

Clinical manifestations of nontuberculous mycobacteria infections

E. Tortoli

Regional Reference Center for Mycobacteria, Microbiology and Virology Laboratory, Careggi University Hospital, Florence, Italy

Abstract

The isolation of nontuberculous mycobacteria (NTM) from clinical specimens has become very frequent in the last years. Such organisms are typically environmental and poorly pathogenic for humans; they can, however, be responsible for opportunistic diseases in subjects presenting with various predisposing conditions. Pulmonary infections are responsible for the most frequent disease caused by NTM, although the relevance of mycobacterioses involving other parts of the body is increasing. The risk of disseminated infections characterizing immunocompromised patients is well known, and those numbers are steadily rising. The lymph nodes, cutis and soft tissues, as well as bone and joints, are also important targets of NTM infection. The problems concerning the assessment of the clinical significance of NTM, along with a consideration of the more frequent NTM pathologies, are the major objectives of this review.

Keywords: MOTT, mycobacterial disease, mycobacteriosis, nontuberculous mycobacteria, review

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Corresponding author and reprint requests: E. Tortoli, Regional Reference Center for Mycobacteria, Microbiology and Virology Laboratory, Careggi University Hospital, Piastra dei Servizi, viale Morgagni 85, 50134 Firenze, Italy
E-mail: e.tortoli@libero.it.

Introduction

Nontuberculous mycobacteria (NTM), of which at present more than 130 species are known, are typical environmental organisms; they have been frequently isolated from water, but also from soil, dust and plants. Contact with contaminated environments may occasionally be responsible for infection in humans and animals, with the possibility of transmission from human to human being practically excluded [1]. The large majority of NTM are not pathogenic for humans, but almost all can behave as opportunists and thus be responsible for disease in the presence of predisposing conditions.

The different species are almost equally divided between rapid growers (which develop visible colonies on solid media within 7 days) and slow growers (which require longer incubation times). Growth rate, as opposed to other phenotypic characteristics (e.g. colony pigmentation), has clinically important repercussions. Rapid and slow growers differ in their antimicrobial susceptibility [2]; furthermore, slow growers are most often responsible for pulmonary and lymphonodal diseases, whereas rapid growers prevalently affect cutis, bones and joints [3].

Pulmonary Infections

The lung can be easily affected by inhalation of aerosolized mycobacteria and is by far the most frequent site of human mycobacteriosis. Two clearly distinct pictures exist.

First, in HIV-negative patients, the disease is undistinguishable from tuberculosis and is characterized by a very slow progression [4]. The manifestations range from absence of symptoms to cavitary disease, and an X-ray may reveal fibrosis, upper lobe cavitation, nodular or parenchymal opacity, and pleural thickening. The population most affected is elderly patients with predisposing pulmonary conditions (e.g. silicosis, obstructive pulmonary disease, pneumoconiosis, previous tuberculosis, bronchiectasis or cancer). The symptoms include cough, fever, weight loss, weakness and respiratory insufficiency [5].

Second, in AIDS, patients the radiographic picture is often normal or may reveal mediastinal or hilar adenopathy, and the progression is very rapid. The most frequent symptoms are cough, fever and weight loss. The patients are predominantly severely immunocompromised and have a CD4 lymphocyte count lower than 100/ μ L. In recent years, the widespread use of highly active anti-retroviral treatments

(HAART), comprising efficacious preventers of extreme lymphocyte depletion, has drastically reduced the frequency of mycobacterial pulmonary disease in HIV-positive patients.

The NTM most frequently responsible for disease belong to the *Mycobacterium avium* complex (MAC) with its two major species *M. avium* and *Mycobacterium intracellulare* [6]. The typical disease affects primarily elderly men with restrictive or obstructive pulmonary conditions, and presents a clinical picture of localized chronic pneumonia. By contrast, Lady Windermere syndrome affects elderly women without predisposing pulmonary conditions, but often presenting anatomic abnormalities of the chest [7].

In Europe, infections caused by *Mycobacterium xenopi* [8] and, particularly in Scandinavian countries and in Great Britain, those caused by *Mycobacterium malmoeense* [9] are very frequent, whereas, in the USA, infections caused by *Mycobacterium kansasii* are by far more prevalent [10].

It is common knowledge that patients afflicted with cystic fibrosis, a genetic disease, are highly susceptible to bacterial infections of the chest. Recently, infections as a result of NTM have increasingly been reported, with several species [11], mainly *Mycobacterium abscessus* and closely-related species, more frequently affecting children, and with members of MAC being more frequently isolated from adults.

In lipoid pneumonia, which is a specific form of lung inflammation that develops when lipids enter the bronchial tree, a strong association with the isolation of mycobacteria, predominantly comprising rapid growers [12], has been reported, although a causal correlation has not been demonstrated.

Hypersensitivity pneumonitis is an occupational disease very frequent among people using metal-working fluids. The isolation of various species of rapidly growing mycobacteria from the aerosols produced in such factories has led to the hypothesis that mycobacteria, more likely than the fluids themselves, could be responsible for the hypersensitivity [13]. Again, rapid growers, and in particular *Mycobacterium immunogenum*, are the species most frequently involved.

As opposed to what happens in other parts of the body, in many cases, the isolation of an NTM from the respiratory tract poses a problem rather than providing a solution. The risk of contamination of the sputum by environmental mycobacteria is high and the mis-attribution of clinical significance to the finding would imply not only a useless treatment for the patient, but also loss of sight of the real cause of disease.

No substantial agreement exists at present regarding colonization, considered by some to be a nonpathogenic condition, and by others to be an early phase of disease [14]. A correct assessment of the clinical significance, which is estimated to accompany no more than 30% of the isolations, requires close collaboration between the clinician and the

TABLE 1. Clinical and microbiological criteria for diagnosing nontuberculous mycobacterial lung disease [15]

Clinical (both required)

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules
- and
2. Appropriate exclusion of other diagnoses

Microbiological

1. Positive culture results from at least two separate expectorated sputum samples; if the results from one are nondiagnostic, repeating sputum smears and cultures should be considered
- or
2. Positive culture result from at least one bronchial wash or lavage
- or
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or acid fast bacilli) and positive culture for NTM or biopsy showing mycobacterial histopathological features (granulomatous inflammation or acid fast bacilli) and one or more sputum or bronchial washings that are culture positive for NTM
 4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination
 5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded
 6. Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on the potential risks and benefits of therapy for individual patients

NTM, nontuberculous mycobacteria.

microbiologist and, in some cases, the pathologist. The guidelines of the American Thoracic Society [15] (Table 1) provide strict criteria that apply in the presence of pneumopathy, for which any cause other than NTM has been excluded.

Important microbiological information concerns not only the bacterial load and the number of isolations, but also strain identification. Several species are known to be more prone than others to cause pulmonary disease; this is the case of *M. malmoeense* and *Mycobacterium szulgai* and, among rapid growers, of *M. abscessus*. Furthermore, the role of biopsy in cases in which granulomatous lesions with (but also without) acid fast bacilli are detected is decisive.

Lymphonodal Infections

Lymphonodal infection as a result of NTM is typically an infantile disease affecting, in most cases unilaterally, cervical lymph nodes [16]. The route of infection is most likely the mouth and the childhood habit of bringing hands and objects to the mouth may well explain the particular susceptibility of infants to this pathology. The size of neck swelling, which is painless, varies considerably and fistulization is not rare. Antimicrobial treatment is generally ineffective, and healing almost always requires surgical excision of the lymph nodes involved [17]. The intervention, however, resolves the situation in no more than 80% of cases, with the remaining 20% being characterized by relapse.

A major change in recent decades involves the aetiology of cervical lymphadenitis; *Mycobacterium scrofulaceum*, previously considered the prevalent cause of the disease, became quite rare, whereas *M. avium* is isolated more and more frequently [18]. Interestingly, the incidence of lymphadenitis caused by *M. malmoense* is growing also in countries other than Scandinavia and the UK where this species is known to be endemic. The number of isolations of recently-described species from lymph nodes, among them *Mycobacterium lentiflavum* [19] and *Mycobacterium bohemicum* [20], is steadily increasing as well as frequently reported.

A very peculiar kind of lymphadenitis, affecting both superficial and deep lymph nodes, develops in immunocompromised patients, particularly during immune system restoration that follows treatment with HAART. The disease, known as immunoreconstitution syndrome [21], is a paradoxical reaction of the lymphatic system to a pre-existing, undiagnosed mycobacterial infection.

Cutis and Soft Tissues Infections

NTM infections of cutis and soft tissues (hand, elbow, knee and foot being the main sites) are characterized by granulomatous lesions developing a few weeks after infection. Satellite lymph nodes also may be affected and evolution to ulceration and cellulitis, and even to cutaneous dissemination, is not rare. The most common sources include contact with contaminated water or infected fish, traumas and surgical wounds.

The cutaneous infection caused by *Mycobacterium marinum*, which mostly affects those who own aquariums and other people in contact with fish, is the best known. The lesion, usually at the hand or the forearm, is initially nodular but may subsequently ulcerate; the sporotrichoid form is characterized by small nodules along lymphatic ducts [22]. Spontaneous healing of the lesion is very rare. *Mycobacterium marinum* is a photochromogenic species with optimal growth at 32°C; when incubated at this temperature, mature colonies develop in <2 weeks, whereas the standard incubation at 37°C may be responsible for growth failure. Clinical suspicion is therefore a major prerequisite for a successful microbiological diagnosis.

Other fish-borne cutaneous lesions, mainly caused by *Mycobacterium fortuitum* and *Mycobacterium chelonae*, have also been reported.

Mycobacterium ulcerans is the aetiological agent of Buruli ulcer [23], the third most common mycobacterial disease after tuberculosis and leprosy; it is particularly frequent in Africa and Australia. Large necrotizing ulcers, characterized by the presence of heavy loads of strongly cytotoxic,

extracellular, bacilli, develop in the extremities, mainly in children. The lesions are painless and the disease is not fatal, but the development of large scars is highly invalidating. The most important treatment is surgical excision followed by skin transplantation. Waters of lakes and rivers are thought to be the natural reservoir of *M. ulcerans*. Growth in culture requires incubation at temperatures lower than 32°C and is slow; most strains grow poorly in culture.

Mycobacterium haemophilum [24], also a psychrophile species, may be responsible for painful soft tissue abscesses, sometimes relapsing, in immunocompromised patients, mainly organ transplanted, HIV-infected or lymphoma patients. Infections caused by *M. haemophilum* often remain undiagnosed because growth of the mycobacterium in culture requires, in addition to incubation at an unusual growth temperature, media that is enriched with blood derivatives.

Many rapid growers are often involved in post-traumatic or post-surgical infections; the species most frequently reported include *M. fortuitum*, *M. chelonae* and *M. abscessus*, but increasingly reported are cases caused by recently described new species, such as *Mycobacterium goodii* [25] and *Mycobacterium massiliense* [26].

Outbreaks of cutaneous mycobacterioses, almost always attributable to rapid growers, are increasingly reported worldwide. The infectious agent is accidentally introduced into the host by injection (multidose vaccines, local anaesthetic) or because of the use of contaminated disinfectants, mostly on the occasion of cosmetic interventions.

Bone and Joint Infections

Infections involving joints and bones often originate from traumas (e.g. open fractures) or surgical interventions. The joint functionality is often severely compromised and evolution to osteomyelitis is not rare. Articular rheumatism and steroid treatment are major predisposing conditions. Antimicrobial treatment is poorly effective when not combined with surgical toilette.

A number of mycobacterial species have been repeatedly reported to be involved: *M. haemophilum*, *M. kansasii*, MAC, *Mycobacterium asiaticum*, *Mycobacterium flavescens*, *M. szulgai*, *M. xenopi* and, among the rapid growers, *Mycobacterium thermoresistibile* and *M. goodii* [25].

A not negligible portion of cases of spondylodiscitis have a mycobacterial aetiology, with those attributable to NTM being as frequent as those caused by *Mycobacterium tuberculosis*. Both rapidly and slowly growing species may be involved; among the latter, *M. xenopi* is one of the leading causes [27].

Disseminated Infections

Disseminated mycobacterial infections develop almost always in severely immunocompromised people; the best known are those that affect HIV-infected patients.

The respiratory apparatus and the gastrointestinal tract are the two major routes of infection. The main symptoms and signs include high fever, diarrhoea, weight loss, abdominal pain, sweating, hiccups, anaemia, hepatomegaly and splenomegaly. The progression of disease may be very rapid and even fatal. Blood culture on media specific for mycobacteria is the procedure of choice for the diagnosis of such disseminated infections.

Disseminated MAC was one of the first opportunistic infections detected in AIDS patients [28]; it has been estimated to affect approximately 50% of subjects with CD4 lymphocyte counts less than 100/ μ L [6]. In such patients, infections caused by *M. avium* are four-fold more frequent than those due to *M. intracellulare*, which is an unexpected proportion given that, in HIV-negative people, the involvement of the two species overlaps.

The number of NTM species reported as responsible for disseminated infections in AIDS patients is large; among them, *Mycobacterium genavense*, a species which remains frequently undiagnosed because of its inability to grow on conventional solid media, has been estimated to be involved in no less than 10% of the cases attributable to MAC [29].

Mixed infections have also been reported [30].

Several species, among these MAC and *M. genavense*, appear to share a privileged involvement in AIDS-disseminated infections. Such relatedness still remains unexplained, in particular for those species that are not very common in the environment or poorly pathogenic.

Presently, disseminated NTM disease is quite rare in HIV-infected patients [31]; the use of HAART allows the maintenance of the level of CD4 lymphocytes clearly above the level at risk for such infections and, when not possible because of resistance of the HIV strains, a prophylactic treatment is sufficient in most cases to keep the risk under control. However, the frequency of disseminated NTM infections remains on the rise in therapeutically immunosuppressed patients [32] and in those with genetic immunodeficiencies.

An important predisposing condition to disseminated mycobacterial infections is the immunosuppression established to prevent the rejection of transplanted organs. The number of reports concerning kidney and bone marrow transplantation is particularly high and many species are involved. Among them, an important role appears to be played by *M. haemophilum* [24].

Disseminated mycobacterial infections, which, although not rare, remain in many cases undiagnosed, may develop concomitantly with antineoplastic therapies of cancer, in particular of hairy cell leukaemia and chronic myeloid leukaemia [33]. They originate, in most cases, from infected catheters and should be suspected when a patient remains febrile despite negative blood cultures (performed in media not dedicated to mycobacteria). Particular attention should be paid, in the case of such patients, to avoid confusing mycobacteria unexpectedly grown on common media with contaminants, because of their coryneform aspect [34]. Once the mycobacterial nature of the infection is acknowledged and the contaminated catheter is removed, proper treatment is, with high probability, successful.

Catheter-related sepsis, mainly as a result of rapidly growing mycobacteria, has also been reported in hemodialysis patients [35] and in surgical patients, primarily following cardiac operations.

In recent years, the administration of antibodies against interferon (IFN)- γ has become a frequent practice for the treatment of many immunomediated inflammatory diseases. A side effect of the impairment of macrophagic activation, consequent to the biological therapy, is the increased predisposition to mycobacterial infections. A number of cases, mostly disseminated, have been reported, some of which do not respond to treatment [36].

Among genetic immunodeficiencies, the most liable to disseminated mycobacterial infections are idiopathic CD4 lymphopenia [37], the mutations of IFN- γ -specific receptors, and the production of anti IFN- γ antibodies.

Conclusions

Opposite attitudes may be presented by clinicians with regard to NTMs. They are in fact considered harmless organisms by some, and the cause of a difficult-to-diagnose disease by others.

The truth is, as always, halfway between the opposing attitudes, and a correct diagnosis requires an unbiased clinical evaluation of diagnostic data. An important contribution can come from microbiology, provided that the organism is carefully identified and proper methodologies are adopted. An approximate identification may lead to the under- or overvaluation of the role of an isolate, whereas, on the other hand, the use of unsuitable media and/or cultural conditions may be responsible for missing significant pathogens. A correct identification is at the basis of a proper treatment which, because of the unreliability of NTM susceptibility testing, must necessarily be based on data from the literature

and take into account the different susceptibility patterns that characterize rapidly and slowly growing species. As expected, collaboration of the clinician and the microbiologist is crucial.

Transparency Declaration

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