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Medical Imagery

Dissemination of localized *Mycobacterium malmoense* infection in an immunocompromised patient

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ABSTRACT

A 75-year-old woman with a history of immunosuppressive treatment for rheumatoid arthritis and non-Hodgkin lymphoma, was referred to our reference centre for treatment of tenosynovitis caused by *Mycobacterium malmoense*, which had disseminated due to immunosuppressive therapy. This rare diagnosis was made after years of treatment for supposed rheumatoid arthritis. The patient presented with relapsing tenosynovitis with wounds on her right middle finger and wounds on her left lower leg, despite 3 months of adequate therapy (rifampicin + ethambutol + clarithromycin). Therapy was intensified with amikacin, clofazimine, moxifloxacin, and interferon-gamma due to the lack of response. Amputation of the right middle finger was necessary due to advanced disease. Treatment was further complicated by a paradoxical reaction, requiring prednisone treatment, which ultimately led to cure.

Case report

A 75-year-old woman was referred to our reference centre for non-tuberculous mycobacterial tenosynovitis of the right middle finger 8 years after first presentation. The patient had first presented with tenosynovitis of the right middle finger and arthritis of the right wrist in 2008, which was presumed to be a seronegative, non-erosive rheumatoid arthritis. Histological analysis of a biopsy specimen showed chronic inflammation, not specific to rheumatoid arthritis. Bacterial cultures remained negative at this time. The tenosynovitis was first treated with non-steroidal anti-inflammatory drugs and local corticosteroid injections, with good effect. Later, arthritis of the right wrist and tenosynovitis relapsed. As a result, the patient started treatment with methotrexate.

One year later, the tenosynovitis deteriorated and exploratory surgery was performed. Granulomatous inflammation was found in pathology samples, but cultures remained negative. Over the next 6 years, the disease slowly progressed and therapy with etanercept, adalimumab, certolizumab, tocilizumab, abatacept, and clarithromycin monotherapy proved unsuccessful. At this point she was diagnosed with non-Hodgkin lymphoma, which was treated with chemotherapy and radiotherapy. After this period, due to a relapse of symptoms, localized corticosteroid injections, gold injections, methotrexate, and prednisone were tried, and also proved unsuccessful.

Eight years after initial presentation, a biopsy of synovium of the wrist yielded growth of *Mycobacterium malmoense* and antimycobacterial treatment with rifampicin, ethambutol, and clarithromycin was initiated. At the start of antimycobacterial therapy, the immunomodulatory treatment for rheumatoid arthritis was halted.

At referral, the patient presented with an infection of the right middle finger with an open wound and a swollen right wrist. Despite 3 months of adequate antimycobacterial treatment, there was no clinical improvement. She also had bursitis of the right elbow, arthritis of the left wrist, and wounds on her left lower leg with erythema and fluctuating swelling, which had recently emerged. Physical examination showed a slender woman (BMI 20.5 kg/m^2), without fever or abnormalities on chest examination. A chest X-ray showed no abnormalities. Magnetic resonance imaging (MRI) of the left lower leg showed subcutaneous fluid collections, but no signs of osteomyelitis. Autoimmune serology and HIV serology remained negative and radiographs of both hands did not reveal erosions typical of rheumatoid arthritis. At admission, the patient switched ethambutol to clofazimine due to adverse events, i.e. visual impairment.

During admission a positron emission tomography-computed tomography (PET-CT) was performed, which showed multiple sites of inflammation in the right hand and lower arm, left hand and lower left leg, right-sided olecranon bursitis, and a spinous process of vertebra L5 (Figure 1). Puncture fluid from the olecranon bursa grew *M. malmoense* after 8 weeks of incubation on Lowenstein–Jensen medium; the isolate proved susceptible to all antibiotics in the treatment regimen. Mycobacterial blood cultures remained negative. Due to the possible progression of disease, moxifloxacin, amikacin, and subcutaneous interferon-gamma were added to the rifampicin + clofazimine + clarithromycin regimen. Relapse or new haematological malignancy was ruled out by bone marrow biopsy. Interferon-gamma was discontinued due to a severe flu-like

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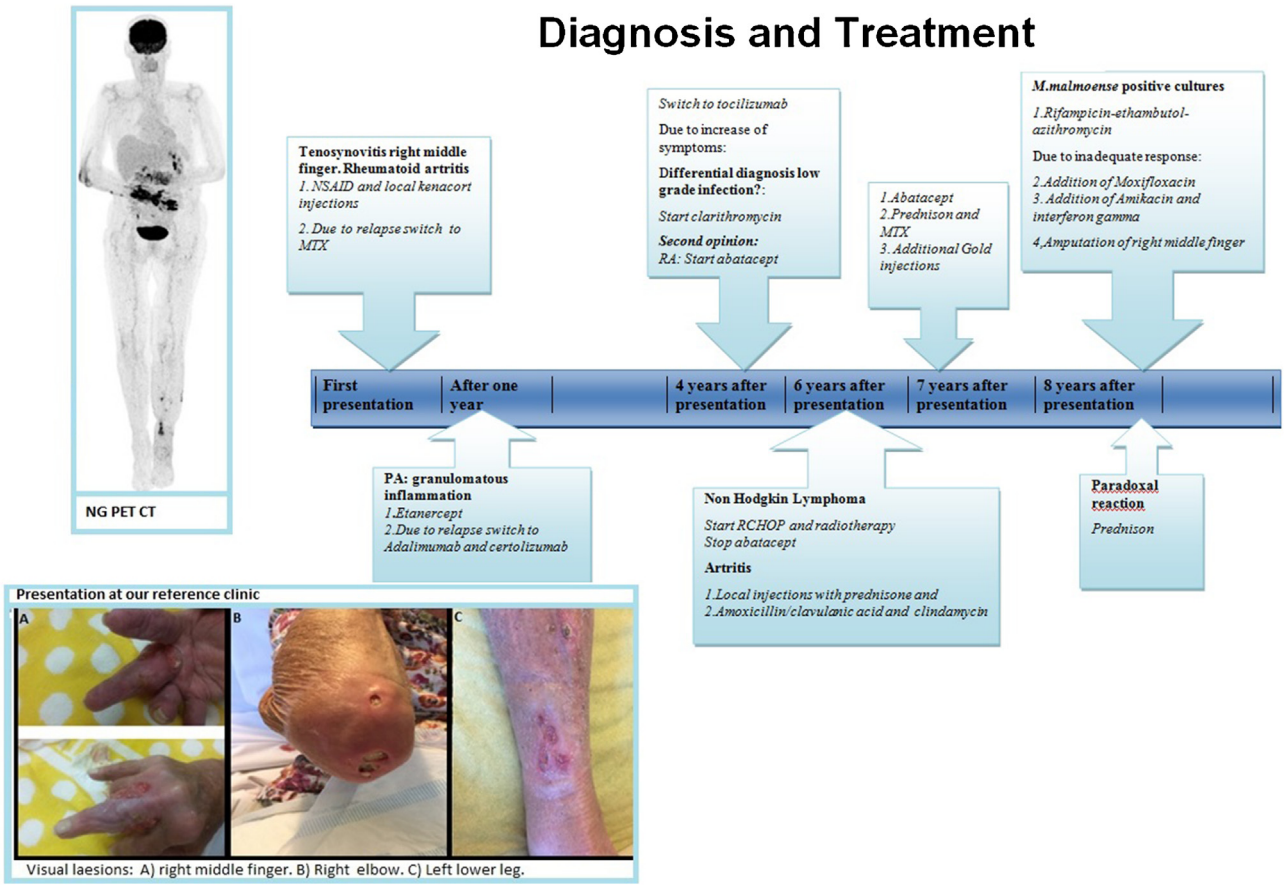

Figure 1. PET-CT Lesions are visible in the right hand and lower arm, matching infection. Lesions in the left hand and left lower leg, as well as two spots in the intestines and possibly the spinous process of L5, are consistent with infection. Pictures of the right hand, right elbow and left lower leg are provided as well.

syndrome. Eventually, amputation of the right middle finger was performed. Histology of the amputated finger showed granulomatous inflammation with acid-fast rods in auramine stains.

A paradoxical reaction was considered as a possible explanation for the lack of improvement. Prednisone (starting dose of 1 mg/kg, follow by a slow tapered schedule) was given and led to rapid marked improvement of the patient's clinical signs and symptoms. After almost 4 months, prednisone could be stopped, as follow-up PET-CT imaging confirmed the decrease in severity of inflammation.

Due to adverse events, consisting of cutaneous reactions, antimycobacterial drugs were halted after 9 months. As immunomodulatory treatment had been halted and the paradoxical reaction had waned, it was estimated that the treatment had been of a sufficient duration. One year after cessation of antibiotics, the patient has not had a recurrence of *M. malmoense* disease.

Discussion

This patient was suffering from relapsing tenosynovitis for years. This was at first attributed to rheumatoid arthritis, although different treatments did not have the desired effect. Eventually, the diagnosis of disseminated *M. malmoense* infection was made.

Based on the lack of response to all of the different treatments given for rheumatoid arthritis, it is hypothesized that *M. malmoense* tenosynovitis was the most likely diagnosis from the beginning and that the patient probably had not suffered from rheumatoid arthritis. Yet, with the many injections and wounds present over time, *M. malmoense* may also have been inoculated later in the course of disease.

Due to the immunomodulatory medication use, the mycobacterial disease had the opportunity to disseminate. After interrupting the immunosuppressive drugs and starting the antimycobacterial drugs, the immune system recovered and different lesions at sites to which *M. malmoense* had spread became apparent. This was first interpreted as a poor clinical response, but eventually as a paradoxical reaction. As a result, prednisone was started, which had a good effect. Although paradoxical reactions are well described in the treatment of tuberculosis (Melboucy-Belkhir et al., 2010), almost no case reports on non-tuberculous mycobacteria (NTM) are available. Theoretically, a similar paradoxical response as seen in tuberculosis could be expected in the treatment of NTM as well. In this case, the cessation of anti-inflammatory drugs used for rheumatoid arthritis might have contributed to the paradoxical response.

As a differential diagnosis, Poncet's disease was also considered. Poncet's disease was first described in tuberculosis patients in 1897. It is a rare presentation of reactive polyarthritis, without mycobacterial involvement of the joint. After infection, as a result of systemic immunization, sensitized CD4+ cells together with bacterial antigens migrate to the joints and cause arthritis (Sharma et al., 2016). In the case presented herein, the positive cultures eventually ruled out Poncet's disease.

The incidence of *M. malmoense* infections has increased since 1980, especially in northern Europe (Hoefsloot et al., 2008). Pulmonary infections are the most frequent disease manifestation (Hoefsloot et al., 2009). Extrapulmonary *M. malmoense* infection is rare, except for lymphadenitis in children and tenosynovitis (Hoefsloot et al., 2008). Dissemination is only observed in patients with severely impaired immunity (Zaugg et al., 1993). In this case,

the patient had multiple causes of impaired immunity, not only due to immunosuppressive medication, but also due to for instance non-Hodgkin lymphoma.

The diagnosis of *M. malmoense* disease was further complicated by the fact that *M. malmoense* is a slow-growing Mycobacterium that can take up to 8 weeks to grow in mycobacterial culture. Supplementing the medium with pyruvate and acidification of the medium to a pH of 6 can help to increase the growth rate of *M. malmoense* and ensure its detection (Katila et al., 1989). Direct detection of NTM in clinical samples by molecular techniques can further increase the sensitivity of mycobacterial diagnostics (Deggim-Messmer et al., 2016).

In conclusion, immunosuppressive medication can cause dissemination of otherwise localized infections with *M. malmoense*. The diagnosis and treatment of *M. malmoense* tenosynovitis can be challenging. Paradoxical reactions should be considered in the case of treatment failure.

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Ethical approval

No ethical approval was required as it is a case report.

Conflict of interest

Wouter Hoefsloot and Sanne Zweijpfenning have received funding for other non-related research from Insmed.

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