Unusual association of diseases/symptoms

Infrapatellar bursitis with *Mycobacterium malmoense* related to immune reconstitution inflammatory syndrome in an HIV-positive patient

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Summary

The immune reconstitution inflammatory syndrome (IRIS) after starting antiretroviral treatment for HIV infection can be caused by a great variety of pathogens. Among these are non-tuberculous mycobacteria (NTM), with *Mycobacterium avium* complex being the most commonly described finding. Antimycobacterial treatment of NTM in cases of IRIS is controversial. We report the case of a 39-year-old man diagnosed with HIV-1 infection during admission to hospital with *Pneumocystis jirovecii* pneumonia (PCP) and a CD4 cell count of 60/μl. The patient started antiretroviral treatment and made an uneventful recovery from the PCP diagnosis, but was readmitted after 2.5 months with a purulent infrapatellar bursitis on the left knee. A surgical procedure was performed and *Mycobacterium malmoense* was grown from the pus from the bursa. The patient recovered without supplemental antimycobacterial treatment. To our knowledge, this is the first report on IRIS caused by *M malmoense*.

BACKGROUND

Infection with non-tuberculous mycobacteria (NTM) occurs with an increasing incidence not only in immunocompromised patients, but also in immunocompetent individuals.^{1–2} Although the vast majority of NTM disease in patients with HIV infection is caused by *Mycobacterium avium* complex (MAC), other NTM are also important pathogens.^{3–4} *Mycobacterium malmoense*, first described in Sweden in 1977 by Schröder and Juhlin, is the second leading cause of NTM disease in Sweden and has with increasing frequency been isolated in Northern Europe where it is primarily presenting with pulmonary manifestations; disseminated disease has also been described.^{5–9}

We present a case history with isolation of *M malmoense* from an infrapatellar purulent bursitis in a patient with HIV after starting antiretroviral treatment.

CASE PRESENTATION

A 39-year-old man presented to the emergency department at a tertiary hospital with a 6-month history of unintended weight loss (22 kg), severe fatigue, dry irritative cough and severe shortness of breath during physical activity. The patient was febrile without focal symptoms and underwent an extensive examination including a transthoracic echocardiography, chest film, spiral CT, ultrasound of the testis and CT of thorax and abdomen. The latter revealed a single lymph node enlargement in the right hilus region, otherwise no abnormal findings were revealed. Biochemical tests showed an elevated erythrocyte sedimentation rate of 34 mm/h, a normal leucocyte count with mild neutropenia ($1.56 \times 10^9/l$) and lymphopaenia ($0.83 \times 10^9/l$), and slight anaemia with an Hb of 7.7 mmol/l.

The patient had a medical history with arthroscopic surgery for a meniscus injury in his left knee in 2000 and 2003, an episode of unexplained urine retention in 2005

and an operation for a perianal abscess in 2007. Further, he had a travel history with a stationing in the Balkans in 1994 as a soldier, a vacation trip to Egypt in 2001 and to Croatia in 2008. He had no history of drug abuse, and he had been in a stable monogamous relationship for 15 years, apart from a sexual contact with a man 6–8 years previously. His wife and children were all healthy. Finally, in 1995 his mother had a recurrence of pulmonary tuberculosis, for which she was successfully treated. The entire family was examined for tuberculosis—none were found latently infected.

The patient was referred to the Department of Infectious Diseases at our hospital and was found to be alert and oriented with fever, progression in respiratory symptoms and seborrhoeic dermatitis. The only other subjective complaint was intermittent pain from the left knee, which was normal at inspection. The patient tested positive for HIV-1 with a CD4 count of 60/μl and a plasma HIV-RNA of 1 500 000 copies/ml. Because of the respiratory symptoms, *Pneumocystis pneumonia* (PCP) was suspected and empirical treatment with sulphamethoxazole/trimethoprim at a standard dose of 1600 mg/320 mg four times a day was started. The PCP diagnosis was subsequently confirmed with a positive fluorescence microscopy for *Pneumocystis jirovecii* on broncho-alveolar lavage fluid.

Three weeks after the patient tested positive for HIV, antiretroviral treatment was started in the outpatient clinic with Efavirenz 600 mg once a day emtricitabine 200 mg and tenofovir disoproxil 245 mg od. Five weeks after starting treatment, the CD4 cell count had risen to 240/μl with a decrease in plasma HIV-RNA to 2600 copies/ml.

Two-and-a-half months after the HIV diagnosis, the patient was hospitalised with increasing pain for 1 week in his left knee as the only subjective symptom. On arrival, the patient was afebrile with a clinically suspected

Figure 1 Ultrasound of the patients left knee with the finding of a soft tissue process anterolateral measuring 25 cm×19 cm×0.7 cm.

prepatellar bursitis anterolateral at the left knee, which was not, at that time, aspirated. The patient was treated with a short course of 2 days with intravenous dicloxacillin 1 g four times a day and discharged without antibiotics.

After 14 days, the patient was re-admitted due to increasing pain from his clinically suspected prepatellar bursitis. An ultrasound was performed finding a deep infrapatellar bursitis (figure 1). An aspiration was performed with purulent matter and an incision was done; the cavity was rinsed and was left to heal. There was not sent material for pathology. Antibiotic treatment with intravenous dicloxacillin tid was commenced, but stopped after 3 days because direct microscopy of pus showed many acid-fast bacilli and the pus was without bacterial growth. No steroids were used. The *Mycobacterium tuberculosis* gamma-interferon releasing assay (QuantiFERON-TB) was negative. An x-ray of the left knee showed no sign of osteomyelitis. As localised atypical mycobacteriosis was suspected as part of immune reconstitution inflammatory syndrome after initiation of antiretroviral treatment, it was decided to observe the patient without extended antibiotic treatment. Two weeks after the surgical procedure, the CD4 cell count was stable at 250/ μ l with a further decrease in plasma HIV-RNA to 380 copies/ml.

Three weeks after the incision of the infrapatellar purulent bursitis was performed, the final microbiology results showed no PCR amplification of atypical mycobacterium, and a negative PCR for *M. tuberculosis*. However, growth of *M. malmoense* MGIT in the culture medium was identified by means of InnoLipa species (from Innogenetics, Technologiepark 6, 9052 Gent, Belgium) with clear hybridisation to *M. malmoense* specific probes (1, 2, 13 and 18) (16–23 S amplification followed by hybridisation to the species-specific probes).¹⁰ At follow-up in our outpatient clinic after 2, 11 and 26 weeks, the wound healed and left only slight scarring. The patient suffered from a depression and a post-traumatic stress disorder, but was somatically well without signs of ongoing infection with atypical mycobacteriosis.

DISCUSSION

M. malmoense has been isolated from environmental sources such as water and soil.³ Over the past three

decades, the incidence of *M. malmoense* infections, compared with other NTM, has increased especially in Northern Europe. This could largely be attributed to the increased awareness of mycobacteria as potential pathogens, the improved laboratory methods and perhaps the discontinuation of BCG vaccination of newborns as suggested in other studies.^{5 11 12}

M. malmoense infection is rarely associated with invasive disease in immunocompetent hosts, but is well described in patients with underlying pulmonary disease or in otherwise immunocompromised patients.^{6 7 13 14} Patients frequently present with pulmonary disease, as the most common site of infection and the presentation is much similar to infection with other non-tuberculous mycobacteria and *M. tuberculosis*.¹⁵ Uncommon sites of infection have been reported, such as the skin, bones and joints.^{5 7 16–23} Furthermore, infection with *M. malmoense* has a tendency to distribute in two peaks: in children with cervical lymphadenitis and in adults with predominant pulmonary infections.⁵

The risk of disease from NTM increases with the severity of immunodeficiency. In HIV-infected individuals, a CD4 cell count below 50 cells/mm³ is a risk factor for NTM disease.²⁴ The patient in our case had a nadir CD4 count of 60 cells/mm³. A few weeks before the clinical presentation of the infrapatellar purulent bursitis, the patient started antiretroviral treatment leading to a risk of immune reconstitution inflammatory syndrome (IRIS), the paradoxical worsening of pre-existing infectious processes after the start of therapy. IRIS with known or previously undiagnosed mycobacterial infection has been frequently described among HIV-infected patients. The vast majority of NTM infections resulting in IRIS are due to MAC, but cases of IRIS related to infection with a variety of NTM have been described (table 1).^{5 25–30}

The infection was localised with no sign of joint or bone involvement, no supplementary antimycobacterial treatment was thus given following the surgical incision of the infrapatellar purulent bursitis. Currently, there is no consensus for treatment of *M. malmoense* infection. In vitro susceptibility testing does not necessarily correlate with the in vivo activity of the antimicrobial agent or the

Table 1 Reported cases of immune reconstitution inflammatory syndrome associated with NTM

Reference	Number of patients	NTM	IRIS presentation
Phillips <i>et al</i> ²⁵	1	<i>Mycobacterium simiae</i>	Fever Hepatosplenomegaly
Phillips <i>et al</i> ^{26*}	51	MAC (N=43) <i>Mycobacterium genavense</i> (N=2) Smear positive and culture negative (N=6)	Peripheral lymphadenitis Pulmonary-thoracic disease Intra-abdominal disease Miscellaneous presentations
Lawn <i>et al</i> ^{24*}	80	MAC (N=64) <i>Mycobacterium xenopi</i> (N=4) <i>M genavense</i> (N=1) <i>Mycobacterium scrofulaceum</i> (N=1) <i>Mycobacterium kansasii</i> (N=2) <i>Mycobacterium leprae</i> (N=6) BCG (N=2).	Peripheral lymphadenitis leprosy and reversal reaction Pulmonary-thoracic disease
Puthanakit <i>et al</i> ²⁷	14	MAC (N=4) <i>Mycobacterium Scrofulaceum</i> (N=3) <i>Mycobacterium kansasii</i> (N=1) <i>Mycobacterium simiae</i> (N=1) <i>Mycobacterium bovis</i> (N=3) BCG (N=2)	Peripheral lymphadenitis Pulmonary-thoracic disease Intra-abdominal disease Subcutaneous abscesses
Leone <i>et al</i> ²⁸	1	<i>M xenopi</i>	Pulmonary infection
Shelburne <i>et al</i> ²⁹	11	MAC	Localised lymphadenitis hepatosplenomegaly

*Some of the references are overlapping.

BCG, Bacille Calmette-Guerin; IRIS, immune reconstitution inflammatory syndrome; MAC, *Mycobacterium avium* complex; NTM, non-tuberculous mycobacteria.

clinical outcome, but a combination including clarithromycin, rifampicin and ethambutol have been used.^{3 31}

To our knowledge, the isolation of *M malmoense* as part of an IRIS in an HIV infected patient has not been reported previously. Given the rise in incidence of infection with *M malmoense* this case highlights the importance of considering atypical infection as an important differential diagnosis in particularly immunocompromised patients.

Learning points

- ▶ In HIV-infection, the immune reconstitution inflammatory syndrome secondary to starting antiretroviral therapy can be caused by *Mycobacterium malmoense*.
- ▶ Localised infection with *M malmoense* can be treated with surgery alone without supplementary antimycobacterial treatment, even in HIV-infected patients with low CD4 cell counts.
- ▶ PCR for atypical mycobacteria is optimised for microscopy-positive sputum, which must be borne in mind when the method is used on other materials, for example, pus, in which it does not work satisfactory.
- ▶ Atypical infection with atypical clinical presentation, for example, infrapatellar bursitis caused by *Mycobacterium malmoense*, should be considered as a differential diagnosis in severely immunocompromised patients.

Acknowledgements We would like to thank MSc PhD Vibeke Østergaard Thomsen for critically reading the manuscript and assisting with the diagnostic procedures.

Competing interests None.

Patient consent Obtained.

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Leth S, Jensen-Fangel S. Infrapatellar bursitis with *Mycobacterium malmoense* related to immune reconstitution inflammatory syndrome in an HIV-positive patient. *BMJ Case Reports* 2012;10.1136/bcr-2012-007459, Published XXX

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