

Widespread *Mycobacterium marinum* Infection

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Sir,

Mycobacterium marinum is a mycobacterium that causes localized infection with granuloma in the skin in humans, also known as swimming pool granuloma (1, 2). It is found in fresh- and salt-water fish, and infection often occurs when trauma of a person's skin is followed by exposure to fish tank water. The disease occurs primarily at the site of inoculation and normally remains localized, and heals after some months treatment with antibiotics. Lesions are usually solitary and present as papules or nodules that may ulcerate. Sporotrichoid distribution of new lesions may occur, spreading proximally along sites of lymphatic drainage. Rarely, deeper infection, such as tenosynovitis, osteomyelitis or arthritis occurs, and widespread disease may occur in patients with immunosuppression (3, 4).

CASE REPORT

A 48-year-old man with symptoms of arthritis was referred to a department of rheumatology in February 2006 by his general practitioner. The symptoms started 6 weeks earlier with sudden swelling and pain in the right hand. Two weeks previously he had bruised his hand at work. At the time of referral a rash had evolved on the dorsum of the hand. There were no signs of infection or fever. He had a normal X-ray of the right hand, routine laboratory tests within the normal range and a negative *Chlamydia* test. The right hand and wrist showed distinct oedema and erythema, and there was impaired function of the hand, with defective extension of all fingers.

He had no personal or family history of rheumatic disease. The initial diagnosis was rheumatoid arthritis or reflex dystrophy. Ultrasonic examination suggested no intra-articular inflammation. Bone-scintigraphy showed increased activity in the right hand. The patient was started on treatment with prednisolone 25 mg/day, but with no symptomatic relief. Several ultrasound scans were performed during the next months, showing tenosynovitis and tendovaginitis of the extension tendons and bursitis of the right elbow. Additional blood tests were analysed, and immunoglobulin M (IgM) rheumatic factor, human leukocyte antigen B27 and anti-cyclic citrullinated peptide antibodies were all within the normal range. He continued to experience pain despite 20 mg prednisolone daily and treatment with salazopyrin was initiated along with a single injection of 80 mg depo-medrol.

During the following weeks he developed hard red nodules on his forearms (Fig. 1), and was attended by a dermatologist (one of the authors). Swimming pool granuloma was suggested since both the clinical presentation and the fact that the patient had a freshwater aquarium supported this diagnosis. Two biopsies were taken; one for histology and one for culturing of *Mycobacteriae*. Both biopsies were coloured for acid-fast bacilli. Neither of the biopsies showed acid-fast bacilli, granulomatous changes or other histopathological indicators of mycobacterial infection, and there was no growth of mycobacterium in the cultures. The histological examination suggested that the patient had Sweet's syndrome, and since this can be associated with rheumatoid arthritis, this diagnosis was accepted and the prednisolone dose was increased.



Fig. 1. Primary rash on the right arm. This photograph was taken at the first referral to a dermatologist.

Because of the continuous worsening of the symptoms despite therapy, the patient was referred to another department of rheumatology. At the time of referral the treatment was 15 mg methotrexate weekly combined with 75 mg prednisolone daily. Additional examinations were performed, including dual-energy X-ray absorptiometry-scan, positron emission tomography (PET) scan, magnetic resonance (MR) scan of the sacroiliac joint, a new skin biopsy and a synovial biopsy from the affected right wrist. The PET scan showed activity in the subcutis, but no tumours, MR scan did not show any changes in the sacroiliac joints, and the biochemistry of the blood showed slightly increasing C-reactive protein (CRP). The biopsy from the synovialis showed severe acute and chronic inflammation.

The prednisolone dose was reduced, but this was followed by increased pain and involvement of new joints.

From here there was a rapid clinical deterioration, with involvement of additional joints and the skin of arms, legs and body. By this time the patient had fever, weight-loss and decreasing haemoglobin and leukocytes. Methotrexate was discontinued and pulse steroid therapy was initiated with good initial effect on the pain, but rapid relapse. Preceded by relevant examinations, including tuberculin skin test, Quanti-feron®-TB gold test (Cellistis International, Carnegie, Australia) and chest X-ray, which were all normal, treatment with infusion of 300 mg infliximab (Remicade, Schering-Plough, Ballerup, Denmark) was initiated, and 3 infusions were given, before the treatment was discontinued due to lack of effect (Figs 2 and 3). A new skin biopsy was then performed, showing infiltration with neutrophil granulocytes and, in the periphery of the biopsy a structure that was interpreted as the beginning of a granuloma. A mycobacterium infection of the

skin was suggested and this time acid-fast bacteria, later sub-typed as *M. marinum* were found.

DISCUSSION

This case illustrates difficulties associated with the diagnosis of *M. marinum* infections, especially in patients undergoing immunosuppressive treatment. The mean duration of symptoms before diagnosis was reported to be 6.8 and 7.1 months (2, 5). The diagnosis is often based on histological findings, such as granuloma formation, and the presence of acid-fast bacilli found by culture and polymerase chain reaction (PCR). However, a study including 166 patients with *M. marinum* found that only 76% of biopsies showed the classical granuloma, and only 31% showed the presence of acid-fast bacilli (2).

Even though the diagnosis in the present case was suspected when a dermatologist first evaluated the patient, no tell-tale diagnostic signs were found. The previously initiated prednisolone treatment, a well-known inhibitor of granuloma formation, is thought to have prevented granuloma formation in the early stages of the patient's disease. Normally 60–80% of patients with *M. marinum* infection have a positive tuberculin test (6). In this case the test was performed in accordance to guidelines prior to treatment with infliximab, but was found to be negative. It is speculated that the intense immunosuppressive treatment with prednisolone and methotrexate played a role.

Infection with atypical *Mycobacteria* during treatment with tumour necrosis factor (TNF)-alpha inhibitors (infliximab) has been reported previously (3, 4, 7). It is suggested that this treatment also contributed to the widespread disease in the case presented. The diagnosis



Fig. 3. After the immunosuppression the infection was widespread, here illustrated by a photograph of the face.

of *M. marinum* infections in immunosuppressed patients is not simple, and often makes special requirements of the diagnostic procedure; and it must be concluded that the patient's history (skin injuries, aquariums, swimming pools), as well as repeated skin biopsies, is sometimes the only clue to *M. marinum* infections.

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Fig. 2. Right arm after the massive immunosuppression.