



## Unusual swelling of the hand and multiple nodules over the body – beware of mycobacteria

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**Atypical mycobacteria can cause rare and atypical infections of the hand. We report the case of an immunocompetent 46-year-old male initially presenting with thumb felon and progressively developing symptoms of carpal tunnel syndrome, tenosynovitis of multiple fingers and a sporotrichoid lymphocutaneous infection causing chronic cutaneous lesions all over the body. We would like to highlight the diagnostic and therapeutic difficulties of these atypical infections, which mimic other conditions and can cause a lot of morbidity.**

**Keywords:** Mycobacteria, Mycobacterium Marinum, hand infection, tenosynovitis, sporotrichoid lymphocutaneous infection, diagnosis, treatment.

### INTRODUCTION

Mycobacterium Marinum is a nontuberculous mycobacterium that can cause superficial and deep tissue infections (tenosynovitis, septic arthritis, osteomyelitis) of the hand leading to a great amount of morbidity. Tenosynovitis of one finger of the dominant hand or a solitary nodule (fish tank granuloma) on the hand after exposure to contaminated water or fish is suspicious of such infections<sup>1-3</sup>. Misdiagnosis and delay of treatment are very common because of atypical presentations mimicking several other conditions such as carpal tunnel syndrome, tenosynovitis, nodular lymphangitis or rheumatic diseases<sup>4-7</sup>. In order to avoid the spread of these infections to deeper tissues leading to poor prognosis, it is important to diagnose them early on and to initiate antimycobacterial treatment as soon as possible combined with debridement in case of deep infections<sup>8</sup>.

### CASE REPORT

This case report describes the story of a 46-year-old male who was treated at our clinic 9 months after the beginning of his symptoms in the right hand. He has no previous medical history except for a Gilbert's syndrome, is a non-smoker, in good health and in good vaccination order.

Initially, the patient presents himself at another hospital with symptoms of a right thumb felon. There is a small wound on his thumb with a suspicion of entrance of a foreign body into the wound (which is assumed to be the starting point for the infection). The patient had been working on a wooden bed and may have had a splinter entering his thumb. He is treated by the administration of antibiotics (Amoxicilline-Clavulanate) during 20 days after a small purulent discharge from this wound. Despite the treatment, there is persistent erythema and oedema of the thumb. A hand surgeon is consulted, antibiotics are discontinued and wet dressings applied on the thumb. A surgical intervention of incision, drainage and excision of all infected tissues is done 2 weeks after a new purulent discharge. Tissue samples were taken during the operation and bacteriological cultures came back negative. Unfortunately, after the operation, the swelling of the thumb gradually worsens and diffuses to the palm of the hand. The patient begins complaining about symptoms of carpal tunnel syndrome. A local injection of corticosteroids helps to alleviate symptoms, without making them disappear. This is when slow-growing skin nodules appear on the patient's left thigh, left flank and left arm and even on his back some weeks later.

There is a spontaneous evolution of some of these nodules towards the formation of abscesses with a purulent discharge. A few of these abscesses are

drained in the emergency room of a second hospital and one is surgically excised in yet another hospital but the different bacteriological samples taken during these procedures always returned negative. Anatomopathological analysis describes an « abscessed granulomatous reaction ». The patient developed bronchiolitis for which he was treated by antibiotics (Azithromycin) with favourable result.

In the meantime, his right-sided carpal tunnel symptoms continue to bother the patient. After a new corticosteroid injection that doesn't improve the situation, the patient undergoes a surgical release (about 4 months after his initial thumb swelling).

Seven months after the beginning of his symptoms, the help of a specialist of infectious diseases is sought. The patient undergoes numerous medical exams (blood/urine tests and cultures, echocardiography, exercise stress test, chest x-rays, CT-scan, PET-CT, bronchoalveolar lavage,...) but no clear diagnosis can be made. Differential diagnosis consists of sarcoidosis, tuberculous or nontuberculous granulomatosis, nocardiosis and lymphoma.

Nine months from the initial thumb swelling, after the treatment of an episode of folliculitis on the left thigh by antibiotics, new skin nodules appear on the patient's right hand palm (base of thumb and of 5th finger). He is treated by the same hand surgeon in the hospital where he initially presented himself. Abundant synovitis was encountered and surgically excised in two stages separated by 3 days.

This is when, because of unfavourable post-operative evolution, the patient is referred to our hospital. We thus see him for the first time after having

undergone 4 surgical interventions on his right hand as well as 2 corticosteroid injections. He is afebrile and has tenosynovitis of the first and fifth fingers, big palmar nodules in the region of the head of the first and fifth metacarpals (Fig. 1a,b) and disseminated papulonodular skin lesions not only on the right upper extremity but also on the back, the right knee, the left thigh, flank and arm. It is also at this point that we find out that the patient had been in contact with fish tank water. He had been cleaning the fish tank of his mother a few weeks before his symptoms started.

After multidisciplinary discussion, the patient undergoes a surgical debridement of his right hand. Tissue samples for histopathological analysis and microbiological cultures are taken. Histopathology shows a granulomatous reaction and direct examination by Auramine-Rhodamine stain is positive for atypical mycobacteria. The final results of the cultures come back positive for a *Mycobacterium Marinum* after 3 and a half weeks. After surgery, we immediately started an empiric antibiotic treatment including Amikacin, Rifampicin, Azithromycin, Ethambutol and Ceftriaxone against suspected nontuberculous mycobacteria and nocardiosis. Ceftriaxone is discontinued 3 days later (absence of nocardia) and so is Amikacin 2 weeks later because of the low probability of a virulent mycobacterium. Tri-therapy is continued for 11 weeks, before having to stop Rifampicin because of leukopenia and hepatic cytolysis on blood examination.

Almost 4 months later, there is a resurgence in swelling of the right hand and of symptoms and swelling at the carpal tunnel under the residual



Fig. 1 — a,b: First presentation at our hospital: big palmar nodules in the region of the head of the first and fifth metacarpals of the right hand. c: Post-operative status 3 months after the last surgical debridement.

bitherapy. A new debridement with tenosynovectomy is undertaken and tissue samples are analysed. Histopathology confirms necrotizing granulomatous tenosynovitis but the direct examination and microbiological cultures remain negative. Bitherapy is maintained after surgery.

After initial improvement, the swelling in the region of the carpal tunnel and the distal wrist relapses 2 months later. Our specialists in infectious diseases contact the Belgian national reference centre for infections by atypical mycobacteria and realize that Azithromycin is not effective on the patient's *Mycobacterium Marinum*. He had thus been on the equivalent of a monotherapy by Ethambutol. Bitherapy is discontinued for 2 weeks, after which we do a final debridement with tenosynovectomy at the wrist. Directly after surgery a tri-therapy consisting of Rifampicin, Clarithromycin and Minocycline is initiated and continued for 6 months.

After 3 months, the patient regains good function of his right hand and wrist. Small residual swelling remains at the wrist (Fig. 1c), but the patient's median nerve slowly recovers from multiple surgical interventions. At one-year follow-up after the last surgery, he has recovered a normal hand and wrist with full range of motion (ROM), good grip strength (98% of contralateral side) and the absence of symptoms of carpal tunnel syndrome. Although he has been the victim of a Parsonage-Turner syndrome almost 10 months after his last surgery, the evolution is satisfactory under the current physiotherapy.

## DISCUSSION

The presentation of infections by nontuberculous mycobacteria is very atypical. A quick diagnosis and subsequent treatment are mandatory because invasive hand infections can rapidly cause permanent morbidity such as deformity, stiffness and loss of function<sup>9,10</sup>. Diagnosis of these infections remains nevertheless challenging.

### *Epidemiology*

The most common presentation of *Mycobacterium Marinum* infection, as described by Balagué et al.<sup>4</sup>, is an immunocompetent (93%) male (60%) of about 58 years suffering from tenosynovitis of 1 finger (74%) of the dominant hand (93%) after fish or water inoculation. This finger is stiff in half of the cases. Nodules, ulcerations, erythema and paraesthesia are rare clinical features (2-4%). Patients are usually afebrile and have cold and painful swelling without

redness. Serum inflammatory markers are generally normal.

The annual incidence of *Mycobacterium Marinum* infection is estimated to be around 0.09 per 100,000 inhabitants per year in France and up to 0.27 per 100,000 inhabitants per year in the USA.

The prevalence of *Mycobacterium Marinum* was of 4.5% of water samples taken around a swimming pool in Italy<sup>11</sup>.

*Mycobacterium Marinum* is a species that typically causes superficial infections after contact of damaged or abraded skin with contaminated water from aquariums, pools, salt water or natural water supplies.

It rarely causes deeper infections because this species needs cooler temperatures for optimal growth (25-32°C) than those found inside the human body<sup>8,12,13</sup>. The incubation period ranges from 3 weeks up to 9 months, which may contribute to delay in diagnosis.

Disseminated infections are even rarer and almost only seen in immunocompromised patients<sup>3,14</sup>.

### *Diagnosis*<sup>4,15-19</sup>

In our case, by the time of referral to our hospital, the 46-year-old male patient had a disseminated infection (although he was immunocompetent) and had involvement of two fingers of his dominant hand, the thumb and fifth finger. These are the two least involved fingers in nontuberculous mycobacterial infections according to Balagué et al.<sup>4</sup>. The patient had associated nodules, erythema, paraesthesia and stiffness of the involved fingers. He was afebrile and serum inflammatory markers were normal. He had been cleaning the fish tank of his mother a few weeks before his initial symptoms appeared, but there was no history of skin lesions prior to this exposure.

There had been a false initial diagnosis (53%) of thumb felon and carpal tunnel syndrome which led to a delay in treatment and to the use of corticosteroid injections (23%) in an already infected hand/wrist<sup>4</sup>.

Because of the existence of what seemed to be a sporotrichoid lymphocutaneous infection causing nodules in the hand, forearm and axilla, but also the existence of nodules on the back, flank, thigh and knee the differential diagnosis included sarcoidosis, tuberculous or nontuberculous granulomatosis, nocardiosis and lymphoma<sup>15,16</sup>. Diagnostic exams had little contributory effect, only surgical debridement and analysis (histopathology, culture and Polymerase Chain Reaction) of tissue samples in the hand helped making the right diagnosis of an infection by *Mycobacterium Marinum*.

This corroborates data of the literature where a high index of suspicion and the analysis of tissue samples taken during surgery are described as being the cornerstone of diagnosis and treatment<sup>17-19</sup>.

It took almost 10 months to establish the correct diagnosis for our patient.

#### *Treatment*<sup>4,9,12,17-27</sup>

This case underlines the need for a multidisciplinary approach with one coordinator (e.g. specialist in infectious diseases) to lead diagnostics and treatment and prevent delay<sup>20</sup>. Our patient has been treated by several doctors in 3 different hospitals before being referred to our centre. A good coordination of all medical examinations and the gathering of all medical history by one lead investigator could have avoided this diagnostic delay. Once the right diagnosis was made, the correct treatment could be initiated<sup>21</sup>. Literature tells us that in case of delayed diagnosis or locally advanced disease there is a need to associate antimycobacterial therapy with extensive surgical debridement<sup>12</sup>. This contrasts with tuberculous hand infections where conservative treatment is usually sufficient. Amongst the unfavourable prognostic factors for conservative management of atypical mycobacterial infections, we can find prior corticosteroid injections, a discharging sinus and persistent pain<sup>22</sup>.

There is only little information about the choice and duration of antimycobacterial drugs used in nontuberculous mycobacterium infections. Resistance to commonly used antitubercular drugs has been pointed out<sup>23</sup>, but on the other hand, a case of *Mycobacterium Marinum* skin infection treated effectively by monotherapy of Doxycycline has been reported<sup>24</sup>. Early diagnosed superficial infections may thus respond sufficiently to drug therapy alone. More advanced or chronic infections will need surgical debridement<sup>25</sup>.

After the excision of all necrotizing components and the opening of all fluid compartments, it is commonly admitted to initiate empiric antimycobacterial treatment. Drug therapy by Clarithromycin, Rifampicin and Levofloxacin is continued until final species identification and susceptibility results are available<sup>4</sup>.

In our case Azithromycin was used, as we didn't know which mycobacterium species was involved. Later on, when the response to antimycobacterium therapy was incomplete, we decided to switch to Clarithromycin instead of Azithromycin. Under concurring circumstances of side effects of one drug (Rifampicin)

and resistance to another (Azithromycin), the patient had thus been under the equivalent of a monotherapy by Ethambutol, which was not enough to treat his advanced infection.

This highlights that reassessing therapy and diagnosis when there is insufficient response to treatment is essential<sup>26</sup>.

According to individual expert opinions, antimycobacterial drugs should be continued for at least 6 months and should not be taken for longer than 12 months<sup>4,27</sup>.

First signs of clinical improvement (less swelling and stiffness) appeared 3 months after the last surgery under the right antimycobacterial therapy and hand rehabilitation. Hand and finger motion exercises and fluid drainage were performed with a hand therapist three times per week.

Delayed clinical response is typical of these infections and may take up to 6 months (median of 3 months<sup>4</sup>). It seems to be independent of the combination of antimycobacterial drugs used and of the number of surgeries performed.

According to the literature<sup>4</sup>, patients needing multiple operations had poor clinical outcomes though (only 40% had good ROM) and residual stiffness was often encountered.

Fortunately, even though our patient had delayed diagnosis and underwent numerous surgical interventions, his functional outcome is quite satisfactory. He has complete ROM and only a little bit of persistent swelling in the region of his carpal tunnel.

Our patient is now considered « cured » because of an event-free follow-up of more than 12 months after the correct diagnosis and treatment.

## CONCLUSION

Raising awareness of invasive mycobacterial infections amongst doctors and people at risk of exposure to contaminated water is of paramount importance. When treatment is not effective, medical history and the treatment itself should be reassessed in order to establish the right diagnosis, which allows initiating the right treatment.

The diagnosis is challenging and should be made as soon as possible, based on a multidisciplinary approach with one main coordinator. As there may be resistance to commonly used antitubercular drugs, appropriate antibiotic choice and duration are crucial. The sooner a thorough surgical debridement is done and the final species identification and susceptibility

results are available, the better the chances of reducing complications and lasting morbidity.

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