Case report

Arthritis associated with adjuvant mycobacterial treatment for carcinoma of the bladder

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SUMMARY A patient who developed an inflammatory polyarthritis following intravesical administration of bacillus Calmette-Guérin (BCG) used in the treatment of bladder cancer is described. An inflammatory synovitis comprising predominantly T lymphocytes was demonstrated on synovial biopsy. The synovitis resolved spontaneously within 14 days in this 'human model' of adjuvant arthritis.

Key words: BCG induced arthritis, rheumatoid arthritis, *Mycobacterium tuberculosis*.

Adjuvant arthritis is a chronic disease inducible in susceptible strains of rats by immunisation with Freund's adjuvant containing *Mycobacterium tuberculosis*.¹ Recent work has highlighted the role of mycobacterial antigens in the induction of the disease, and it has been shown that an antigen of *M tuberculosis* shares a cross reactive epitope with an antigen in articular cartilage.^{2,3} The disease may be transmitted in rats by transfer of arthritogenic clones in the absence of mycobacterial antigen.^{4,5} More recently, T lymphocytes from rheumatoid arthritic patients have been shown to exhibit an augmented response to a fraction of mycobacteria cross reactive with cartilage.⁶

In this paper we report a patient who developed an inflammatory polyarthritis while receiving treatment with intravesical BCG used as an antimitotic agent. This demonstrates a model of disease induction in a human, comparable with experimental adjuvant arthritis.

Case report

A previously healthy 80 year old man was found to have in situ transitional cell carcinoma of the bladder, which was removed cystoscopically.

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Twenty six months later check cystoscopy showed a recurrence of the lesion, and a treatment regimen of intravesical BCG (Glaxo live attenuated) was started. Twenty vials, each containing 10 units percutaneous BCG BP, were diluted to 50 ml with normal saline and instilled into the bladder. Five similar doses were given at weekly intervals thereafter.

On the day of the sixth and final treatment he gave a 24 hour history of arthralgia related to the knees, elbows, and shoulders, associated with profound stiffness and functional impairment. An erythrocyte sedimentation rate of greater than 100 mm/h prompted an initial diagnosis of polymyalgia rheumatica. Treatment was started with prednisolone 10 mg daily, and he was referred to the rheumatology outpatient clinic for assessment.

When seen three days later he was admitted to the ward completely incapacitated by pain and stiffness in many joints. He had soft tissue swelling and effusions in both knees, together with pain and swelling of the right shoulder and of several metacarpophalangeal joints. The erythrocyte sedimentation rate was still raised to >100 mm/h. He also had a raised C reactive protein of 162 U (normal range <5). Serum uric acid, immunoglobulin, and complement (C3 and C4) concentrations were normal. Tests for rheumatoid factor, antinuclear antibodies, and anticollagen (types 1 to 6) antibodies were negative. There were no radiological abnormalities of the affected joints. Joint fluid, urine, and blood

cultures were sterile, including culture for mycobacteria. The cellular composition of the synovial fluid consisted of 80% polymorphs. Results of HLA tissue typing were A1,30; B18,57; DR3,—.

Arthroscopy of the left knee showed an active synovitis with villous formation and hyperaemia of the synovial membrane and substantial surface fibrin. Synovial biopsy showed hyperplasia of the synovial lining layer to a maximum of four cells depth, with incorporation of surface fibrin (Fig. 1). Deep to the lining layer there was an intense diffuse perivascular infiltrate containing macrophages, lymphocytes, and plasma cells. Discrete lymphocytic aggregates with germinal centre formation were not observed. The inflammatory infiltrate consisted almost entirely of T cells (CD3) (Leu 4; Becton

Dickinson), with a T helper (CD4) (Leu 3a; Becton Dickinson) to T suppressor (CD8) (UCH T4; Seward) ratio of 1.28. Staining for B cells (CD22) (Dako-CD22; Dakopatts) was negative.

Staining and culture for acid fast bacilli were negative. Routine immunofluorescence showed fibrinogen staining of lining layer and vessel walls and occasional positive staining of plasma cells for IgG, but no interstitial deposits of IgA, IgM, C3, and C1q were seen.

Treatment with a non-steroidal anti-inflammatory drug was started and his prednisolone dosage tailed off. Clinical recovery was rapid over a 14 day period. At present, nine months later, he remains asymptomatic with no joint signs and a normal erythrocyte sedimentation rate.

Fig. 1 Synovial biopsy specimen showing surface fibrin (arrows) in an expanded lining layer and a perivascular infiltrate of lymphocytes, monocytes and plasma cells. (Haematoxylin and eosin.)

Discussion

The patient described in this paper is the first reported to show a histologically proved synovitis associated with intravesical BCG treatment. This shows that the synovitis is characterised by an infiltration of mononuclear cells, without demonstrable mycobacteria in the joint. This presentation satisfies the current concept of a reactive arthritis following an infective trigger.

Local BCG is now widely used in the treatment of many neoplasms.⁷ Specific application of this treatment to bladder cancer is well established,^{8,9} and there are several reported cases of adverse reaction to treatment. Joint disease described as arthritis or arthralgia was found in 0.5% of 1278 patients in a retrospective review.¹⁰

In a further study intradermal BCG injections used in the treatment of advanced malignancies caused an arthritis in 10 of 159 patients.¹¹ Clinically these patients appeared to suffer from a symmetrical small joint polyarthritis associated with a negative rheumatoid factor. As with our patient stiffness was a prominent symptom. Synovial fluid showed increased neutrophil counts. Synovial biopsy was performed in one patient and showed a chronic synovitis.

It has been postulated that the beneficial effect of BCG treatment in cancer is due to an enhancement of cell mediated immunity. Clinical evidence for this is demonstrated by the correlation of tumour regression with conversion of the purified protein derivative skin test to positive and indirectly by the development of high titres of antibody to BCG.⁹

If this patient represents a human model of adjuvant induced arthritis a cross reaction between a mycobacterial antigen present in BCG and a host antigen might have resulted in a clinical synovitis. The histology of the synovitis of our patient resembles that seen in the animal model,¹² with a predominance of lymphocytes and plasma cells, and is seen in other forms of human inflammatory synovitis, including reactive arthritis following genital or enteral infections.¹³

In the skin the reaction to tubercle antigen is modulated by HLA phenotype, and HLA-DR4 has been associated with high responsiveness to antigens specific for *M tuberculosis*.¹⁴ It is interesting to speculate whether the intensity or duration of the

arthritis would have differed if the patient described in this paper had carried the HLA-DR4 phenotype rather than HLA-DR3, and subsequently developed rheumatoid disease. The low incidence of a reactive arthritis following BCG administration or tuberculosis suggests that the interaction of mycobacterial antigens with HLA-DR4 is too simplistic a model for explaining the induction of rheumatoid arthritis. Nevertheless, further study into such arthritides may help to establish the important determinants in predisposition to chronic autoimmune joint diseases.

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