

## Cutaneous *Mycobacterium haemophilum* Infections in Immunocompromised Patients in a Dermatology Clinic in Singapore

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### Abstract

**Introduction:** *Mycobacterium haemophilum*, a nontuberculous mycobacterium (NTM) that was first described in 1978, is a pathogen that can cause an array of symptoms in immunocompromised patients, predominantly cutaneous. **Clinical Picture:** We report our hospital's experience with the first 3 patients diagnosed with this infection from 1994 to 2002. All were women; one had systemic lupus erythematosus (SLE), one had mycosis fungoides and the last had Sjogren's syndrome with recurrent bacterial infections, although the specific nature of her immunocompromised state has not been defined. All were HIV negative. All 3 women presented with cutaneous lesions – the first with recurrent erythematous plaques on the limbs and back, the second with tender nodules and abscesses on the knees, and the third with papular eruptions on the cheek. **Treatment/Outcome:** All responded to a combination of antibiotics and are presently still undergoing treatment and follow-up. **Conclusion:** Infections caused by *M. haemophilum* occur mainly in immunocompromised patients. They can present with a variety of cutaneous manifestations, which require a high index of suspicion and coordination between the treating physician and the laboratory for diagnosis. Combination antibiotic treatment is recommended, and patients should be followed up after treatment to survey for possible relapse.

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**Key words:** Antibiotics, Immunocompromised, *Mycobacterium haemophilum*

### Introduction

*Mycobacterium haemophilum* is a nontuberculous mycobacterium (NTM) that is increasingly recognised as a cause of cutaneous, joint, or pulmonary infections in immunocompromised patients and lymphadenitis in children. To date, less than 100 patients with this infection have been reported worldwide. Sopolinsky et al<sup>1</sup> first identified and named the organism in 1978 in an Israeli woman with cutaneous ulcerating lesions and Hodgkin's disease. This blood-loving, slow-growing aerobe has a distinctive culture requirement for laboratory isolation, necessitating supplementation of growth media with ferric-containing compounds such as ferric ammonium citrate or hemin.<sup>2</sup> It is a fastidious organism that grows optimally at 30°C to 32°C, as opposed to 37°C, which is the optimum temperature for most other pathogenic mycobacteria.<sup>2</sup> These unique growth requirements mean that standard isolation techniques used for other mycobacteria are inadequate for the isolation of the bacterium, and it is thought that this organism may have been responsible for some cases of

infections in the past in which acid-fast bacilli (AFB) were identified in specimens but cultures were negative.<sup>3</sup> To date, the largest series of patients from a single institution consisted of 23 patients seen over a 10-year period at Memorial Sloan-Kettering Cancer Center in New York.<sup>3</sup> The first case report from Singapore was in a patient with systemic lupus erythematosus (SLE) being treated with mycophenolate mofetil, who presented with recurrent cellulitis of the leg.<sup>4</sup> This particular patient was not seen at the National Skin Centre, a tertiary dermatological referral centre in Singapore, from where we report our experience with the first 3 patients seen at our institution from 1994 to 2002.

### Case Reports

Details of the 3 patients are summarised in Table 1.

#### Case 1

A 59-year-old Chinese woman with a known history of SLE of more than 30 years, with multiple medical problems

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Table 1. Summary of Clinical Features of Patients

Patient details	Significant medical history	Clinical presentation	Histology/Tissue cultures	Treatment and outcome
59-yr-old Chinese female	SLE for 30 years Previous pulmonary TB Ischaemic heart disease Osteoporosis Urinary calculi Glaucoma	1994 – erythematous plaques on thighs and right shin	Granulomas in dermis, AFB seen Cultures negative for MTC, NTM	Clarithromycin Ciprofloxacin started Slow improvement after 6 weeks Rifampicin Isoniazid Ethambutol added Improvement seen after another 6 weeks Total 13 months treatment with clinical resolution
		1998 – erythematous plaques on forearms	Granulomas in dermis, no AFB Cultures negative	Relapse suspected. Same 5-drug regimen for 18 months with clinical resolution
		2001 – erythematous plaque on back	Superficial and deep perivascular lymphocytic inflammation, AFB seen <i>M. haemophilum</i> identified Resistant to rifampicin, ethambutol, ciprofloxacin Sensitive to clofazimine, clarithromycin, rifabutin	Rifabutin Clarithromycin Currently on long-term treatment with clinical improvement
64-yr-old Chinese female	Cutaneous vasculitis requiring systemic steroids and azathioprine Mycosis fungoides with previous PUVA phototherapy, topical nitrogen mustard treatment	2002 – tender nodules on calf and knees 2 months after azathioprine started	Infective panniculitis No AFB seen Tissue cultures negative for MTC, NTM	Started on cotrimoxazole two tablets daily Improved after 6 weeks, then patient defaulted treatment
		Nodules enlarged and tender again	Granulomatous dermatitis, AFB seen <i>M. haemophilum</i> cultured	Clarithromycin Ciprofloxacin given with good improvement after 3 months
42-yr-old Chinese female	Sjogren’s syndrome Crohn’s disease Splenectomy following infarct after <i>Burkholderia cepacia</i> sepsis Allergy to ciprofloxacin	2001 – 1 year history of non-pruritic erythematous papules on right cheek	Superficial and deep perivascular dermatitis No AFB seen Tissue cultures negative for MTC, NTM	Clarithromycin for 3 months with partial improvement
		2002 – lesions persistent	Similar histology, AFB positive this time <i>M. haemophilum</i> cultured	Clarithromycin Doxycycline given for 12 months with clinical resolution within 3 months Plan is for 18 months of treatment

AFB: acid-fast bacilli; MTC: *Mycobacterium tuberculosis* complex; NTM: non-tuberculous mycobacteria

including previous pulmonary tuberculosis (successfully treated with 9-month regimen containing rifampicin, isoniazid and ethambutol), ischaemic heart disease, hypertension, glaucoma, steroid-induced osteoporosis and left renal calculi, was first seen in 1994 for scaly, erythematous plaques on the thighs and right shin. A biopsy from the left thigh revealed granulomas in the

dermis, consisting of giant cells, macrophages with AFB and lymphocytes. Cultures for *M. tuberculosis* and NTM then were negative. The clinical impression was that of a nontuberculous mycobacterial infection, and she was started on clarithromycin 500 mg twice daily and ciprofloxacin 500 mg twice daily. As initial improvement was slow, rifampicin, isoniazid and ethambutol were added to her

drug regimen after 6 weeks. Clinical improvement of the cutaneous lesions was noted after a further 6 weeks. She was treated for a total of 13 months with clinical resolution of the lesions. In February 1998, she presented again with erythematous plaques on the forearms. Biopsy showed granulomas in the dermis, but no AFB was seen. Cultures were negative. A recurrent NTM infection was suspected, and the infectious disease physician restarted her on the same 5-drug regimen to cover both tuberculosis and NTM infection. The patient showed clinical response and completed 18 months of therapy this time. However, 1 year after she had stopped antibiotic therapy, she presented in May 2001 with an erythematous tender plaque on the back. Skin biopsy showed a superficial and deep perivascular lymphocytic inflammation in the dermis, with AFB identified. This time, tissue culture was positive for *M. haemophilum*. Special arrangements were made for sensitivity testing to be done at the National Jewish Center in the United States, and results showed resistance to rifampicin, ethambutol and ciprofloxacin, but the strain was sensitive to clofazimine, rifabutin and clarithromycin. The patient is currently on rifabutin and clarithromycin and followed-up by the infectious disease physician. The current plan is for chronic suppression with this drug regimen. The patient is currently well and has responded to treatment.

#### Case 2

A 64-year-old Chinese woman was first seen at our centre in 1985 for cutaneous vasculitis. Extensive investigations including screens for collagen markers, malignancies and systemic infections, such as hepatitis B and C and tuberculosis were negative. This patient also had a significant history of histologically confirmed mycosis fungoides, diagnosed in 1991. She presented with multiple poikilodermatous patches on the trunk. She was treated with phototherapy (systemic psoralen and ultraviolet A radiation or PUVA) and topical nitrogen mustard with some improvement, but subsequently declined further therapy. Presently, she has declined further therapy for the mycosis fungoides, and remains clinically stable.

The clinical activity of her vasculitis varied but flared badly in 2001, requiring treatment with oral prednisolone 20 mg daily, dapsone 50 mg and colchicine. However, response to treatment was suboptimal and in December 2001, dapsone and colchicine was stopped and azathioprine 100 mg daily was commenced. Two months later, she complained of tender nodules on her left calf and both knees (Fig. 1), with 2 erythematous nodules on the dorsum of her right hand (Fig. 2). Biopsy showed an infective panniculitis, with no evidence of vasculitis. AFB was not seen. Clinical impression was that of an atypical mycobacterial infection. Cultures for *M. tuberculosis* and

NTM were negative. She was started on cotrimoxazole while cultures were pending and there was initial improvement. However, the patient stopped medications on her own after 6 weeks and, within 2 weeks of cessation of therapy, the nodules on her knees began to enlarge and became fluctuant and tender once again. A repeat biopsy showed the presence of AFB this time, and tissue cultures yielded *M. haemophilum*. She was treated with clarithromycin 500 mg twice daily and ciprofloxacin 500 mg twice daily and there was marked clinical improvement within 3 weeks. Presently she is well, with almost complete resolution of the cutaneous lesions after 3 months of therapy. The plan is for her to complete 18 months of therapy.

#### Case 3

A 42-year-old Chinese woman with a 5-year history of Sjogren's syndrome and Crohn's disease presented at the centre with a 1-year history of recurrent non-pruritic erythematous papules on the right cheek (Fig. 3). She had a history of recurrent bacterial infections including documented episodes of salmonella bacteremia and an episode of *Burkholderia cepacia* sepsis that resulted in a splenic infarct and abscess requiring splenectomy. She was followed up closely to exclude an underlying lymphoma, but all investigations were negative. Nitroblue tetrazolium test did not reveal any defects in neutrophil function, and serum immunoglobulins and complement levels were normal. The exact nature of her immunocompromised state has not been elucidated. She had not been on any immunosuppressive therapy when the symptoms developed. An initial biopsy of the lesions on the cheek revealed a superficial and deep perivascular infiltrate of lymphocytes, but no AFB was seen. Cultures for *M. tuberculosis* and NTM were negative. A subsequent repeat biopsy of the right cheek papules showed a dense infiltrate of lymphocytes, plasma cells and exudates of neutrophils present around congested thick-walled vessels. This time, AFB were identified on Ziehl-Neelson stain. Culture was positive for *M. haemophilum*. As the patient was allergic to ciprofloxacin, she was commenced on clarithromycin 500 mg twice daily and doxycycline 100 mg twice daily. She responded well to the treatment, with resolution of the lesions within 3 months, and is currently still undergoing treatment. The plan is to maintain her on antibiotic therapy for at least 18 months.

#### Discussion

Mycobacteria other than *Mycobacterium tuberculosis* were recognised soon after the discovery of the Koch's bacillus. These 'atypical' mycobacteria or nontuberculous mycobacteria (NTM) comprise a diverse group of more than 50 species, including many saprophytes. NTM that



Fig. 1. Case 2 – Tender plaques on both knees.



Fig. 2. Case 2 – Erythematous nodules on dorsum of hand.

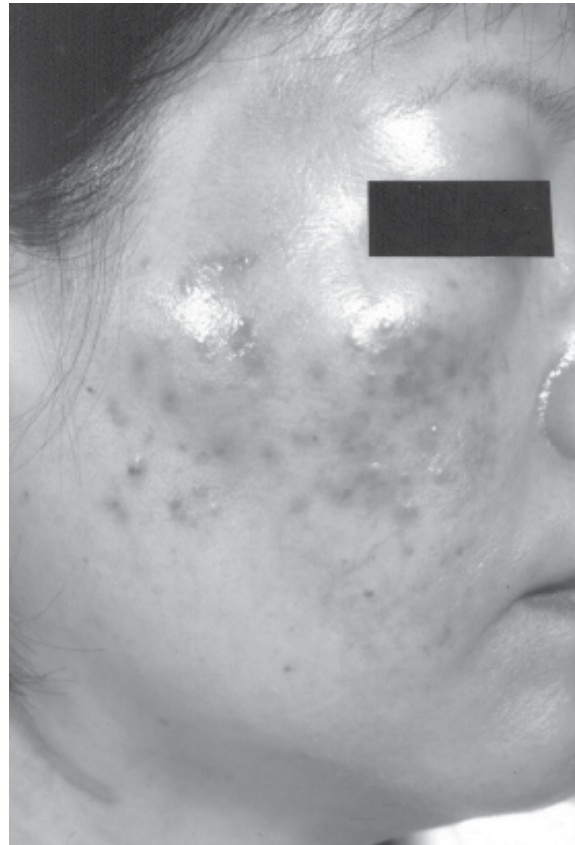


Fig. 3. Case 3 – Erythematous papules on the right cheek.

infect humans are opportunistic pathogens which are found in patients who are immunosuppressed due to AIDS or other causes, and occasionally cause disease in patients with normal immune systems.

*M. haemophilum*, an organism of low virulence, has emerged as a pathogen in patients who are immunocompromised. Its unique growth and temperature requirements are the main reasons it was not discovered earlier. Much is still unknown about this organism; it primarily affects patients who are immunocompromised, but has lately been reported as a cause of a pulmonary nodule in an adult who was apparently immunocompetent<sup>5</sup> and has also been identified as a cause of cervical lymphadenitis in children who are otherwise well.<sup>6</sup> The source and means of acquisition are not known, and many questions about the epidemiology remain unanswered.

Cutaneous and subcutaneous manifestations are the most common clinical presentations reported in the literature. In the largest reported series of patients to date, the clinical manifestations varied from erythematous papules or nodules that become tender and suppurative, to cysts, scaly plaques, or focal panniculitis.<sup>3</sup> The clinical features exhibited by the

patients in our series are similar. It is postulated that the organism's restricted temperature requirements cause a predilection for lesions to grow on relatively cooler areas of the body.<sup>7</sup> Non-cutaneous features of *M. haemophilum* infection include pneumonia,<sup>7</sup> lymphadenitis in children,<sup>8</sup> septic arthritis,<sup>9</sup> and osteomyelitis.<sup>10</sup>

Skin biopsy specimens often reveal AFB, and the most common histopathological feature is that of a mixed granulomatous and suppurative reaction.<sup>11</sup> In this histological reaction pattern, there is a neutrophilic infiltrate with multinucleated giant cells seen. Biopsy specimens of skin lesions may also show granulomatous panniculitis and caseating or noncaseating granulomas. Patients with AIDS may have poorly formed granulomas.<sup>11</sup> It is important to note that characteristic histology may sometimes be lacking if a representative lesion is not sampled. In our patients, the biopsies did not reveal AFB in some of the specimens sampled, even though the clinical suspicion was that of a cutaneous NTM infection. The histology in some of our patients also showed the classical dimorphic inflammatory response, with an infiltrate consisting of both lymphocytes and polymorphonuclear neutrophils. This emphasises the need for repeat biopsies when clinical suspicion is high. Our first patient was immunocompromised due to her underlying SLE as well as immunosuppressive therapy;

the second patient had underlying mycosis fungoides as well as treatment with azathioprine. The cause of our third patient's recurrent bacterial infections has not been fully elucidated as yet.

*M. haemophilum* is a fastidious organism. In our cases, initial cultures were all negative, and *M. haemophilum* was identified only on subsequent sampling. The timely diagnosis of *M. haemophilum* infections requires communication between clinicians and personnel in the microbiology laboratory, and the laboratory should be informed if *M. haemophilum* infection is suspected.

There are presently no standard guidelines on antibiotic treatment of *M. haemophilum* infections. Our patients responded to various combinations of clarithromycin, ciprofloxacin, doxycycline, rifabutin and ethambutol. Based on published data, Saubolle et al reported that *M. haemophilum* is usually susceptible to ciprofloxacin, clarithromycin, rifabutin and rifampicin, and shows variable susceptibility to amikacin, doxycycline, minocycline, cotrimoxazole and cefoxitin, among others.<sup>2</sup> Some authors recommend a 3-drug regimen that contains a macrolide, a rifamycin, and a quinolone.<sup>3</sup> Two of our 3 patients did well with a 2-drug regimen. The first patient was the only one who had antimicrobial sensitivity tests done, and in this case, ciprofloxacin and rifampicin resistance was detected. She was also the most severely immunocompromised patient and had the longest documented period of recurrent infections. It is likely that resistance to ciprofloxacin and rifampicin was acquired in this case. To minimise this, we would recommend at least dual drug therapy. The other 2 patients treated with dual drug therapy were not severely ill, and in view of the potential for drug interactions and allergies, we would prefer to utilise 3 or 4 drugs only in patients who are more ill. The duration of therapy remains unknown. Our first patient is likely to require chronic suppression in view of her multiple documented recurrences and development of resistance. The plan is to treat the other 2 patients for 18 months, followed by close monitoring.

In conclusion, clinicians should be aware of the clinical manifestations caused by this emerging pathogen. The definitive diagnosis is made by cultures, with the microbiology laboratory being informed that this organism is suspected. Timely institution of appropriate antibiotics and close follow-up for clinical response are required.

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