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Atypical mycobacterial cutaneous infections in Hong Kong: 10-year retrospective study

香港非典型分枝桿菌皮膚感染：十年回顧研究

Objective. To review the epidemiology of atypical mycobacterial cutaneous infection in Hong Kong.
Design. Retrospective study.
Setting. Social Hygiene Service (Dermatology Division), the largest dermatological referral centre in Hong Kong.
Patients. Patients with a diagnosis of atypical mycobacterial cutaneous infection based on clinical features, histopathology, with or without a positive culture during the period 1993 to 2002.
Main outcome measures. Epidemiological data, clinical features, histology, microbiological investigation, and treatment response.
Results. Of 345 394 dermatological cases presented over the 10-year period, 33 (0.0096%) cases (19 male, 14 female) of atypical mycobacterial cutaneous infection were diagnosed. The most common type of infection was caused by *Mycobacterium marinum* (n=17, 51.5%), followed by *Mycobacterium avium-intracellulare* (n=3, 9.1%) and *Mycobacterium chelonae* (n=2, 6.1%). The upper limb, especially the hands and fingers, was the most common (69.7%) site of involvement. Tissue culture was positive in 18 (54.5%) cases. All biopsies showed granulomatous histology. Thirty-two patients received treatment and 31 responded. Twenty-six were treated with oral tetracycline group of antibiotics (minocycline, doxycycline, tetracycline). The duration of treatment ranged from 8 to 54 weeks (mean, 24 weeks). Mild transient adverse effects to treatment were reported in six cases.
Conclusion. Atypical mycobacterial infection is rare in Hong Kong. Because of the low sensitivity of traditional culture techniques, atypical mycobacterial infection may be underdiagnosed if only culture-confirmed cases are included. Polymerase chain reaction provides a rapid and sensitive method to improve diagnostic accuracy. Tissue culture is crucial to determine antimicrobial susceptibility. In our study, tetracycline group of antibiotics, especially minocycline, was an effective treatment, particularly in cases caused by *Mycobacterium marinum*.

目的：回顧香港非典型分枝桿菌皮膚感染的流行情況。
設計：回顧性研究。
安排：社會衛生科（皮膚病分組），即全港最大的皮膚病科轉介中心。
患者：在1993至2002年間，根據臨床特徵、病理組織學檢查和種菌培養結果，被診斷患上非典型分枝桿菌皮膚感染的病人。
主要結果測量：流行病學數據、臨床特徵、組織學檢查、微生物學調查和對治療的反應。
結果：上述十年間的345 394宗皮膚病例中，有33宗（0.0096%）診斷為非典型分枝桿菌皮膚感染（19男，14女），其中以感染了海洋分枝桿菌最為普遍（17宗，51.5%），其次為鳥結核分枝桿菌（3宗，9.1%）和分枝桿菌屬細菌（2宗，6.1%）。主要影響部位為上肢（69.7%），特別是手掌和手指。有18宗病例（佔54.5%）的組織培養呈陽性。所有活組織檢查都顯示有肉芽腫病。32名病人接受治療，其中31人有反應。26人以口服四環素類抗生素（如美諾四環素、多西環素和四環素）治療，治療期介乎8至54個星期（平均為24個星期）。6名病人出現輕微的短暫副作用。
結論：非典型分枝桿菌皮膚感染在香港十分罕見。由於傳統的培養技術敏感度不足，如果只計算組織培養確診的個案便會低估非典型分枝桿菌皮膚感染的情況。聚

Key words:
Mycobacterial infections, atypical;
Mycobacterium marinum*;*
Polymerase chain reaction;
Skin diseases, bacterial

關鍵詞：
分枝桿菌感染，非典型；
海洋分枝桿菌；
聚合酶連鎖反應；
病膚病，細菌性的

Hong Kong Med J 2006;12:21-6

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合酶連鎖反應是一個快速和敏感度高的方法，可改善診斷的準確性。組識培養對了解抗菌感受性十分重要。我們的研究顯示，四環素類藥物（特別是美諾四環素）是有效的治療藥物，尤其是對因海洋分枝桿菌致病的個案。

Introduction

Atypical mycobacteria are found ubiquitously in the environment. They can be pathogenic in humans and cause various types of infections, including those of the skin. There have been only a few epidemiological studies of atypical mycobacterial (AM) infections reported but none in Hong Kong. We conducted a retrospective analysis of AM skin infections in Hong Kong. This study aimed to determine the pattern of infection; clinical, histological, and microbiological features of the disease; and the response to therapeutic intervention.

Methods

During a 10-year period from 1993 to 2002, we conducted a retrospective epidemiological study of AM infections in patients who attended out-patient clinics of the Social Hygiene Service, which is the largest dermatological referral centre in Hong Kong. Potential cases were identified by searching the histological database. All biopsies reported as granulomatous inflammation and mycobacterial infection were identified, and the corresponding records were retrieved and studied. Patients with a clinical diagnosis of AM infections and granulomatous inflammation on histological examination were included. When recruiting patients, histology and culture results were interpreted in conjunction with the clinical picture and the clinical response to treatment. A negative result did not necessarily exclude a patient since positive culture rates are not high. Patients under study were further classified according to the organism isolated. Patients with a clinical diagnosis of AM infections based on granulomatous histology, and good response to therapeutic trial but negative cultures were categorised as unclassified. The epidemiological data, clinical features, histological and microbiological results together with treatment outcome were analysed.

Results

Between 1993 and 2002, 345 394 new dermatological patients attended the out-patient clinics of the Social Hygiene Service, Hong Kong. Thirty-three (0.0096%) cases of AM infections were identified—17 (51.5%) *Mycobacterium marinum*, 3 (9.1%) *Mycobacterium avium-intracellulare* (MAI), 2 (6.1%) *Mycobacterium chelonae*, and 11 (33.3%) unclassified. Patients' age ranged from 21 to 75 years (median, 48 years). The duration of lesion varied from 10 days to 10 years (median, 12 months), and all biopsies revealed granulomatous inflammation (Table 1).

A total of 32 cases were treated—one patient with MAI defaulted from follow-up after biopsy and received no treatment. Lesions were cured in 20 patients and improved in 11 although the latter defaulted from further follow-up; one patient showed no improvement. Treatments for the 32 patients are shown in Table 2.

Duration of treatment in all patients ranged from 8 to 54 weeks (mean, 24 weeks). One patient prescribed cotrimoxazole-trimethoprim failed to respond. No mortality was recorded. Adverse reactions to treatment were temporary and reported by six (18.2%) patients—impaired liver function (n=5; four due to tetracycline, one due to anti-tuberculosis [anti-TB] drug), and renal impairment induced by amikacin (n=1). Tetracycline group (doxycycline, minocycline, and tetracycline) alone or combined with anti-TB drugs provided effective treatment for 16 patients with *M marinum*, one patient with MAI infection, and 10 patients with unclassified infection (n=27, 100%).

In patients with *M marinum*, 16 (94.1%) responded to treatment. Of these, 13 were treated with oral tetracycline alone (9 minocycline; 4 doxycycline); anti-TB drugs were used in three cases—in the first case, anti-TB drugs (isoniazid [H] + rifampicin [R] + pyrazinamide [Z]) were commenced in one patient before tissue culture results were available and switched to minocycline when *M marinum* was confirmed; in the second case, anti-TB drugs (HRZ + ethambutol [E] → RE + clarithromycin) were prescribed by a chest physician but stopped due to poor response and the development of thrombocytopenia, minocycline was prescribed after a repeated skin biopsy; in the third case, anti-TB drugs (HRZ) were prescribed by an orthopaedic surgeon in addition to minocycline. One patient was allergic to tetracycline; cotrimoxazole-trimethoprim (2 tablets twice a day) was unsuccessful after 9 weeks and the patient defaulted from follow-up. Seven (41.2%) patients reported a history of trauma, of whom six (85.7%) had a positive culture. Seven of 10 patients with no history of trauma were infected with *M marinum* (6 skin biopsies; 1 joint fluid). There was no statistical association between trauma and culture result (Fisher's exact test, P=0.603). Four patients had been exposed to fish or a fish tank: two were fishermen and two kept fish. Two were culture-positive. There was no statistical association between contact with fish and culture result (Fisher's exact test, P=0.219).

In the three patients with MAI infection, one male patient developed a left knee lesion that persisted for 3 years after trauma. The organism was sensitive to clarithromycin, ethambutol, ciprofloxacin, rifampicin, and amikacin. The lesion resolved after 1 year of minocycline (100 mg twice a day). Two female patients were immunocompromised. One was an in-patient with stage 4B peripheral T-cell lymphoma. She was lost to follow-up after biopsy. The other was receiving methotrexate for myositis and developed a left index finger lesion that persisted for 6 months. She was

Table 1. Atypical mycobacterial infection of the skin

	Mycobacterium marinum	*Mycobacterium avium-intracellulare*	*Mycobacterium chelonae*	Unclassified	Atypical mycobacterial infection
No. of cases	17 (51.5%)	3 (9.1%)	2 (6.1%)	11 (33.3%)	33
Ethnic	16 Chinese; 1 Nepalese	3 Chinese	2 Chinese	11 Chinese	32 Chinese; 1 Nepalese
Male:female	1.83:1	1:2	0:2	1:1.75	1.36:1
Median age (range) [years]	44 (21-75)	44 (33-68)	67 (66-68)	48 (24-71)	48 (21-75)
Median duration of lesion (range)	12 m (10 d-10 y)*	21 m (6 m-3 y)*	6.5 m (1 m-1 y)	12 m (1 m-3 y)	12 m (10 d-10 y)
Site of infection					
Upper limb	16 (94.1%), with hands/fingers in 11 (64.7%)	1 (33.3%) with hands/fingers infected	0	6 (54.5%), with hands/fingers in 4 (36.4%)	23 (69.7%), with hands/fingers in 16 (48.5%)
Lower limb	Knee (n=1, 6%)	1 (33.3%)	1 (50%)	4 (36.4%)	7 (21.2%)
Others	-	Face/neck (n=1, 33.3%)	Abdomen/thigh (n=1, 50%)	Buttock (n=1, 9.1%)	Buttock (n=1, 3.0%); abdomen/thigh (n=1, 3.0%); face/neck (n=1, 3.0%)
Morphology					
Plaque	12 (70.6%)	3 (100%)	0	6 (54.5%)*	21 (63.6%)*
Subcutaneous nodules	0	0	1 (50%)	0	1 (3.0%)
Papulonodules/nodules	3 (17.6%)	0	0	2 (18.2%)	5 (15.2%)
Ulcer	1 (5.9%)	0	1 (50%)	2 (18.2%)	4 (12.1%)
Scar	1 (5.9%)	0	0	0	1 (3.0%)
Sporotrichoid spread	2	0	0	1	3
Immunocompromised	0	2	1	1	4
Trauma history	7 (41.2%)	1 (33.3%)	1 (50%)	6 (54.5%)	15 (45.5%)
Exposure to fish/fish tank	4	0	0	0	4
Acid-fast bacilli detected					
In histology specimen	3	2	1	0	6 (18.2%)
In crushed smear	0/12	0/2	0/2	0/7	0/23
With tissue culture	12 skin biopsies, 1 joint fluid (76.5%)	3 skin biopsies (100%)	1 skin biopsy (also blood culture), 1 ulcer swab (100%)	0	18 (54.5%)
Mean duration of treatment (range) [weeks]	19.6 (8-36)	53 (52-54)	52 (52)	20.5 (8-32)	24 (8-54)
Outcome					
Healed	9	2	2	7	20
Improved	7	0	0	4	11
No improvement	1	0	0	0	1
Defaulted without treatment	0	1	0	0	1

* Data were missing in one case

Table 2. Treatments for patients with atypical mycobacterial infection of the skin

Treatment	No. of patients			
	Mycobacterium marinum, n=17	*Mycobacterium avium-intracellulare*, n=2	*Mycobacterium chelonae*, n=2	Unclassified, n=11
Oral tetracycline only (n=24)				
Doxycycline	4	-	-	-
Minocycline	9	1	-	9
Doxycycline/tetracycline	-	-	-	1
Anti-tuberculosis drugs* initially but switched to minocycline (n=2)	2	-	-	-
Antibiotics (n=6)				
Cotrimoxazole-trimethoprim	1†	-	-	1
Anti-tuberculosis drugs (HRE)	-	-	1	-
Anti-tuberculosis drugs (HRZ) + minocycline	1	-	-	-
Clarithromycin + levofloxacin + ethambutol	-	1	-	-
Amikacin + ciprofloxacin + clarithromycin	-	-	1	-

* Anti-tuberculosis drugs (isoniazid [H] + rifampicin [R] + pyrazinamide [Z]: HRZ + ethambutol [E] → RE + clarithromycin)
† This patient failed to respond

prescribed anti-TB therapy (HREZ) by a chest physician and developed drug-induced hepatitis 2 weeks later. Treatment was switched to clarithromycin 500 mg, levofloxacin 500 mg, and ethambutol 1 g daily and

continued for 1 year. The lesion resolved despite in-vitro resistance to rifampicin, clarithromycin, and ethambutol.

One of the two patients with *M chelonae* infection was prescribed steroids and anti-TB therapy (HR) for steroid-dependent asthma and pulmonary tuberculosis. She was hospitalised for systemic *M chelonae* infection under the care of physicians. She presented with multiple subcutaneous nodular lesions on her abdomen and thighs. The organism isolated from her blood and skin biopsy was sensitive to clarithromycin, amikacin, and kanamycin but resistant to ofloxacin. She was treated with intravenous amikacin, oral ciprofloxacin, and clarithromycin. Amikacin had to be stopped because of nephrotoxicity. Ciprofloxacin and clarithromycin were continued for a year and the infection was cured. The other patient presented with multiple ulcers on her lower limbs for 1 year after trauma. An acid-fast bacilli (AFB) was seen in the histology but the organism was isolated from the ulcer swab and not the biopsy. It was susceptible to kanamycin, amikacin, and imipenem. She was prescribed anti-TB drugs (HRE) for a year by a chest physician and the ulcers healed.

All patients in the unclassified group responded well to antimicrobial treatment (9 minocycline, 1 doxycycline/tetracycline, 1 cotrimoxazole-trimethoprim). One patient had dermatomyositis and was taking steroids and immunosuppressants. One patient developed transient mild liver impairment on minocycline.

Discussion

Atypical mycobacterial infection of the skin is caused by a group of non-tuberculous mycobacterial organisms. *Mycobacterium marinum* is the most common and causes cutaneous infection in immunocompetent individuals. It was first isolated in 1926[1] but the first human skin infection was not reported until 1951.[2] Other well-reported pathogens include MAI, *Mycobacterium ulcerans*, *M chelonae*, and *Mycobacterium fortuitum*. The route of infection is mainly via inoculation or trauma. *Mycobacterium chelonae* and *M fortuitum* are associated with injection and occur more often in immunocompromised individuals. Immunosuppression is associated with more florid and disseminated disease.

Atypical mycobacterial cutaneous infection is rare in Hong Kong: only 33 (0.0096%) cases were diagnosed out of 345 394 new cases in 10 years. This is comparable with the results of a 10-year survey in Thailand.[3] The disease pattern is also comparable with other reports,[3,4] in which *M marinum* accounts for over 50% of AM infections. The number of *M marinum* infections reported varies greatly[3-9]—from two cases over 8 years[5] to 63 cases over 3 years.[8] Most surveys have been confined to *M marinum*,[3,6-9] and include only culture-confirmed cases.[3-5,7-9] A report from Singapore[6] identified 38 cases over 3 years although the organism was isolated from only one patient. The diagnosis was made principally on clinical and histological grounds. The number of patients included depends on the diagnostic or inclusion criteria. We included patients with a compatible clinical picture, histology, and response to appropriate antimicrobial therapy with or without positive culture. Polymerase chain reaction (PCR) for non-tuberculous mycobacteria is not available in our service.

In patients with *M marinum*, 76.5% were culture-positive, comparable with the 70% to 80% positive rate reported in other studies.[10] The overall positive tissue culture was nonetheless 54.5% in this study. This illustrates that culture is specific but not sensitive. The sensitivity of histological examination in detecting AFB was even lower (n=6, 18.2%), again in keeping with other series.[3,6,7] One report had an exceptionally high detection rate (5 of 8).[5] The ability to find AFB depends on the organism load in the specimen and is determined by the type of tissue reaction. More organisms can be found in suppurative lesions but fewer or none in granulomatous infiltration. All our specimens showed granulomatous inflammation and thus account for the low sensitivity. Two *M marinum*, two MAI, and one *M chelonae* were isolated in these six cases; *M chelonae* from an ulcer swab, the other two organisms from skin biopsy and one was culture negative. There was no statistical association between the detection of AFB in the histological examination and culture result (Fisher's exact test, P=0.186). Polymerase chain reaction is now available and is more sensitive and rapid in identifying the causative organism, thus affording the advantages of a more accurate diagnosis with consequent prompt treatment.[5,11] Nonetheless results should be interpreted cautiously with the clinical context since false positives can occur due to the ubiquity of atypical mycobacteria in the environment. Tissue culture remains an important tool for testing antimicrobial susceptibility and detecting resistant strains. Polymerase chain reaction and culture complement each other in the diagnosis of AM infections.

The pattern of clinical morphology of *M marinum* infection is comparable with other series, with plaque being the most common lesion, followed by papulonodules and ulcer.[6] *Mycobacterium chelonae* presents with the classical features of a subcutaneous mass or ulcer. In our patients, the limbs were the most common site of involvement because of previous trauma. The upper limb, especially the hands and fingers, were the predilected sites of infection as reported in other studies.[7,8]

In this study, the incidence of trauma history in *M marinum* infection was lower than that in other studies,[3,4] possibly due to the unreliability of memory recall. Trivial or negligible injury may have been overlooked or forgotten in the long term. We examined the association between trauma history and culture result. In patients with AM infections, 15 reported a history of trauma, eight were culture positive, and seven were negative. Of 18 cases without a trauma history, 10 were culture positive and eight

were negative. No statistical association was found (Chi squared test, P=0.898).

Mycobacterium marinum is found in fresh or salt water, or fish, thus fishermen and those who keep fish are at higher risk. Patients in our series who had contact with fish were fewer compared with other series.[3,6,8] This may be due to underreporting, wearing gloves when cleaning an aquarium or handling fish, or just a smaller fishing industry in Hong Kong. There was no statistical association between trauma history, fish contact, and culture result in *M marinum* infection.

Oral tetracycline, most often minocycline, was prescribed for most patients in this series. Only four patients reported transient mild adverse effects with tetracycline that demonstrated high efficacy and a low side-effect profile. We concur with other reports that tetracycline monotherapy, especially minocycline, is an effective and safe treatment for immunocompetent patients with *M marinum* skin infection.[12,13]

Cotrimoxazole-trimethoprim[3,6] and anti-TB drugs[3,7] are also effective in *M marinum* and MAI infections. *Mycobacterium chelonae* is resistant to traditional anti-TB drugs.[14] Clarithromycin monotherapy has been reported effective in *M chelonae* cutaneous infection in immunocompetent[11] and immunocompromised subjects,[15,16] and has also demonstrated in-vitro activity against other atypical mycobacteria such as MAI and *M marinum*.[17] The clinical response may nonetheless not correlate with in-vitro antimicrobial susceptibility results.[18] In our series, three patients responded to antibiotics to which the organisms showed in-vitro resistance (two MAI) or that were not tested (*M chelonae*). The antimicrobial susceptibility test serves as a guideline for management. Therapeutic agents should be chosen based on the known susceptibility pattern of the specific species and adjusted if necessary according to the clinical response and the final sensitivity results. Local hyperthermic therapy has also been reported useful in treating AM infections.[19,20]

There were limitations to this study. We included only patients with AM skin infections who attended our dermatological clinics. This may not reflect the complete epidemiological picture in Hong Kong since some patients present to other specialties such as orthopaedic surgery. Nonetheless, this study was conducted in the largest dermatological referral centre in Hong Kong, it undoubtedly provides useful information about AM skin infections in the region. In addition, if PCR for non-tuberculous mycobacteria was available, the diagnostic accuracy could be enhanced and more confirmed cases could be identified.

Conclusion

Atypical mycobacterial infection is rare in Hong Kong. *Mycobacterium marinum* infection is the most common because it is occupation- and hobby-related. Diagnosis should be based on clinicohistological features and response to appropriate antimicrobials regardless of culture results. With the availability of new sensitive technology such as PCR, more AM infections can be confidently diagnosed. Nonetheless PCR should be interpreted with caution since false-positive results are possible. We recommend minocycline 100 mg twice a day as the optimum treatment in immunocompetent subjects infected with *M marinum*. It is effective, safe, and convenient when given as monotherapy. Clarithromycin is reported active against most atypical mycobacteria and is useful in *M chelonae* infection. Combination chemotherapy may be a better choice in other AM infections and in immunocompromised subjects. The chosen regimen should be correlated with the common sensitivity test pattern of the specific mycobacterial species and modified if necessary according to the therapeutic response and final sensitivity results.

Acknowledgement

The authors thank Dr Po-tak Chan for his statistical analysis.

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