For Debate . . .

Do Lymphocytes Protect the Rheumatoid Joint?

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Summary

The pathology of the synovial membrane in rheumatoid arthritis can be characterized by the prominence of two major features which appear to vary independently of one another. These are synovial lining-cell proliferation and infiltration with inflammatory cells, predominantly lymphocytes. In a series of 42 synovectomies from 36 patients it has been shown that extensive joint damage is associated with a synovial picture of marked lining-cell proliferation and a sparsity of lymphocytes. Cases with heavy lymphocyte infiltration tend to show less damage to articular cartilage and bone despite a similar duration of disease. These results have been compared with the picture in leprosy, where a similar pathological spectrum is associated with changes in cell-mediated immunity necessary for the control of infection.

Introduction

In most diseases a histological study of the involved tissue will give some indication of the activity and severity of the disease and frequently of the prognosis. Recently such diverse conditions as Hodgkin's disease¹ and leprosy² have been classified on the basis of the extent of lymphocyte infiltration of the diseased tissue, and in both cases a heavy infiltrate of lymphocytes is said to favour a better prognosis.

In rheumatoid arthritis synovial inflammation is the most evident part of the clinical picture and is the earliest and most constant pathological feature. Yet there is a widely held belief that no correlation exists between synovial changes and the duration, activity, or stage of progression of the disease.³ The two most characteristic features of the rheumatoid synovium are proliferation of synovial lining cells and an infiltration of inflammatory cells, mainly lymphocytes and plasma cells. The proportions of these two features vary widely from case to case, but so far no attempt has been made to relate these variations to the damage produced in individual joints.

This study was primarily designed to correlate lysosomal enzyme concentration in homogenates of tissue removed at synovectomy with the histological findings and with the surgeon's estimate of cartilage and joint damage. A preliminary study, however, showed that it was also possible to classify and correlate the degree of lining-cell proliferation with the enzyme levels and joint damage. At the same time it was

noted that many of the less damaged joints showed a heavy infiltrate of lymphocytes. This paper reports the results of grading lining-cell proliferation and inflammatory-cell infiltrations and compares these gradings with the degree of joint damage.

Materials and Methods

Synovial tissue was obtained at synovectomy from 42 joints in 36 patients with rheumatoid arthritis (20 male, 16 female). All satisfied standard diagnostic criteria for "classical" or "definite" disease.⁴ The mean age of the patients was 49 years (range 16-74) and the duration of disease in the operated joint varied from 8 months to 10 years (mean 3.8 years). Material came from 37 knees, two elbows, one hip, one wrist, and one shoulder joint. Smaller joints were not studied since enough synovial membrane was needed to provide at least three blocks of tissue from representative areas in each joint. Often up to six blocks were selected to cover macroscopically different parts of the synovium. More sections were taken from the predominant type of surface in each joint, which tended to be either flat or villous. Since at least 1 cm of synovial surface was required in each block to give an adequate impression of the type of synovium tissues from punch biopsies and smaller joints were excluded. At the time of operation the surgeon graded the joint damage in the following way: grade 1, synovitis only, cartilage and bone appeared normal; grade 2, early pitted erosions along bone-cartilage junction, cartilage appeared normal; grade 3, extensive erosions, thinned cartilage; and grade 4, extensive erosions and cartilage damage, joint structures considered to be permanently damaged.

The synovial membrane was fixed in neutral phosphate-buffered 10% formalin and sections were stained with haematoxylin and eosin. Sections were examined without knowledge of the patient's identity or grade of joint damage. The degree of synovial lining-cell proliferation and the infiltration of lymphocytes were given a grade of 1 to 4 depending on an assessment of increasing numbers of cells. Six weeks later the slides were rearranged and regraded without reference to the previous reading. The grading of synovial lining cells was the same in 37 of the 42 joints at each assessment and of the lymphocyte infiltration in 35 joints. In most cases a third grading was made and on no occasion did the result differ by more than one grade at each of the three readings.

Results

The microscopical picture of the synovium varied between a villous and a flattened appearance, as seen macroscopically, but only minor differences were noted within individual

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sections and from area to area in a joint. The pattern was usually consistent over the three to six sections from the one joint and a reproducible grading of the two basic features was therefore possible. In Fig. 1 a massive palisade of synovial lining cells is shown which was present throughout most of the synovial surface in all sections from this joint. This was classed as grade 4. In Fig. 2 the lining cells are arranged in a thin horizontal layer. Despite the more villous nature of the

FIG. 1—Massive palisade of lining cells covering a synovial stroma which contains few infiltrating cells. (H. and E. $\times 63$.)

FIG. 2—Synovial surface composed of small lining cells arranged horizontal to the surface. The stroma is heavily infiltrated with lymphocytes and a germinal centre is present. (H. and E. $\times 63$.)

tissue the number and size of lining cells are clearly smaller than in Fig. 1. In Fig. 2 there is a massive infiltrate of lymphocytes, and a germinal centre is visible. Focal collections like this appeared in all blocks in this case, and lymphocyte infiltration was recorded as grade 4. By contrast lymphocytes were sparse in Fig. 1, where grade 1 was applied. Though these are extreme examples the grading of intermediate degrees was only a little more difficult. In some joints a pronounced surface cell palisade was associated with an extensive infiltration of lymphocytes, while in other cases numbers of both cells were generally small.

A study of the clinical features indicated that disease duration was not significantly correlated with histological pattern (Figs. 3 and 4). For example, the heavy palisade of surface cells shown in Fig. 1 occurred nine months after the disease onset. A sparsity of lymphocytes could not be related to oral corticosteroid therapy nor to massive salicylate or other anti-inflammatory drug therapy. None of the 36 patients had received the immunosuppressive drugs cyclophosphamide or azathioprine. The comparison of joint damage recorded by the

surgeon with the grading of lining-cell proliferation is shown in Fig. 5. A direct correlation is apparent and a χ^2 analysis on a 2×2 table, as indicated in Fig. 5, gave a statistically significant figure of 5.12 ($P < 0.05$). Joint damage is compared with the grade of lymphocyte infiltration in Fig. 6, and an inverse relation is strikingly shown. The χ^2 value is 9.47 ($P < 0.01$).

In the six patients where synovium was available from two joints both the degree of joint damage and the pathological picture showed only minor differences. There was no correlation between the duration of disease in the biopsied joint

FIG. 3—Comparison of lining-cell proliferation and duration of disease in the biopsied joint (37 joints).

FIG. 4—Comparison of lymphocyte infiltration and duration of disease in the biopsied joint (37 joints).

FIG. 5—Comparison of lining-cell proliferation with joint damage (42 joints).

FIG. 6—Comparison of lymphocyte infiltration with joint damage (42 joints).

FIG. 7—Comparison of duration of disease in the operated joint with joint damage (37 joints).

and the grade of joint damage (Fig. 7). Tests for rheumatoid factor were persistently negative in three patients. All had moderately heavy synovial lymphocyte infiltration recorded as grade 3.

Discussion

No single synovial change in rheumatoid arthritis is specific. There are gross changes other than those selectively studied in this project but most are not suitable for correlation with the operative findings. Abnormalities in synovial blood vessels are common to all cases. Areas of necrosis and fibrin deposits are too patchy to be useful markers, and neutrophils are more a feature of the synovial fluid than the membrane. We have already reported a relation of three "minor" pathological findings with certain clinical features and disease severity. These are the rheumatoid giant cell, bone and cartilage debris, and haemosiderin seen within the synovial membrane.⁵ But the two "major" features considered here are likely to be much more important in understanding the disease pathogenesis and hence the joint destruction.

What has been shown is a histological spectrum comprising synovial lining-cell proliferation and lymphocyte infiltration, which appear to vary independently of each other. The extent of lining-cell proliferation correlated directly with cartilage and erosive joint damage. It is known that many of these lining cells contain enlarged lysosomes,^{6,7} and there is circumstantial evidence that these enzymes are involved in damage to cartilage in rheumatoid joints.^{8,9} We have unpublished observations which relate the concentrations of lysosomal enzymes in homogenates of synovial tissue to the joint damage. The stimulus to lining-cell proliferation and to lysosomal enlargement in this disease is unknown, but there is a reawakening of interest in the possible role of micro-organisms.

The more surprising part of this study was the finding that a heavy infiltrate of immunocytes, predominantly lymphocytes, appears to provide some protection against damage to cartilage or bone. Neither the presence of lymphocytes nor the degree of joint damage was related to disease duration. A heavy infiltrate of lymphocytes was seen within a year of the disease onset and in synovium removed after 10 years of persistent inflammation in the one joint. All patients were on some form of antirheumatic drug, but the use of any specific drug such as corticosteroids did not appear to influence the pathological picture.

The plasma cells of the rheumatoid synovium have been shown to be a site of origin of immunoglobulins including the rheumatoid factor,¹⁰ and the possible role of immunoglobulins in the pathogenesis cannot be denied.¹¹ Cytotoxic effects of lymphoid cells have been shown in vitro¹² and there is some evidence of blast transformation of lymphoid cells in rheumatoid synovia with related tissue damage.¹³ The principal infiltrating cell in most cases, however, is the small lymphocyte, and the lymphocyte is important in cell-mediated immune processes.

In a recent review, Turk¹⁴ described cellular immunity in leprosy in terms of a histological spectrum which may be relevant to rheumatoid arthritis. At one extreme is lepromatous leprosy, the severe progressive form of the disease, and this is noteworthy for the virtual absence of lymphocytes in the lesions. The apparent loss of cell-mediated immunity is thought to be the reason for the uncontrolled growth of *Mycobacterium leprae* in the tissues. In tuberculoid leprosy (a milder form of the disease) pronounced lymphocyte infiltration is a feature of the lesions, and the organism is found with difficulty if at all. It is thought that cell-mediated immunity is necessary for the elimination of the mycobacteria, which can spread through the tissues despite the presence of circulating humoral antibodies. Patients with lepromatous leprosy have high levels of circulating antimycobacterial antibodies and can develop skin lesions due to deposition of immune complexes containing immunoglobulins, complement, and soluble mycobacterial antigens.¹⁵ These lesions take the form of a vasculitis.

Our findings suggest that there is a similar spectrum of disease in rheumatoid arthritis and that this may be related to a variation in cell-mediated immune processes, as reflected by lymphocyte infiltration of the synovium. This could be independent of circulating humoral antibody as represented by the rheumatoid factor. The role of rheumatoid factor is controversial but it is accepted as an antibody against an antigen present in the IgG fraction of serum.¹⁶ It is found in a variety of diseases characterized by prolonged antigenic stimulation including bacterial infections.¹⁷ There is a recognized correlation between the presence of a high titre of rheumatoid factor and the development of a vasculitis.¹⁸

Cell-mediated immune processes also appear necessary for the defence of the body against other organisms, such as protozoa, fungi, and a wide range of viruses.¹⁴ A renewed interest in the possible virus aetiology of rheumatoid arthritis has been noted,¹⁹ and it is suggested that a study of the lymphocyte-deficient synovia may be rewarding in seeking a possible causative organism.

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