelonae/abscessus* group	-	clarithromycin + amikacin	good
4	59, F	cervical lymphadenitis	*M. chelonae/abscessus* group	rheumatoid	clarithromycin + netilmicin	good
5	47, F	cervical lymphadenitis, osteomyelitis, Sweet's synd.	*M. chelonae/abscessus* group	-	clarithromycin + amikacin, surgery	poor
6	52, F	cervical lymphadenitis, Sweet's synd.	*M. chelonae/abscessus* group	-	clarithromycin + amikacin + ciprofloxacin	good
7	40, M	cervical & inguinal lymphadenitis, Sweet's synd.	*M. chelonae/abscessus* group	-	clarithromycin + amikacin, surgery	poor
8	24, F	neck abscess	*M. chelonae/abscessus* group	-	drainage	loss f/u
9	27, F	breast abscess	*M. chelonae/abscessus* group	-	drainage	loss f/u
10	40, F	chronic subcutaneous nodule	*M. chelonae/abscessus* group	-	clarithromycin + amikacin	good
11	18, F	subcutaneous nodule on tattoo	*M. chelonae/abscessus* group	-	excision,	good
12	27, F	chronic skin ulcer and subcutaneous abscess	*M. chelonae/abscessus* group	SLE	clarithromycin + amikacin + doxycycline	good
13	52, F	skin plaque	*M. chelonae/abscessus* group	-	clarithromycin + ciprofloxacin	good
14	34, M	genital ulcer and inguinal abscess	*M. fortuitum* group	HIV infection	clarithromycin + amikacin + co-trimoxazole	good
15	38, M	pneumonitis	*M. chelonae/abscessus* group	HIV infection	- (died before getting the culture result)	dead
16	41, F	otitis media, mastoiditis, sigmoid sinus thrombosis	*M. chelonae/abscessus* group	-	clarithromycin + amikacin + imipenem	poor
17	44, M	corneal ulcer	*M. fortuitum* group	-	co-trimoxazole + cefazolin* + gentamicin*	good
18	39, M	corneal ulcer	*M. chelonae/abscessus* group	-	clarithromycin + fusidic acid + amikacin*	good
19	66, F	corneal ulcer, endophthalmitis	*M. chelonae/abscessus* group	hypertension	tetracycline + cefazolin* + gentamicin*	good
20	24, F	endophthalmitis	*M. chelonae/abscessus* group	-	enucleation + chloramphenicol*	good

*eye drop preparation, Sweet's synd.= Sweet's syndrome

Table 2. Pathologic findings of the infected tissue.

Infected tissue and pathological diagnosis	AFB	Number of specimens
Lymph Node		
Nonspecific lymphadenitis	-	1
Acute/chronic inflammation	-	2
Acute and chronic lympadenitis with focal fibrosis	+	2
Acute suppurative lynphadenitis	+	1
Suppurative granuloma with eosinophilia	+	1
Suppurative granuloma with caseous necrosis	-	1
Caseous granuloma	-	1
Granulomatous lymphadenitis	-	2
Non-caseating granulomatous lymphadenitis	-	1
Mixed lymphoid cells with vascular proliferation	-	1
Tonsils		
Pleomorphic reticulosis	+	1
Bone		
Necrotic tissue with acute inflammation	-	1
Acute inflammation with multinucleated giant cells	-	1
Skin and Soft Tissue		
Chronic inflammation	-	1
Chronic inflammation with excoriation	+	1
Suppurative granulomatous inflammation	-	2
Suppurative and focal granulomatous inflammation	+	1
Necrotizing granulomatous inflammation	-	1
Mastoid and Middle Ear		
Chronic inflammation with epitheloid granuloma	-	2
Granulomatous inflammation with caseous necrosis	-	1
Cholesteatoma	-	1

organisms. Seventeen cases in the study had received medical treatment and 14 of these (82.4%) had a good clinical outcome. The other 3 cases with poor clinical outcomes needed concurrent surgical treatment.

DISCUSSION

Rapidly growing mycobacterial infections in humans are primarily caused by the *M. chelonae/abscessus* group and *M. fortuitum* group[1]. Both groups grow on routine bacteriologic media, as well as mycobacterial media, within seven days[24]. The organisms are increasingly recognized as pathogens and the clinical syndrome is variable. According to the main organ involvement, the cases in the present study could be grouped into 5 groups: lymphadenitis, skin and soft tissue infections, pulmonary infection, ear infection, and eye infection. Three cases of the lymphadenitis group were considered as disseminated infection because of simultaneous multiple bone infections or multiple areas of lymphadenitis.

Among 20 cases, only 4 cases were considered to be immunocompromised hosts, consisting of 2 cases with HIV infection, 1 case with SLE on steroid therapy, and 1 case with rheumatoid arthritis on steroid therapy. The higher proportion of immunocompetent patients in the present study compared to the previous study[20] suggested that rapidly growing mycobacterial infections may occur in apparently normal hosts. The incidence of the *M. chelonae/abscessus*-group infection was higher than the *M. fortuitum*-group infection in the present report, consistent with the previous studies[10,11,20].

Seven from 20 patients in the present study presented with lymphadenitis. The number was higher than that in a recent review which identified 54 cases of rapidly growing mycobacterial infections since 1960, and showed only 3 cases of lymphadenitis[20]. The nodes involved in these patients were cervical, supraclavicular, or intraabdominal lymph nodes. The pathology of the various tissues was nonspecific and not diagnostic. Though some specimens showed positive acid fast bacilli, they could not be differentiated from tuberculosis, the more common disease. Culture for mycobacteria was more specific and helpful. There were 4 from 7 cases of lymphadenitis with associated Sweet's syndrome that was supported by clinical and

Table 3. Susceptibility patterns of rapidly growing mycobacteria to antibiotics.

	Antibiotics *M. chelonae/abscessus* group			*M. fortuitum* group		
	All tested (strains)	Susceptible (strains)	%	All tested (strains)	Susceptible (strains)	%
Penicillin	13	0	0	2	0	0
Cefoxitin	13	0	0	1	1	100
Imipenem	10	7	70.0	1	1	100
Gentamicin	13	7	53.8	3	3	100
Amikacin	13	13	100	3	3	100
Netilmicin	13	13	100	3	3	100
Tobramycin	13	13	100	3	3	100
Ofloxacin	13	0	0	2	2	100
Ciprofloxacin	11	1	9.1	1	1	100
Lincomycin	11	1	9.1	3	0	0
Erythromycin	13	5	38.5	3	0	0
Chloramphenical	4	0	0	2	1	50
Co-trimoxazole	13	2	15.4	3	3	100
Tetracycline	10	0	0	2	2	100
Fosfomycin	7	0	0	2	0	0
Vancomycin	12	1	8.3	1	1	100
Teicoplanin	10	1	16.7	1	0	0
Fusidic acid	9	2	22.2	2	1	50

histological evidence. All of them were infected by the *M. chelonae/abscessus* group. This finding would support the previous studies[25,26] that reported Sweet's syndrome associated with the *M. chelonae/abscessus*-group infection. The authors observed that 3 from 4 cases with Sweet's syndrome had recurrence of the skin lesions when there were clinical relapses of lymphadenitis. The authors' observation and previous data may alert the physician to rapidly growing mycobacterial infection when the patient comes with lymphadenitis and Sweet's syndrome.

The seven cases who presented with skin and soft tissue infection in the present study comprised of skin and subcutaneous infection, nodule on tattoo, neck, breast, and inguinal abscesses. The forty-one from 54 patients who presented with this entity in an earlier mentioned review[20] demonstrated that skin and soft tissue are common sites of infection. Acid fast stain is helpful for recognition of mycobacterial infection. This finding suggests doing acid fast stain in tissue and particularly pus from the abscess, to achieve rapid diagnosis of mycobacterial infection. However, the culture for mycobacteria is needed for the definite diagnosis of rapidly growing mycobacterial infection.

The case of pulmonary infection in the present study was a patient with advanced symptomatic HIV. Because the patient had prior pulmonary tuberculosis, the diagnosis of *M. chelonae/abscessus*-group pulmonary infection had to be made from the findings of new lung infiltration, two positive sputum cultures and one positive acid fast stain[21]. Pulmonary infection, as this patient was a possible presentation of rapidly growing mycobacterial infection, especially in the immunocompromised condition.

The case of otitis media and mastoiditis in the present study was chronic and did not respond to many conventional antibiotics. Diagnosis was made after awareness of mycobacterial infection. The patient had a poor response to medical and surgical treatment. This might be another site of rapidly growing mycobacterial infection that was difficult to treat. The previous study including 21 patients with chronic otitis media caused by rapidly growing mycobacteria had documented that treatment for this entity is difficult, requiring debridement and prolonged antibiotic therapy[27]. Tympanostomy tube placement may have been a risk factor for this infection in this case.

Three from 4 cases of eye infection in the present study had a previous eye injury, consistent with a previous study of 22 patients that 91 per cent had a previous eye injury[11]. The case with endophthalmitis and operation for enucleation had a history of penetrating eye injury 3 years prior to the infection. From previous reports[28,29], eye surgery can be another risk for endophthalmitis.

Treatment for rapidly growing mycobacterial infection is difficult because of resistance to conventional antituberculous drugs and to many antibiotics, and relapse of the disease is common. Two cases with lymphadenitis and one case of otitis media in the present study who had poor outcome demonstrated the difficulty of treatment. Though a prior study suggested that primary treatment was local excision of the affected lymph nodes[5], many subsequent studies reported the success of medical treatment with and without surgical treatment[2-4,6-20]. Seventeen cases in the present study had received medical treatment and 14 of these (82.4%) had a good clinical outcome. The other 3 cases with poor clinical outcomes needed concurrent surgical treatment.

Antimicrobial susceptibility of the *M. chelonae/abscessus* group and *M. fortuitum* group were different[30]. All strains of *M. fortuitum* are suseptible to co-trimoxazole[30], ciprofloxacin and ofloxacin[31] and some strains are susceptible to cefoxitin, doxycycline, and erythromycin[30] while less than 20 per cent of the *M. chelonae/abscessus* group are susceptible to these drugs[30,32-34]. The susceptibility patterns of these drugs in the present study revealed similar results.

Amikacin has been a promising drug for the *M. chelonae/abscessus* group and *M. fortuitum* group from a previous study since 1978[35] and the following study by Swenson proved this finding[30]. From the present study, all strains of the *M. chelonae/abscessus* group and *M. fortuitum* group were susceptible to amikacin and netilmicin. Clarithromycin is another drug actively inhibiting both groups of the organisms and 10-50 times more potent than erythromycin against the *M. chelonae/abscessus* group. Unfortunately, before 1999 the authors had not performed the susceptibility of the organisms to clarithromycin in clinical practice because the disc was not available. However, a previous study by Chittasobhaktra, et al that enrolled some patients from the present study showed that 91.7 per cent of the *M. chelonae/abscessus* group and 71.4 per cent of *M. fortuitum* group were susceptible to clarithromycin by Etest MIC study[36]. The other 28.6 per cent of *M. fortuitum* were intermediately resistant to clarithromycin. Imipenem was the only beta-lactam active against the *M. chelonae/abscessus* group for 39 per cent of strains in a previous study[32]. Seventy per cent of the cases infected by *M. chelonae/abscessus* group in the present study were susceptible to imipenem. Because of the variations in susceptibility by and within species subgroups, the authors recommend doing the susceptibility testing if the test is available.

The clinical trials of rapidly growing mycobacterial infections are scanty. A clinical trial of clarithromycin for cutaneous infection due to *M. chelonae* suggests that clarithromycin may be the drug of choice[37]. However, the later reports of rapid development of resistance to clarithromycin monotherapy for *M. chelonae* infection[38] and quinolone monotherapy for *M. fortuitum* infection[33] suggest that combination therapy may be more proper.

Medical treatment of the patients in the present study consisted of 2 or 3 drug combinations. The outcome of treatment varied among each group of the diseases. Most of the patients with lymphadenitis had a good clinical outcome. The cases with poor clinical outcomes had a higher number of involved lymph nodes at first presentation and they needed surgical resection. This may suggest that multiple lymph node involvement is one possible determining factor of clinical outcome. Relapse was common in this group, especially cases with multiple node involvement. The authors recommend using at least 3 effective drugs for medical therapy and continuing for a long time. Surgical resection if possible is helpful for patients with lymphadenitis.

Patients with cutaneous infection responded well to the treatment but an extensive skin lesion also needed surgery. Drainage of the abscess was indicated if present. Successful topical amikacin monotherapy for keratitis was reported in a study but 75 per cent needed early keratectomy[11]. The authors strongly recommend using at least 2 or 3 effective, topical and systemic drugs for medical therapy of keratitis. A case with endophthalmitis may need surgery to control the disease. Since a previous study reported that more patients with concurrent corticosteroid therapy failed to respond to medical therapy [10], the authors recommend avoiding corticosteroid therapy in these patients.

In conclusion, rapidly growing mycobacterial infections present with various clinical syndromes. The diseases can occur in apparently normal hosts. Awareness of the organisms can lead to the correct diagnosis and proper treatment. Definite diagnosis needs culture for mycobacteria since the pathology is non-specific. Clinical responses varied. Relapse was common particularly in the cases with lympha-

denitis. Medical therapy including 2-3 susceptible drugs is recommended. Surgical resection is indicated in cases with failed medical therapy and/or clinical relapse.

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การติดเชื้อมัยโคแบคทีเรียที่เจริญเร็ว : ขอบข่ายของโรค ความไวของเชื้อต่อยาพยาธิวิทยาและผลการรักษา

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วัตถุประสงค์ : ได้ทำการรวบรวมกลุ่มผู้ป่วยที่มีการติดเชื้อมัยโคแบคทีเรียที่เจริญเร็ว เพื่อศึกษาในด้านขอบข่ายของโรค ความไวของเชื้อต่อยา พยาธิวิทยา และผลการรักษา

วิธีการ : เป็นการศึกษาแบบย้อนหลังในผู้ป่วยที่มีการติดเชื้อมัยโคแบคทีเรียที่เจริญเร็ว ในโรงพยาบาลรามาธิบดี ตั้งแต่เดือนมกราคม พ.ศ. 2536 ถึงเดือนมิถุนายน พ.ศ. 2542

ผลการศึกษา : มีผู้ป่วยทั้งหมด 20 รายและผู้ป่วยส่วนใหญ่ไม่มีโรคประจำตัว มีผู้ป่วยเพียง 2 รายที่ติดเชื้อเอ็ชไอวี อาการนำทางคลินิกคือ ตุ่มน้ำเหลืองอักเสบ (7) การติดเชื้อของผิวหนังและชั้นใต้ผิวหนัง (7) การติดเชื้อที่ตา (4) การติดเชื้อที่ปอด (1) และการติดเชื้อที่หูชั้นใน (1) ผู้ป่วย 4 จาก 7 รายที่เป็นตุ่มน้ำเหลืองอักเสบมี Sweet's syndrome ร่วมด้วย เชื้อก่อโรคเป็นเชื้อในกลุ่ม *Mycobacterium chelonae/abscessus* 17 รายและกลุ่ม *Mycobacterium fortuitum* 3 ราย ผลการทดสอบความไวของเชื้อต่อยาพบว่าไวต่อยา amikacin, netilmicin และ imipenem. เชื้อในกลุ่ม *M. fortuitum* ไวต่อยาต้านจุลชีพมากกว่าเชื้อในกลุ่ม *M. chelonae/abscessus* พยาธิวิทยาของเนื้อเยื่อที่ติดเชื้อมีความหลากหลายตั้งแต่ไม่จำเพาะจนถึงเป็น caseous granuloma ผลการรักษาสอดคล้องกับผลการทดสอบความไวของเชื้อต่อยา ผู้ป่วยส่วนใหญ่ได้ผลการรักษาดี การรักษาใช้ยาร่วมกันตั้งแต่ 2 ตัวขึ้นไป การรักษาโดยการผ่าตัดได้ทำในรายที่เป็นไปได้เพื่อระบายเชื้อออก โดยเฉพาะในรายที่ดื้อต่อยาหลายขนาน

สรุป : การติดเชื้อมัยโคแบคทีเรียที่เจริญเร็วสามารถเกิดขึ้นได้ในผู้ป่วยที่ปกติ อาการทางคลินิกมีความหลากหลาย การตรวจทางพยาธิวิทยาไม่จำเพาะต่อโรคนี้และจำเป็นต้องอาศัยการเพาะเชื้อ ผลการรักษาแตกต่างกัน แต่พบว่าสอดคล้องกับผลการทดสอบความไวของเชื้อต่อยา การศึกษาเพิ่มเติมจะช่วยให้การรักษาโรคเหล่านี้มีประสิทธิภาพมากขึ้น

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