



Comprehensive Approach to Infections in Dermatology



Foreword
Bhushan Kumar

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Dedications

I dedicate this book to my parents, Smt Santosh Rustagi and Sh ML Rustagi for their unconditional love and support, my husband, best friend, and mentor Dr Dinesh Singal for the motivation and belief in me, and to my wonderful children Suvina and Ramit for taking pride in whatever I do in my professional career.

Archana Singal

I would wish to thank my parents, Smt Shanno Devi Grover and Sh Shiv Kumar Grover as well as my parents-in-law, Smt Anita Kubba and Shri Manmohan Kubba for their constant and unflinching support; and my children, Samira and Bhavya for allowing me to work at home. Last but not the least, I wish to thank my husband, Dr Samir Kubba who has been my pillar of strength, favorite punching bag, friend, mentor, and guide, all rolled into one!

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Foreword

It is a great pleasure and privilege to have been asked to write this foreword. This book represents a very substantial and useful contribution in the field of infections in dermatological medicine.

There has been continuing discovery of new pathogens causing skin infections and also the emergence of non-pathogens becoming pathogenic as in patients with HIV/AIDS or in those with continued immune suppression. There has been distressing resurgence of skin infection in certain populations combined with reduced drug susceptibilities or resistance of major pathogens to significant number of antimicrobial agents. All this demands that health workers across the discipline have accurate knowledge and understanding of all these infections. Many will search for and get answers from the internet for many of their queries but the gains from an integrated scientific overview that gives systematically all the knowledge, advances made, and practical applications are many. An objective of this book is to enable generalists and even specialists from clinical and laboratory disciplines to recognize the various clinical presentations and to understand the use of modern investigative methods to identify the pathogens and assess their sensitivity.

To keep currency with a constantly evolving body of knowledge a group of highly distinguished authors, experts in their field representing many disciplines from all over India would probably make "Infections in Dermatology" rank among the best publications on such an important subject. It will help the readers to navigate confidently in the ongoing information explosion.

I am sure the book will be a great source of information and education to all who are involved in the various clinical presentations, diagnosis and treatment of cutaneous infections. Topics of contemporary interest relevant to diagnosis and future therapies are emphasized, adding to the usefulness of the book. There is something for everyone, dermatologist, pathologist, physician, infectious disease specialist and even an interventionist.

Congratulations to Professor Archana Singal and Dr Chander Grover for this great achievement.

Bhushan Kumar

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Preface

Infections continue to contribute significantly to morbidity and mortality worldwide, particularly in the developing world. Despite the global availability of antibiotics, advances in the development of newer agents and dedicated healthcare endeavors to improve sanitation, management of infections remains a daunting task. Given the suitable climatic conditions of tropical countries like India, such as high temperature, humidity and overcrowding, dermatological infections tend to be rampant in regions conducive for their persistence. It is unfortunate that despite the fact that management of skin infections contributes to a large chunk of dermatological, pediatric and general physicians' practice, there is no book dedicated to addressing this issue in detail. Although the World Wide Web provides easy and instant access to unlimited information regarding any medical condition, there cannot be parallel for a handy reference textbook that is readily accessible in the clinic or consulting room, or that can be read at leisure. This book promises to be an anthology of infections and their management from a dermatological perspective.

Infections constitute the bulk of dermatologic practice in most areas. In areas where they are not common, they tend to be "exotic", and thus even more difficult to identify or diagnose. This text aims to be a valuable companion and tool for both the practicing as well as in-training dermatologists. Moreover, since the first contact of a patient with a skin infection is often a general physician or a pediatrician, this text will serve as a ready reckoner and quick reference for such practitioners to manage the infection judiciously at their level or consider timely referral to the dermatologist.

As dermatologists, we commonly encounter all skin infections including bacterial, mycobacterial, viral, fungal, and parasitic. Therefore, the contributors of this book are aptly placed to address the nuances and finer details of these disorders. The contemporary published texts have primarily been authored by Western dermatologists, whose encounter with these infections is relatively rare. The novelty and exclusivity of this textbook stems from its presentation from an Indian perspective, enriched with years of clinical and research experience of Indian authors in dealing with these infections. We have attempted to spawn a comprehensive and illustrated guide to infectious dermatological diseases in India, which will aid in recognition of both common as well as rare manifestations through a prodigious assortment of clinical photographs. The credit for each specially contributed photograph finds mention in the figure legend; for the photographs provided by the author of a chapter, no separate acknowledgment has been provided. An attempt to enhance the readers' retention of concepts and clinical focus, the text has been condensed into key points whenever deemed important.

The book exhaustively covers all important and relevant skin infections: bacterial, mycobacterial (including tuberculosis and leprosy), fungal, viral, protozoal and parasitic infestations, and sexually transmitted infections (STIs). For each of these, well-defined sections on epidemiology, clinical features, differential diagnosis and management approach have been included. Description of clinical presentation to the detail and exhaustive differential diagnoses ensure an in-depth comprehension of each infection. Details of diagnostic and/or therapeutic procedures in-vogue have been meticulously integrated. A step-by-step approach to bedside diagnostic procedures makes this book a quick reference guide. Preventive measures including vaccination have also been outlined wherever applicable. The book seeks to provide a critical, yet practical approach to treatment. Obsolete remedies have been omitted. Therapeutic management discusses the most effective and safest remedies that have been time-tested and also backed by the extant high-quality evidence. Latest therapeutic guidelines for specific infections have been dealt with in relevant chapters.

The liberal use of tables, graphics, and other forms of illustrations make this book a reader-friendly, must-have manual, not only for a dermatologist but for pediatricians, physicians and general practitioners alike. While compiling a text of this magnitude, following clear-cut demarcations in various chapters often becomes a challenging task. We have encouraged our contributors to make each chapter readable as an independent entity.

The listing of references is quite detailed, covering the latest information in literature at the time of going to press. An effort to omit old references that are mainly of historical interest has been made, except where absolutely necessary.

A whole-hearted and sincere attempt has been made to eliminate any errors in the text; however, if present, the responsibility lies with the editors and authors. We welcome reader's criticism and suggestions, which will help us improve and refine subsequent editions of the book. Please feel free to communicate with us and give your suggestions.

Archana Singal
Chander Grover

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We are grateful to all the authors and co-authors for sparing their valuable time and sharing their expertise in dealing with the various dermatological infections. They have put in their best efforts in compiling an up-to-date educational material with excellent clinical photographs.

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Nontuberculous Mycobacterial Infections

Namrata Chhabra, Kabir Sardana

ABSTRACT

Cutaneous infections caused by nontuberculous mycobacteria (NTM) that used to be considered unusual have become frequent nowadays, particularly in immunocompromised individuals. Based on the growth rate of these organisms in culture, these are classified into rapid growing and slow growing mycobacteria. *M. fortuitum*, *M. chelonae* among the rapidly growing mycobacteria and *M. marinum*, *M. ulcerans* among slow growing mycobacteria, commonly cause cutaneous infections. It is important for a dermatologist to know the varied clinical spectrum and laboratory findings of NTM, since the diagnosis can be easily missed unless there is strong clinical suspicion supported by laboratory confirmation. In this chapter, we have tried to elucidate important NTM causing skin and soft tissue infection, their diagnosis and management.

■ INTRODUCTION

Pinnars first isolated nontuberculous (atypical) mycobacteria in 1931. He also observed that these organisms were different from *M. tuberculosis* in being nonvirulent in the guinea pig model, and poorly responsive to antituberculous therapy. Their importance as human pathogens was appreciated way back in the 1950s. However, infections with nontuberculous mycobacteria (NTM) have become a growing clinical concern over the past two decades due to their association with acquired immune deficiency syndrome (AIDS), recognition of the increasing incidence of NTM infections among patients without AIDS and the multidrug-resistant nature of some of the organisms.

Nontuberculous mycobacteria is composed of species other than the *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. africanum*, *M. bovis*) and *M. leprae*.

Previously these were known as “atypical mycobacteria” or “mycobacteria other than *M. tuberculosis* (MOTT)” or “environmental bacterioses”. Till date over 160 different species and subspecies of mycobacteria have been included in the “List of Prokaryotic Names with Standing in Nomenclature” but the total number of mycobacterial species is constantly rising due to improved microbiological techniques for isolating NTM from clinical specimens and, more importantly, due to advances in molecular techniques for defining new species.¹

■ EPIDEMIOLOGY

Defining the epidemiology of NTM is challenging for several reasons.² First, humans are thought to contract the infection directly from environmental sources. There has been no published report of direct or indirect

patient-to-patient respiratory spread of NTM with the sole exception of an outbreak of respiratory *M. abscessus* disease in inpatient population with cystic fibrosis.³ Second, exposure to the omnipresent NTM is likely extremely common. Third, NTM that colonize the respiratory tract can be isolated in respiratory samples in the absence of disease. Lastly, in most regions of the world, NTM disease is not reportable to public health authorities; therefore, epidemiological and surveillance data are not readily available. Despite obstacles in the study of the epidemiology of pulmonary NTM, available evidence suggests that the prevalence of pulmonary NTM disease has increased dramatically globally over the past three decades.²

Infections with NTM are not limited to immunocompromised patients. Before AIDS-associated disseminated *Mycobacterium avium* complex (MAC) disease, the most common presentation of atypical mycobacteria in the developed world was lung infection in relatively immunocompetent individuals with chronic lung diseases.

The distribution of NTM species worldwide varies by geographic region.⁴ In a modern registry of 20,182 patients, from 30 countries across 6 continents, *M. avium* predominated in North and South America and Europe, while *M. intracellulare* was most frequently isolated in South Africa and Australia. *M. kansasii* is relatively more common in the middle USA, Brazil, England and Wales, Eastern Europe and the metropolitan centers of Paris, London and Tokyo, and the Johannesburg region of South Africa; *M. xenopi* is more common in the northern USA, Ontario-Canada, UK, and some European countries including Hungary, Croatia, and Northern Italy; *M. mageritense* is common in UK and northern Europe but is uncommon in the USA and *M. simiae* is more common in arid regions of the south-western USA, Cuba, and Israel.⁴ Finally, RGM accounting for 10–20% of all NTM isolates worldwide in 2008, proved more prevalent in East Asia.⁴ *M. ulcerans* is limited primarily to warmer climates in Africa, Central America, Southeast Asia, and Australia.

The most common NTM that cause disease in the United States are MAC, *M. fortuitum* complex, and *M. kansasii*.⁵ In the United States, the southern coastal saltwater areas of the Gulf of Mexico and Atlantic Ocean are areas of common infection by *M. marinum*.

Nontuberculous mycobacteria have been observed to be an important cause of morbidity and mortality in Western countries but there is very little data from India. Isolation of NTM from the environment reveals the

epidemiological distribution in a particular region, which is useful in interpreting the efficacy of Bacille Calmette-Guerin (BCG) or to know the species that might lead to disease in AIDS patients in that area.

Paramasivan et al. (1985)⁶ in their pioneering study from a district of Madras state, to test the efficacy of BCG vaccination in prevention of tuberculosis, reported *Mycobacterium avium-intracellulare* (MAI) to be the most frequently isolated species (22.6% of all NTM) followed by *M. terrae* (12.5%) and *M. scrofulaceum* (10.5%). Later in 1994, Kamala et al.⁷ in a study from Madras demonstrated that MAI and *M. scrofulaceum* were present in water and dust and could be isolated from the sputum samples of individuals in that area. *M. fortuitum* was shown to be present in the soil.

Much later in 2004, a similar study from JALMA (Agra, India) has demonstrated among many mycobacteria, the presence of *M. avium*, *M. kansasii*, *M. terrae*, *M. fortuitum* and *M. chelonae* in water and *M. avium*, *M. terrae* and *M. chelonae* in soil.⁸ More recently, in a study from Sewagram, Wardha (Maharashtra, 2009),⁹ NTM were isolated from environment (soil and water) of the AIDS patients with disseminated NTM disease to know the prevalence of environmental NTM species and their correlation with clinical isolates from patients of the same area. A total of 26 NTM isolates belonging to seven different species could be identified. *M. avium* was the only species isolated from both clinical and environmental samples of the same patient.

■ ETIOLOGICAL AGENT AND PATHOGENESIS

Nontuberculous mycobacteria are found in water, wet soil, house dust, dairy products, cold-blooded animals, vegetation and human faeces. The organism is transmitted by inhalation, ingestion or percutaneous penetration, which can result in pulmonary, lymph node or skin disease. The infective agent, route and degree of exposure, and the immune status of the host are important decisive factors that determine the outcome of infection. Traditionally, NTM have been categorized into different groups based on characteristic colony morphology, growth rate, and pigmentation (Runyon system of classification). This system has become less useful as we focus on more rapid molecular systems of diagnostics. In this chapter, we will focus on NTM causing skin and soft tissue infections (Table 1).

TABLE 1: Nontuberculous mycobacteria causing skin and soft tissue infections

	Species
Rapid growers	<i>M. fortuitum</i> group (<i>M. fortuitum</i> , <i>M. peregrinum</i> , the third biovariant complex including <i>M. septicum</i> , <i>M. mageritense</i> , <i>M. porcinum</i> , <i>M. houstonense</i> , <i>M. bonicki</i> , <i>M. brisbanense</i> , and <i>M. neworleansense</i>)
	<i>M. chelonae</i> /abscessus group (<i>M. chelonae</i> , <i>M. abscessus</i> , <i>M. immunogenum</i> , <i>M. bolletii</i> and <i>M. massiliense</i>)
	<i>M. smegmatis</i> group (<i>M. smegmatis</i> , <i>M. goodii</i> and <i>M. wolinskyi</i>)
Slow growers	<i>M. marinum</i>
	<i>M. ulcerans</i>
	<i>M. kansasii</i>
	<i>M. avium</i> complex (<i>M. avium</i> and <i>M. intracellulare</i> , and less commonly, <i>M. chimaera</i> and <i>M. colombiense</i>)
	<i>M. hemophilum</i>
	<i>M. scrofulaceum</i>
	<i>M. szulgai</i>

TABLE 2: Important nontuberculous mycobacteria and their common cutaneous presentation

Species	Cutaneous findings
<i>M. marinum</i>	Localized nodules (fish tank granuloma) Solitary verrucous/ulcerated lesion sporotrichoid lesion
<i>M. ulcerans</i>	Localized and extensively destructive, necrotizing ulcers in immunocompetent hosts (Buruli ulcer)
<i>M. avium</i> complex	Variable skin lesions (multiple ulcers, nodules, ulcerated nodules, abscesses, painless nodules and plaques)
<i>M. hemophilum</i>	Skin and subcutaneous infections in solid organ transplant recipients and human immunodeficiency virus patients
<i>M. fortuitum</i> group	Multiple erythematous subcutaneous nodules, in a sporotrichoid pattern on the distal limbs following accidental trauma, surgery, cosmetic procedures, pedicure (folliculitis), implant surgery
<i>M. chelonae</i> /abscessus group	Infection following surgery, implant surgery, cosmetic and related procedures (e.g., liposuction, tattooing, acupuncture, mesotherapy), spa cleaning

■ CLINICAL DISEASE

There are four main types of disease caused by NTM:

1. Local lesions following traumatic inoculation of acid-fast bacilli (AFB) into the skin or deeper tissues
2. Localized lymph node involvement
3. Pulmonary infections resembling tuberculosis
4. Disseminated disease.

Cervical lymphadenitis is the most common presentation in immunocompetent children.

■ LOCALIZED CUTANEOUS AND SOFT TISSUE INFECTIONS

The commonest NTM that cause cutaneous infection are members of the *M. fortuitum* complex, *M. marinum* and *M. ulcerans*. More than 90% of cutaneous infections are caused by the RGM (*M. fortuitum*, *M. chelonae*, and *M. abscessus*).

Three types of cutaneous lesions caused by NTM are recognized:

- A solitary granulomatous verrucous papule that may occasionally ulcerate and show purulent discharge
- Ascending lymphatic sporotrichoid lesions
- Rare cutaneous disseminated lesions, which occur frequently in immunosuppressed patients.

The common cutaneous presentations of NTM have been enumerated in Table 2.

Warty skin lesions may follow the inoculation of NTM into superficial abrasions. Such infections are usually caused by *M. marinum*. Occasionally other species such as *M. kansasii* and *M. chelonae* cause similar lesions.

M. ulcerans infection leads to necrosis of subdermal tissue and secondary skin ulceration.

Post-injection mycobacterial abscesses are usually due to the rapidly growing species *M. chelonae* and *M. fortuitum*. Occurrence of number of cases of corneal infection by rapid-growing species have been reported, presumably as a result of direct implantation.

M. hemophilum is a rare cause of nodular or ulcerative skin lesions and all reported infections have occurred in immunosuppressed individuals, particularly recipients of renal transplants.

■ ENVIRONMENTAL SOURCE OF NTM

Nontuberculous mycobacteria are ubiquitous in the environment and are frequently isolated from soil or water. Isolates have also been recovered from samples of animals, plant material, and birds. A few species that are known to cause disease, such as *M. hemophilum* and *M. ulcerans*, have rarely been recovered from the environment.

Although an association with an environmental source may be present, a direct link to the environment has not been proven except for healthcare-associated disease and pseudo-outbreak, and no evidence of person-to-person spread has been reported, presumably due to the lower virulence of environmental species. Tap water is considered the major reservoir for most common human NTM pathogens and as such is of increasing public health interest. Species from tap water include *M. gordonae*, *M. kansasii*, *M. xenopi*, *M. simiae*, *MAC*, and *RGM*, especially *M. mucogenicus*.¹⁰ Biofilms, which are the filmy layers at the solid and liquid interface, are recognized as a source of growth and possibly a mode of transmission for mycobacteria.¹¹ Moreover, biofilms may serve to render mycobacteria less susceptible to disinfectants and antimicrobial therapy. Biofilms appear to be present in almost all collection and piping systems, so mycobacteria may often be recovered from these sites. The persistence of pathogenic NTM in water and biofilms has important implications in the epidemiology of infections related to water.

■ SLOWLY GROWING MYCOBACTERIA

This group includes species of mycobacteria that require more than 7 days to reach mature growth. Some species may also require nutritional supplementation of routine mycobacterial media. Cultivation of this species is difficult, as it requires up to several months to grow, so molecular detection and identification are currently more optimal than culture techniques. Organisms that require special nutritional supplements include *M. hemophilum*, which requires hemin for growth (hence its name), and *M. genavense*, which requires mycobactin J and prolonged incubation in broth culture. Most of these slowly growing mycobacteria grow best at 35–37°C, with the exception of *M. hemophilum*, which prefers lower temperatures (28–30°C), and *M. xenopi*, which grows well at 42°C.

M. marinum

M. marinum causes an infection historically recognized as “swimming pool” or “fish tank” granuloma. This common name is derived from the epidemiologic niche of the organism, i.e., fresh, salt and brackish water. The incubation period is typically 2–3 weeks. Occasionally, the incubation period can be as long as 9 months, leading to delay in diagnosis, as important clinical clues in the patient’s history may be overlooked.

Epidemiology

Occupational or recreational exposure to salt or fresh water occurs in the majority of cases. Swimming pools seem to be at risk only when non-chlorinated. Most patients are clinically healthy with a previous local hand injury that becomes infected while cleaning a fish tank, or patients may sustain scratches or puncture wounds from saltwater fish, shrimp, fins, and so forth contaminated with *M. marinum*.

Clinical Findings

The lesions are most often a single small violaceous papule usually involving upper extremity that may progress to shallow, crusty ulcerations and scar formation. Lesions are painful in less than one half of cases.¹² However, multiple ascending lesions resembling sporotrichosis (sporotrichoid disease) can occasionally occur (Fig.1). Among NTMs, *M. marinum* is the most common etiology of this pattern. Regional lymph nodes are, as a rule, not involved and lymphadenopathy is rare and typically mild, and systemic symptoms are unusual. The infection resolves spontaneously in some cases, although complete resolution may take up to 2 years.

Differential Diagnosis

The differential diagnosis is summarized in Box 1.

Box 1: Differential diagnosis

Solitary verrucous/ulcerated lesion

- *Verruca vulgaris*
- Sporotrichosis
- Blastomycosis
- Erysipeloid
- Tularemia
- Tuberculosis verrucosa cutis
- Nocardiosis
- Leishmaniasis
- Syphilis, yaws
- Iododerma
- Bromoderma
- Malignant skin tumors

Sporotrichoid lesion

- Sporotrichosis
- Staphylococcal or group A streptococcal lymphangitis
- Tularemia
- Leishmaniasis
- Nocardiosis
- Actinomycosis
- Anthrax



Figs 1 A–D: Multiple lesions of *M. marinum* infection arranged in an ascending fashion on the right upper limb of a patient

Diagnosis

A history of contact with water, fish tanks, aquaria, etc. combined with granulomatous histology is suggestive of the diagnosis.

Direct microscopy of smears of exudate or pus: AFB can be demonstrated in some cases.

Skin biopsy

Older lesions—more typical tuberculoid architecture is developed with epithelioid cells and langhans giant cells. Intracellular AFB, longer and broader than tubercle bacilli, are detectable in approximately 10% of cases only.

Culture

Positive in 70–80% of cases. *M. marinum* grows at 32°C in 2–4 weeks. Early lesions yield numerous colonies.

Species-specific monoclonal antibody against 56-kDa *M. marinum* antigens may have potential use in rapid culture identification. *M. marinum* infection has also been identified using PCR-reverse cross-blot hybridization assay with species-specific gene probes. This may lead to more rapid diagnosis, but cultures will still be necessary to assess the antibiotic sensitivity of different strains.

Treatment

Treatment options have been enumerated in Table 3. A retrospective study of 16 cases that were culture-positive for *M. marinum* showed that clarithromycin, both on *in vitro* testing and on clinical response, was the drug of choice.¹³ Authors also pointed out that clarithromycin seems to be superior to other drugs due to lack of significant side effects. A reasonable treatment approach would be to treat with two active agents (in the largest

TABLE 3: Treatment of nontuberculous mycobacterial infections

Species	Medical therapy	Other measures
<i>M. ulcerans</i>	Rifampin-streptomycin (or rifampin-clarithromycin) for at least 4 weeks, trimethoprim-sulfamethoxazole 80/400 mg twice daily, nitrogen oxide-releasing topical creams	Surgical excision; local heat (40°C); hyperbaric oxygen
<i>M. marinum</i>	Clarithromycin, minocycline/doxycycline, rifampin, ethambutol, trimethoprim-sulfamethoxazole	Surgical debridement
<i>M. fortuitum</i> complex	Amikacin 15 mg/kg/day in divided doses, doxycycline, minocycline, ciprofloxacin, ofloxacin, trimethoprim-sulfamethoxazole and ceftioxin, at least two agents for serious infections, clarithromycin	Surgical debridement
<i>M. kansasii</i>	Rifabutin + isoniazid + ethambutol ± pyridoxine, azithromycin, moxifloxacin, sulfamethoxazole, clarithromycin	Surgical excision
<i>M. avium</i> complex	Clarithromycin or azithromycin + ethambutol ± rifampin or rifabutin, clofazimine, ciprofloxacin	Surgical excision
<i>M. hemophilum</i>	Clarithromycin + rifampin ± ciprofloxacin or amikacin	Surgical excision

available study, this was most commonly clarithromycin and rifampicin),¹⁴ continued for 1–2 months after resolution of symptoms, typically 3–4 months in total.

M. ulcerans (Buruli Ulcer, Bairnsdale Ulcer)

It is believed to be the third most common mycobacterial infection after tuberculosis and leprosy. The major virulence factor is a lipid toxin, mycolactone, which causes necrosis of fat and subcutaneous tissue.

Epidemiology

This is usually seen in wetlands in tropical countries and northern areas of Australia. Exposure to riverine areas (swamps, lakes, slow-flowing rivers, etc.) that have a humid hot climate is thought to play a role, although the exact mode of transmission is not known. It is believed to be mainly acquired from its aquatic niches following introduction of bacillus into the skin by spiky vegetation. HIV infection does not seem to predispose to *M. ulcerans*.

Clinical Findings

About 70% of patients are children below 15 years of age. The lesions usually begin as single, asymptomatic, firm, mobile subcutaneous nodule commonly involving extremities (lower > upper), which become fluctuant and ulcerate (Fig. 2) after 1 or 2 months. The floor of the ulcer is formed of necrotic fat, and there may be a clear mucoid discharge. Ulcers may heal spontaneously with scarring or may spread to involve large areas of skin or even underlying soft tissue and bone.



Fig. 2: Single ulcerative subcutaneous nodular lesion of *M. ulcerans*

Differential Diagnosis

The Differential diagnosis is summarized in Box 2.

Box 2: Differential diagnosis

Initial phase

- Panniculitis
- Nodular fasciitis
- Cysts
- Foreign body granuloma and other granulomatous diseases

Ulcerative phase

- Fungal infections
- Pyoderma gangrenosum
- Suppurative panniculitis

Diagnosis

Ziehl-Neelsen-stained-smears of exudate or pus

Bacteriological examination of smears from swabs taken from under the rim of the ulcer, or of curettage or biopsy specimens, will reveal clumps of AFB.

Culture

Visible growth often requires 6–8 weeks of incubation at 32°C optimally on routine mycobacteriological media.

Histopathology

Characteristically, there is an extensive involvement of the subcutaneous fat as septal panniculitis. There is poor inflammatory response despite clusters of extracellular bacilli. Ulceration is surrounded by granulation tissue with giant cells but no caseation necrosis or tubercles. AFBs are always demonstrable.

IS2404 PCR, which can be performed directly from ulcer swabs, approaches 100% sensitivity and specificity.¹⁵

Treatment

Treatment options have been given in Table 3. Recent studies suggest that clarithromycin is highly active in vitro against *M. ulcerans*.

M. kansasii

M. kansasii is a slow-growing, photochromogenic bacterium that grows optimally at 37°C. Tap water is the major reservoir of infection for this organism. It is found worldwide, but is particularly prevalent in temperate zones, such as the USA, the UK, northern France and Belgium.

Classically, *M. kansasii* infection produces a granulomatous pulmonary infection in middle-aged men with underlying lung disease. It most commonly affects persons exposed to contaminated water, particularly after local trauma. Most patients who present with very localized, primary cutaneous infection are immunocompetent, whereas the majority of persons with disseminated skin lesions or pulmonary infection are immunocompromised. Skin lesions associated with disseminated *M. kansasii* have increased since the onset of the AIDS epidemic, and *M. kansasii* is the second most frequent cause of disseminated mycobacteriosis in AIDS patients after *MAC*.

As a primary cutaneous disease, *M. kansasii* produces a variety of lesions, usually confined to a distal extremity. Sporotrichoid nodules, verrucous papules, papulopustules with necrotic centres, erythematous plaques, cellulitis, rhinophyma, single and multiple abscesses have all been reported. Papulonecrotic tuberculid skin lesions have been reported in one patient.

The choice of treatment should be determined by in vitro sensitivity. Current recommended guidelines for treatment of *M. kansasii* extrapulmonary disease are rifampicin and ethambutol for 9 months, with continuation of therapy for a total of 15–24 months in those patients who are immunocompromised.

M. hemophilum

M. hemophilum causes cutaneous infections (primarily of the extremities) in immunosuppressed patients, especially in the setting of organ transplantation, long-term high-dose steroid use, or HIV.

M. hemophilum has a special growth requirement for hemin or iron and may present some diagnostic difficulties if iron- or hemin-supplemented media and lower temperatures (incubation at 28–30°C) are not used. In contrast to other NTM, specimens from the lesion are usually AFB smear positive and culture negative. So a presumptive diagnosis is often based on typical caseating granulomas and a negative culture for *M. tuberculosis* in the common clinical setting.

■ OTHER SLOW GROWERS

M. scrofulaceum, *M. szulgai* and *M. avium* are also of dermatological interest.

M. scrofulaceum

Historically, *M. scrofulaceum* has been associated with cervical lymphadenitis in young children, but in recent years the frequency of this infection has declined and there are now more cases caused by *MAC*. Submandibular and submaxillary nodes are usually involved; the disease is often unilateral with few constitutional symptoms, and can resolve spontaneously.

Skin abscesses due to *M. scrofulaceum* infection, chronic ulcerative and nodular skin lesions have also been reported.

M. szulgai

Infection is principally pulmonary, but infections have also involved bursae, tendon sheaths, bones, lymph nodes and skin. Skin lesions include diffuse cellulitis, nodules and sinuses, and multiple inflammatory skin lesions. Intralesional or systemic steroids has been found to be a risk factor for development of skin lesions in most of the patients.

M. avium complex or *M. avium*-intracellulare

The MAC comprises *M. avium* and *M. intracellulare*; these are closely related organisms that cannot be differentiated by standard laboratory methods.

Incidence

Disseminated infections with MAC were rare before the emergence of the AIDS epidemic, but their incidence is now rising sharply. MAC is one of the most common opportunistic bacterial infections in patients with AIDS.

Epidemiology

These organisms are ubiquitous saprophytes, found in tap water, soil, dairy products, animals and house dust. It may be transmitted via inhalation into the lungs, or via water and food. Cutaneous lesions are rare and may be primary after a traumatic inoculation, or secondary to disseminated infection.

Clinical Findings

Skin lesions are of variable appearance and include multiple ulcers, nodules, ulcerated nodules, abscesses, painless nodules and plaques resembling lepromatous leprosy or lupus vulgaris, prurigo nodularis. Sporotrichoid spread and lichen scrofulosorum-like lesions have also been reported.

Differential Diagnosis

The differential diagnosis includes: lepromatous leprosy, lupus vulgaris, prurigo nodularis.

Diagnosis

Tissue-staining for AFB is often negative.

Culture

They are slow-growing organisms with optimal growth at 37°C.

Histopathology

Intracellular AFB without necrosis is present. Spindle cell transformation of macrophages occur forming histoid like lesion, resembling histological features of lepromatous leprosy.

Treatment

The treatment has been discussed in Table 3.

■ RAPIDLY GROWING MYCOBACTERIA^{1,16}

The species of RGM capable of producing disease in humans are the *M. fortuitum* group, the *M. chelonae/abscessus* group, and the *M. smegmatis* group.

The *M. fortuitum* group includes *M. fortuitum* and *M. peregrinum* and the taxon known as the “unnamed third biovariant complex”.

M. chelonae and *M. abscessus*, along with the newly recognized *M. immunogenum*, are members of the group known collectively as the *M. chelonae/abscessus* group. PCR-based methods for identifying the hsp65 gene developed recently can reliably differentiate between members of this group, which are identical on conventional 16S rDNA sequencing.

The *M. smegmatis* group contains *M. smegmatis* and two newly described species, *M. goodii* and *M. wolinskyi*. They cause skin, soft tissue, bone and pulmonary infection, as well as disseminated disease.

M. fortuitum, *M. chelonae* and *M. abscessus*

These organisms are widely distributed in the environment in soil, dust and water and may also be commensal organisms of human skin. They are extremely hardy; members of the *M. fortuitum* group and *M. smegmatis* group can grow at 45°C, and the *M. chelonae/abscessus* group and *M. mucogenicum* resist the activity of organo-mercurials, chlorine, 2% concentrations of formaldehyde and other commonly used disinfectants. Infection typically occurs following trauma, surgery, contact with contaminated medical instruments, implants, tattooing, and post-injection.

Epidemiology

These organisms are commonly isolated from municipal tap water. *M. chelonae* was found as a contaminant in a gentian violet solution and *M. abscessus* has been isolated from contaminated lidocaine (xylocaine) and histamine solutions. Pseudo-outbreaks are most commonly related to contaminated bronchoscopes and endoscopic cleaning machines, and to contaminated hospital water supplies.

The *M. chelonae/abscessus* group is responsible for approximately 95% of disseminated cutaneous infections caused by the RGM. In contrast, localized infections with *M. chelonae* are seen primarily in patients who are immunosuppressed, especially on long-term corticosteroids. Autoimmune diseases such as rheumatoid arthritis and systemic lupus are often predisposing factors. In a study by Wallace and colleagues, 35% of the *M. chelonae* with nonpulmonary infections were seen in localized wound infections.¹⁶

Disease due to *M. abscessus* is somewhat intermediate, as it causes disease in normal hosts and those with immune suppression. Examples of localized wound infection with *M. abscessus* include soft tissue infection of the cheek following an insect bite and vertebral osteomyelitis.

The *M. fortuitum* group accounts for 60% of community-acquired, localized cutaneous infection caused by RGM. Unlike infections with the *M. chelonae-abscessus* group, the patient with *M. fortuitum* localized infection usually has no predisposing immunosuppression. Cutaneous and subcutaneous infections by *M. fortuitum* are caused by colonization of the tissue following accidental trauma, injection of drugs (cortisone), mesotherapy, surgical procedures, or domestic animal bites.

Clinical Findings

The most common presentation is multiple erythematous subcutaneous nodules, in a sporotrichoid pattern on the distal limbs. Other forms of cutaneous involvement range from cellulitis, abscesses, papulopustules to sinuses and ulcers.

Differential Diagnosis

The differential diagnosis includes: foreign body reaction, subcutaneous mycoses and osteomyelitis.

Diagnosis

Histopathology

In the case of abscesses, a biopsy from the wall is more likely to yield the organism than aspirated pus. The presence of both neutrophilic microabscesses and granuloma formation with foreign body-type giant cells is characteristic. Necrosis may occur.

Culture

The organisms grow on routine bacterial culture media, such as 5% sheep blood agar or chocolate agar, within 7 days producing visible colonies between 5 to 7 days at temperatures ranging between 22°C and 45°C.

Treatment (Table 3)

The *M. fortuitum* group is much less drug-resistant than the *M. chelonae/abscessus* group. The macrolides clarithromycin and azithromycin are the only oral agents reliably active in vitro against infections due to the *M. chelonae/abscessus* group. The newer drug tigecycline (a glycycline antibiotic) is promising with its low MIC-values to *M. abscessus*. Clarithromycin is generally the drug of choice for localized disease (but not for disseminated disease) caused by *M. chelonae* and *M. abscessus*. However, the efficacy of macrolide treatment for *M. abscessus* (and the *M. fortuitum* group) is likely diminished by recent recognition that they carry novel *erm* genes that confer inducible resistance. The duration of therapy is usually 4–6 months. Regnier *et al.* reported 16 patients with RGM cutaneous infections after mesotherapy injections (the majority were *M. chelonae*), of which six received triple therapy with tigecycline, tobramycin and clarithromycin as first-line treatment. The median duration of tigecycline therapy was 52 days and all patients fully recovered.¹⁷ In one recent report from India, cutaneous *M. fortuitum* infection was successfully treated with amikacin and ofloxacin combination.¹⁸

Antituberculous agents have no efficacy against any of the RGM, other than ethambutol for *M. smegmatis*, and, therefore, should not be used. Monotherapy with quinolones is not recommended because of the high risk of mutational resistance of the RGM to these agents.

■ IATROGENIC NTM

Sporadic cases of healthcare-associated skin and soft tissue disease have also been described. These cases

include infections of long-term intravenous or peritoneal catheters, postinjection abscesses, surgical wound infections, such as after cardiac bypass surgery, and augmentation mammoplasty.

These include *M. fortuitum* and *M. porcinum* in post-augmentation mammoplasty surgical site infections and outbreaks or pseudo-outbreaks of mycobacterial skin, soft tissue, or bone infections resulting from contaminated fluids, such as ice made from tap water, irrigation or exposure to tap water, injectable medicines, and topical skin solutions or markers.

The contamination of benzalkonium chloride (a quaternary ammonium commonly used as an antiseptic) with *M. abscessus* was responsible for a serious outbreak of *M. abscessus* following steroid injections and this report serves to emphasize the limitations of disinfectants against mycobacteria.¹⁹ Recently, there have been reports of eye disease due to RGM following keratoplasty and laser-assisted *in situ* keratomileusis (LASIK) surgery for correction of myopia.

Other recent outbreaks involving NTM have involved contamination of liposuction equipment with *M. chelonae*, with the same disease strain found in tap water used for rinsing suction tubing.²⁰ Most of the skin and soft tissue disease outbreaks have involved the rapidly growing species *M. fortuitum* and *M. abscessus*. However, an outbreak of four patients with alcohol-resistant mycobacterial species (two with *M. chelonae* and two with *M. nonchromogenicum*) was reported in Hong Kong after acupuncture treatments from 1999 to 2000.²¹ Additionally, between 2003 and 2004, an outbreak of *M. abscessus* occurred in patients from the United States who visited the Dominican Republic for cosmetic surgery for fat removal (known as "lipotourism").²² Although no water samples or environmental samples were available for testing in this outbreak, the reservoir for these types of outbreaks has historically been municipal or hospital water supplies.

Since 2002, several outbreaks of lower-extremity folliculitis due to RGM (*M. fortuitum*, *M. abscessus*, and *M. mageritense* disease), associated with nail salons (foot-spa disease), have been reported. Leg hair removal by wax stripping followed by NTM-contaminated foot baths was followed by indolent folliculitis.²³

Diagnosis

Diagnosis is made from culture and histological examination of biopsy material, along with a compatible

history of exposure, but culture of specific NTM from drainage material or tissue biopsy is the most important since it unequivocally determines the species responsible.

Biopsy is often performed but reliable histological findings are hard to come by and thus are largely of academic interest. The histological changes range from an acute suppurative process to typical granulomatous inflammation and are not species-specific; therefore, identical findings can be observed in infections caused by different NTM.

A *granulomatous inflammatory infiltrate* with tubercloid granuloma formation, sarcoid-like granulomas or rheumatoid-like nodules are frequently present, but dermal or subcutaneous abscesses, a diffuse dermal or subcutaneous histiocytic infiltration, acute or chronic subcutaneous tissue inflammatory infiltrates (panniculitis) or even nonspecific chronic inflammation have also been described. Granulomas in cutaneous NTM infections are usually poorly formed and some neutrophils may be admixed forming suppurative granulomas. This biphasic inflammatory response, consisting of polymorphonuclear abscesses mixed with granuloma formation and necrosis seems to be the most characteristic histopathological pattern in cutaneous NTM infections.²⁴

The different histological patterns noted in cutaneous NTM infections may be related to the immunologic status of the host and the duration of infection.

Treatment of NTM

There is currently a lack of standardized treatment for NTM infection because treatment is dependent on species identification, and the treatment regimes differ between rapid growers and slow growers, and within slow growers (e.g., MAC vs. *M. kansasii*) and rapid growers (e.g., *M. abscessus* vs. *M. fortuitum*). Moreover, intraspecies variation in susceptibility testing is a common finding; and anatomical site of infection, extent of superficial spread and host factors also influence the management. However, based on various studies and trials, the recommended options for management of NTM infections are given in Table 3. Nonpharmacological management of disease includes observation for potential resolution with time or surgical treatment.

Therapy is often required for 3–6 months or more. If clinical suspicion is high for an NTM infection, empiric treatment with clarithromycin can be considered while waiting for culture and sensitivity results.

Treatment of *slowly growing species* may be required for 6–12 months, depending on severity of the disease.

Prevention

Mycobacterium avium complex is the primary NTM species that has been demonstrated to be effectively prevented with pharmacotherapy in selected populations. It has been clearly demonstrated through prospective, randomized trials that pharmacotherapy with rifabutin, clarithromycin, or azithromycin can provide primary prevention of MAC-disseminated infection in patients with AIDS whose CD4 cell count has fallen below 50 cells/mm³. In most cases of cutaneous *M. marinum* infections, fish-tank exposure is the source and may be preventable through the use of waterproof gloves for persons with acute or chronic open skin lesions. Iatrogenic NTM causing skin and soft tissue infections are due to contaminated equipment and instruments. For prevention of these, the instruments should be thoroughly cleansed mechanically after each use, with complete dismantling of parts to ensure removal of all organic soil. This is best achieved by using an ultrasonic technology which is available in some hospitals.

Secondly, it is necessary to limit glutaraldehyde disinfectants and replace it with *ethylene oxide gas sterilization*, as this has been shown to be highly effective in reducing NTM infections following laparoscopy.

SUMMARY

Nontuberculous mycobacteria that commonly cause skin and soft tissue infections are diverse in clinical presentation and geographic prevalence. Cutaneous disease with NTM follows two clinical patterns: Following trauma (accidental or surgical) in immunocompetent patients, usually a single lesion appears in the damaged region 4–6 weeks later and heals spontaneously in 20–30% of patients. However, immunocompromised patients develop disseminated, multiple subcutaneous nodules. The histological findings due to NTM are varied, depending on the immune status of the patient and the duration of disease. Therefore, microbiological confirmation by culture is almost always needed for the definitive diagnosis. A high degree of clinical suspicion followed by culture and susceptibility testing allows the timely and efficient therapy of the patients. Species and subspecies-level identification is important because antibiotic susceptibility and treatment outcome differ significantly depending on the NTM organism cultured.

KEY POINTS

- Nontuberculous mycobacteria are emerging as important causative agents of pulmonary and extrapulmonary disease in HIV seropositive and AIDS patients
- Nontuberculous mycobacteria are ubiquitous in nature and are found as free living saprophytes in various environmental habitats, especially in soil, dust, biofilms and water
- More than 90% of cutaneous infections are caused by the RGM (*M. fortuitum*, *M. chelonae*, and *M. abscessus*)
- Cultures are the most important diagnostic tool to isolate and speciate these NTM so that specific drugs should be administered, since treatment strategies differ with each species
- No strict guidelines exist for treatment of NTM infections. Effective antibiotics are known for each species but should be checked by sensitivity testing.

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