CONCISE REPORT

Myositis and swollen knees: disease or treatment complication?

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Interesting and unusual causes of knee pain in three patients with idiopathic inflammatory myositis seen in the clinic over the past 12 months are reported. Their clinical features are described and treatment discussed emphasising the importance of being able to differentiate between a manifestation of the rheumatic disease and a treatment complication. Publications on this topic are also reviewed.

Idiopathic inflammatory myositis (IM) is a rare but well recognised autoimmune rheumatic disease which may occur on its own or as part of an overlap syndrome with rheumatoid arthritis or systemic lupus erythematosus, for example. Joint pain and swelling are recognised features of myositis, but the use of aggressive immunosuppressive agents to treat IM may result in arthritic complications as exemplified by three cases seen in our unit over the past year.

CASE REPORTS

Case 1

A 67 year old Afro-Caribbean man was diagnosed with polymyositis and pulmonary fibrosis in July 1998. He was Jo-1 antibody positive. Treatment with prednisone and azathioprine was started. He responded well clinically, but his creatine kinase (CK) level remained raised at between 1000 and 2000 U/l (normal range 24–195 U/l). He developed pityriasis rosea in 1999 and molluscum contagiosum in March 2000, which required cryotherapy.

In February 2000 he reported increasing left knee pain around the insertion of the vastus medialis. Some soft tissue swelling was noted and a magnetic resonance imaging (MRI) scan confirmed pes anserine bursa synovitis with no fluid collection. At that time the erythrocyte sedimentation rate (ESR) was 24 mm/1st h (normal range 1–10), CK 1105 U/l (normal range 24–204), and total white cell count $12.4 \times 10^9/l$ (normal range $3–10 \times 10^9/l$) with a slight neutrophilia of $9.8 \times 10^9/l$ (normal range $2.0–7.5 \times 10^9/l$) and slight lymphopenia of $1.10 \times 10^9/l$ (normal range $1.5–4.0 \times 10^9/l$). His pain resolved spontaneously but returned in November 2000. Drug treatment at that time comprised azathioprine 150 mg daily and prednisone 7.5 mg daily. An ultrasound scan of his left knee showed pes anserine bursitis with a fluid collection. Thick white fluid was aspirated and no organisms were seen on Gram stain. The patient then reported a white discharge from his medial left knee. Further fluid was aspirated and on this occasion acid fast bacilli (AFB) were seen on Ziehl-Nielsen staining. *Mycobacterium tuberculosis* infection was confirmed on culture and by polymerase chain reaction examination. Laboratory investigations at this time showed an ESR of 14 mm/1st h, CK 2501 U/l, total white cell count $13.3 \times 10^9/l$ with a neutrophilia and normal lymphocytes. Treatment was started with Rifinah, pyrazinamide, and his prednisone dose doubled. A chest radiograph showed evidence of pulmonary fibrosis but none of pulmonary tuberculosis. No

further chest imaging was obtained. The pain and swelling improved rapidly and treatment was stopped after six months. Laboratory values at this time showed a normal ESR and total white cell count with a CK of 2843 U/l. The knee pain and swelling have so far not recurred. However his IM has relapsed and has required treatment with intravenous immunoglobulin.

Case 2

A 54 year old South-East Asian man developed dermatomyositis in 1983. Jo-1 antibody was negative. Treatment was initially started with prednisone. Methotrexate was added in 1993 and azathioprine and hydroxychloroquine in 1998 because of persisting disease activity. Seven courses of intravenous immunoglobulin were given between January 1999 and November 2000.

The patient reported increasing left knee pain over several months in November 2000. A joint effusion was found and aspirated but was sterile on culture. The patient received a corticosteroid injection to the left knee in January 2000, which helped for two months. His symptoms returned in March 2001 and further fluid was aspirated and sent for culture. No AFB were found on Ziehl-Nielsen staining but *Mycobacterium mageritense* was grown on extended culture. Drug treatment at this time comprised prednisone 15 mg daily, azathioprine 100 mg daily, methotrexate 17.5 mg weekly, folic acid 5 mg five days a week, atenolol 50 mg daily, and bendroflumazide 2.5 mg daily. Investigations showed an ESR of 52 mm/1st h, CK and total white cell count normal. A chest x ray examination was unremarkable, therefore no further chest imaging was performed. Treatment with clarithromycin, rifampicin, and ethambutol was started in May 2001 and the prednisone dose doubled. The effusion recurred in July 2001 and a light growth of *M. mageritense* was seen on extended culture. The fluid has not reaccumulated since. Also in July, there was an increase in the patient's muscle weakness with a rise in CK to 565 U/l. This responded well to a course of intravenous immunoglobulin. Antibiotic treatment is continuing with treatment expected to last for 18 months.

Case 3

A 61 year old Indian man developed polymyositis and pulmonary fibrosis in May 1996. He was Jo-1 positive. Initial treatment was with prednisone and azathioprine but because of increasing disease activity he received a course of intravenous cyclophosphamide in 1997, followed by methotrexate in 1998. Cyclosporin A was given from November 1997 to May 1998 but withdrawn as it was not tolerated. Six courses of intravenous immunoglobulin were given between October 1998 and July 2000.

Abbreviations: AFB, acid fast bacilli; CK, creatine kinase; ESR, erythrocyte sedimentation rate; IM, inflammatory myositis; MAI, *Mycobacterium avium* intracellulare; MRI, magnetic resonance imaging

Figure 1 MRI scan of the left knee showing a synovial based mass extending into the popliteal fossa (A).

Increasing left knee pain was reported in March 2000 and there was no response to intra-articular corticosteroid injections. MRI showed an expanding synovial based mass extending into the popliteal fossa and a coincidental torn medial meniscus (fig 1). An initial biopsy in May 2000 was non-specific. A further biopsy in August 2000 showed a "suggestion of granuloma formation" on histology. Synovial fluid at this time grew *Mycobacterium avium* intracellulare (MAI) on extended culture. Other investigations at this point showed an ESR of 68 mm/1st h, CK and total white cell count normal. The ESR had been raised before the development of knee symptoms. A chest x ray examination showed evidence of pulmonary fibrosis only. No further chest imaging was performed. Treatment at this time comprised azathioprine 150 mg daily, methotrexate 15 mg weekly, prednisone 5 mg weekly, thyroxine 150 µg weekly, and antihypertensive drugs. Treatment was started with clarithromycin and rifabutin but the popliteal fossa swelling increased markedly in size impeding mobilisation. A limited synovial debridement was performed in December 2000 with a resultant increase in range of movement and reduction in pain. Antibiotic treatment was stopped after 13 months, and the patient currently has no knee pain or swelling.

DISCUSSION

IM is a rare condition with an estimated incidence of 0.5 cases per 100 000. Patients with autoimmune rheumatic disease live longer and are more aggressively treated with immunosuppressive agents. For example, 10 year survival in systemic lupus erythematosus has increased from 54% in 1964 to 76% in 1999.¹ Five year survival in IM was 65% in a study in 1996,² and in a cohort of 46 patients at our centre was 83.8% in 2000.³ Hochberg *et al* found that the mean age of death in patients with IM in America increased significantly between 1968 and 1978.⁴

We have described three cases of mycobacterial infection in or around the left knee in men with IM. All met the

classification criteria of Bohan and Peter. Mean age at presentation was 53 years and mean duration of disease before diagnosis of infection was 7.6 years. They have all been receiving immunosuppressive drugs and two patients have received intravenous immunoglobulin.

In a study of 30 cases of *M tuberculosis* (TB) infection in patients with autoimmune rheumatic disease, five had IM.⁵ This is a relatively high number in a rare disease. In comparison, only seven cases of TB were found in patients with rheumatoid arthritis, which has a higher incidence. All had received one or more immunosuppressive agent at some time in their disease course. Of the infections, 34% were pulmonary and 10% osteoarticular. Miliary disease was found in 23% of patients and the remainder had either renal, lymphoreticular, cutaneous, or peritoneal infection.

Atypical mycobacterial infection is commonly seen in immunosuppressed patients. *M malmoense* was first described in Sweden in 1977 and infection is commoner in northern Europe. It is a slow growing bacterium that has not yet been cultured from inanimate sources, in contrast with other atypical mycobacteria. In 221 infections with *M malmoense* reported in Sweden,⁶ none was osteoarticular and the majority were pulmonary in origin. In 38 cases no risk factor for infection could be found. Three cases of *M malmoense* tenosynovitis have been described, which all responded to treatment.⁷ Two patients had risk factors—diabetes mellitus and asthma—during long term prednisone treatment. There are no published reports on *M malmoense* infection in patients with autoimmune rheumatic disease.

MAI—which together with *M avium* forms the *M avium* complex—is also slow growing and found in the air, soil, and water. Portal of entry is commonly through the gastrointestinal tract and can cause severe infection in immunosuppressed patients—for example, those with AIDS. Cases have been reported of MAI infection in dermatomyositis presenting as tenosynovitis⁸ and deep cutaneous infection.⁹ MAI infection of the first metatarsophalangeal joint in a patient with AIDS has also been reported.

Other atypical mycobacterial infections reported include a case of cutaneous *Mycobacterium chelonae* infection in a patient with dermatomyositis.¹⁰

There are no reports of the passage of mycobacterial infection through intravenous immunoglobulin treatment. On the contrary, it is thought that intravenous immunoglobulin is one of the least immunosuppressive treatments available.

The dose of corticosteroids was increased when antimycobacterial treatment was started in our patients. This was to counteract the stimulatory effect of rifampicin on hepatic enzyme induction, which would otherwise lead to a reduction in efficacy of the corticosteroid dose. A case series in 1987¹¹ reported two patients with dermatomyositis who developed muscular tuberculosis. Both patients developed a severe relapse, attributed to the start of treatment with rifampicin. Despite the increase in steroid dose in cases 1 and 2, there were relapses in IM after starting rifampicin, requiring treatment with immunoglobulin.

All three cases occurred in patients whose were born outside the United Kingdom. It is thought that one third of the world population has latent infection with *M tuberculosis*,¹² and in areas of low endemicity, most infections are due to reactivation of latent bacilli. A recent study¹³ applied polymerase chain reaction techniques to macroscopically normal lung tissue in 47 patients from Ethiopia and Mexico who had died of other causes. Fifteen patients were found to have mycobacterial DNA present in alveolar, endothelial, and fibroblast cells. A further study showed that the number of cases of *M tuberculosis* infection in the USA in foreign-born people increased by 2.6% between 1993 and 1998.¹³ The proportion of American cases who were foreign born increased from 29.8% in 1993 to 41.6% in 1998. Most patients were from Mexico, India, or South East Asia, male, and aged between 25 and 44. In case 1,

chest radiography showed no evidence of new or old infection with *M tuberculosis*. This does not rule out latent infection, but further imaging or pulmonary investigations would not have altered the management of our patient as AFB were found from the aspirate.

In conclusion, it is always worth considering atypical infection in patients with autoimmune rheumatic disease who present with musculoskeletal symptoms that do not settle with conservative treatment. It should also be considered in patients born in areas of high endemicity of *M tuberculosis*, even if chest radiographs show no evidence of previous infection. In case 1, symptoms initially resolved spontaneously, but this should not preclude a diagnosis of slow growing bacterial infection, including tuberculosis. In addition, septic synovitis can be misleadingly improved after a corticosteroid injection, as occurred in case 2, possibly leading to a delay in diagnosis or disseminated infection with poor prognosis. Fungal infections should also be considered, which can cause severe joint and soft tissue damage. Tissue should always be sent for mycobacterial and fungal culture and microscopy, though cultures may take several weeks to become positive.

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