Case report

Polyarthritis due to *Mycobacterium kansasii* in a patient with rheumatoid arthritis

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SUMMARY A case of destructive polyarthritis due to infection by *Mycobacterium kansasii* is described in a 68-year-old patient with long-standing rheumatoid arthritis (RA) receiving prednisone and azathioprine therapy. Superimposed infection was suggested by positive Ziehl-Neelsen stains of synovial fluid from the patient's right shoulder and wrists, with confirmation on culture. Histological examination of synovium revealed abundant noncaseating granulomata within subsynovial cellular infiltrates. Treatment with triple antituberculous chemotherapy resulted in substantial extra-articular improvement within 3 months. However, articular destruction progressed unabated. A high index of suspicion is needed to diagnose joint infections in patients with underlying polyarthritis who are receiving immunosuppressive therapy. The progressive joint damage, despite periarticular resolution, may suggest the need for a combination of surgical synovectomy and antituberculous chemotherapy.

Patients with underlying joint disease such as rheumatoid arthritis have an increased susceptibility to developing infection in the involved joints (Kellgren *et al.*, 1958).

In contrast to infections in previously normal joints, infectious arthritis in chronically inflamed joints may be masked by symptoms and signs of the underlying disease. Indeed, the usual local signs of infection such as heat, redness and tenderness and even the systemic manifestations of infection may be absent (Kellgren *et al.*, 1958). Moreover, the use of immunosuppressive therapy in such patients may predispose to unusual infections which in themselves are difficult to detect (Anderson *et al.*, 1973).

The present case of *Mycobacterium kansasii* infection in multiple joints in a patient with rheumatoid arthritis receiving immunosuppressive treatment, illustrates both the propensity of such patients to develop disseminated infections and the high index of suspicion required to detect them.

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Case report

A 68-year-old woman was admitted to the Rheumatic Disease Unit of the Wellesley Hospital in May 1977 because of increasing severity of polyarthritis over a 4-month period. Her illness dated back to 1961 with the onset of a symmetrical polyarthritis compatible with rheumatoid arthritis. In 1971 she was diagnosed as having Felty's syndrome and a necrotising vasculitis. She was treated with 20 mg of prednisone per day, and isoniazid was added because of a previously positive tuberculin skin test (though at that time it was negative). In the same year azathioprine 100 mg per day was added to treat leg ulcers and a severe, rapidly progressive neuropathy.

Her arthritis was only mildly active from 1972 to 1975, though she required reconstructive surgery to her left thumb on 2 occasions during this period. By November 1975 her medications had been reduced to prednisone 7.5 mg per day and azathioprine 50 mg per day. Gradual, painless swelling began in August 1976. From February 1977 she experienced progressively increasing pain in the

small joints of her hands, wrists, and shoulders. At the time of admission she complained of fatigue, night sweats, loss of 5 lb (2.3 kg) weight, morning stiffness extending throughout the day, and markedly reduced shoulder and wrist function. On admission systemic examination was normal except for several cyst-like subcutaneous masses in the right buttock and a residual left foot drop. There were 19 actively inflamed joints as denoted by effusions, stress pain, or joint tenderness. Effusions were present in both wrists, the right elbow, and right knee. The right shoulder had a massive effusion extending both anteriorly and posteriorly. The shoulder was virtually immobile in contrast to August 1976, at which time the range of motion was full. Marked flexor and extensor carpi ulnaris tenosynovitis was present about both wrists (Fig. 1). There were gross rheumatoid deformities with swelling of the metacarpophalangeal joints bilaterally.

Comparison of serial x-rays revealed no progression in the erosive changes in the joints between 1972 and 1976. However, x-rays on admission in 1977 showed the development of marked erosive and destructive changes in the wrists (Figs. 2 and 3) and right shoulder since 1976.

Synovial fluid from the right shoulder and both wrist joints was inflammatory in character, with acid-fast bacilli seen on smear. Cultures later yielded photochromogenic atypical mycobacteria identified as *Mycobacterium kansasii*. Histological examination of synovial biopsy specimens of both wrists revealed marked proliferation of synovial lining cells with subsynovial inflammatory cell infiltrates. Noncaseating granulomas were present in abundance, particularly in the synovium of the

Fig. 1 Extensive flexor and extensor carpi ulnaris tenosynovitis with synovial swelling about the wrists.

Fig. 2 X-rays of the left wrist. Upper—1972. Degenerative joint changes at the first carpometacarpal joint without erosions. Middle—May 1977: Erosion and collapse of the proximal carpal bones with moderate subluxation of the radiocarpal joint. Lower—December 1977: Advanced destruction and collapse of the proximal carpus with further subluxation of the radiocarpal joint and erosion of the radial styloid

Fig. 3 X-rays of the right wrist. Upper—1972: Erosions of all carpal bones with radiocarpal joint narrowing and subluxation. Middle—May 1977: Collapse of the carpus with further erosive changes. Lower—December 1977: Severe collapse and subluxation of the carpus

right wrist (Fig. 4). Nonspecific immunofluorescent staining with rodamine showed fluorescent bacilli compatible with *Myco. kansasii*.

Fig. 4 Synovial biopsy specimen taken from the right wrist in May 1977 showing synovial lining cell hyperplasia with severe subsynovial mononuclear cell infiltration. Numerous noncaseating granulomata with multinucleated giant cells are evident ($\times 63$)

Treatment was begun with isoniazid 5 mg/kg, ethambutol 15 mg/kg, and rifampin 600 mg per day. Subsequent in-vitro sensitivity studies showed the organism to be resistant to isoniazid and ethambutol, but this therapy was continued because of the improvement in articular and constitutional symptoms within 3 months. At that time the effusions in her right shoulder and wrists had decreased and the cystic masses on her right buttock and wrists were much smaller. The improvement was sustained through September 1977, with x-rays showing no further progression.

In December 1977 the patient presented with increasing pain and disability in her right shoulder and both wrists. The improvement in tendon and joint swelling was sustained, but x-rays showed further destruction of the right glenohumeral joint such that the humeral head now articulated with the scapula. Moreover, there was extensive collapse of the carpi bilaterally (Figs. 2 and 3).

Aspiration of the affected joints was unsuccessful. In January 1978 a synovectomy and stabilisation of the left wrist was carried out. Although the synovium appeared grossly normal, histological examination

Fig. 5 Synovial specimen taken from the left wrist in January 1978 showing persistent synovial lining cell hyperplasia subsynovial cell infiltration. Note the absence of granulomata ($\times 63$)

showed extensive subsynovial cellular infiltration (Fig. 5), with pannus invading bone fragments. No granulomata were seen, and a rodamine stain was negative. The possibility of inadequate levels of rifampicin in blood or synovial fluid was explored by obtaining multiple blood rifampicin levels over a 12-hour period and comparing them with those obtained from simultaneous synovial fluid aspiration of the right knee. The results (data not shown) demonstrated levels well in excess of the minimum inhibitory concentrations in both the blood and synovial fluid.

Streptomycin was added in a dose of 500 mg intramuscularly daily for 2 weeks and twice a week thereafter for 6 months despite a negative culture for mycobacteria. Moreover, chloroquine, 250 mg per day, was begun. Six months after starting this therapy no further clinical or radiological progression was observed.

Discussion

The propensity for patients with chronic arthritis to develop a superimposed joint infection has been well documented (Karten, 1969). *Kellgren et al.* (1958) first drew attention to suppurative arthritis complicating rheumatoid arthritis. Since then there have been several reports of septic arthritis superimposed on rheumatoid arthritis (Rimoin and

Wennberg, 1966; Karten, 1969; Myers *et al.*, 1969). The susceptibility to infection in patients with rheumatoid arthritis is increased in the presence of severe long-standing disease, Felty's syndrome, and immunosuppressive therapy (Seinknecht *et al.*, 1977). Moreover, such patients have been shown to be at risk for opportunistic infections with organisms of low virulence such as *Myco. kansasii* (Ortbals and Marr, 1978).

The present case illustrates the difficulty in diagnosing a suppurative process in joints of immunologically compromised patients who have underlying polyarthritis. The insidious onset of infections like *Myco. kansasii* compounds the problem of early diagnosis. Such patients often do not show a local articular response to infection such as heat and erythema. As the present case illustrates, joint pain may merely be out of proportion to that in the other uninfected joints.

Myco. kansasii has been previously reported to cause extrapulmonary infection in man, including fasciitis, tenosynovitis, and arthritis (Girard *et al.*, 1973; Gunther and Elliott, 1976). Although cases of synovial infection by *Myco. kansasii* have been reported, the present case represents only the third with polyarticular involvement (Kelly *et al.*, 1963; Klinenberg *et al.*, 1965). The commonest site of synovial tissue infection has been reported to be tendon sheaths of the hand and wrist, with the joints involved less frequently. Previous reports have described involvement of small joints of the hands with a variety of other atypical mycobacterial infections (Girard *et al.*, 1973; Gunther and Elliott, 1976; Hoffman *et al.*, 1978). Thus a granulomatous process may indeed closely simulate rheumatoid arthritis.

The value of culturing articular tissue to diagnose atypical mycobacterial infections has been emphasised (Hoffman *et al.*, 1978). Although the yield of organisms from synovial or bursal fluid is considerably lower, the present case demonstrates the importance of submitting such fluid for analysis prior to tissue biopsy.

The discrepancy between the tenosynovial and articular responses to treatment raises a question as to the pathogenesis of the progressive joint destruction after therapy. A mycobacterial infection as such would seem unlikely in view of a negative synovial culture from an affected joint, namely, the left wrist. Moreover, the eradication of *Myco. kansasii* is supported by the disappearance of the vigorous granulomatous reaction seen in the infected synovium before treatment. It is conceivable that the granulation tissue generated initially by *Myco. kansasii*, with or without associated rheumatoid disease, led to pannus invasion of bone, causing

mechanical collapse with subsequent use. Klinenberg *et al.* (1965) have suggested that a hypersensitivity reaction to occult *Myco. kansasii* antigen (in the absence of organism proliferation) might act as a mechanism of persistent joint disease. Finally one might speculate that the mycobacterium acted as an adjuvant to locally enhance the rheumatoid process or indeed stimulated an adjuvant form of autoimmune disease directed at articular tissue. A combination of several of these factors might be acting.

The progressive articular destruction raises the problem of the treatment of the arthritis induced by *Myco. kansasii*. Kelly *et al.* (1963, 1967) stressed the need for complete synovectomy of the affected joint and would not recommend antibacterial therapy without synovectomy. Support for this concept comes from a recent review of septic arthritis due to atypical mycobacteria, in which it was noted that periarticular or articular disease in all patients was 'arrested' with combined surgical excision and chemotherapy (Hoffman *et al.*, 1978). It should be stressed, however, that chemotherapy alone has proved effective in patients with fasciitis or destructive polyarthritis (Klinenberg *et al.*, 1965; Hoffman *et al.*, 1978). In the present case the marked periarticular and soft tissue response and the negative cultures following treatment imply that the antimicrobial agents were effective despite the partial in-vitro resistance.

It is conceivable that early synovectomy might have sufficiently reduced the load of organisms locally to prevent pannus invasion and collapse of bone. On this account surgical synovectomy may be justified early in the course of articular infection with *Myco. kansasii* in combination with anti-tuberculous chemotherapy.

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