Lack of correlation of synovial histology with joint damage in rheumatoid arthritis

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Henderson, D. R. F., Jayson, M. I. V., and Tribe, C. R. (1975). *Annals of the Rheumatic Diseases*, 34, 7. Lack of correlation of synovial histology with joint damage in rheumatoid arthritis. Twenty-two patients with rheumatoid arthritis (RA) involving the knee were studied. The systemic features of the disease were graded and the extent of knee involvement was quantified in terms of the clinical, radiological, and arthroscopic appearances. Adequate synovial biopsies were obtained from 21 patients. In these patients no correlation could be found between the severity of any of the features on histological examination nor between any of these features and the extent of local joint damage, inflammation, or the severity of the systemic disease.

It has been thought that the histological features of RA do not reliably indicate the degree of activity or prognosis of the disease and that they are not specific for that condition (Hamerman, Sandson, and Schubert, 1963). Indeed, Waxman and Sledge (1973) were unable to distinguish histologically between rheumatoid and osteoarthritic synovia.

Recently, however, Muirden and Mills (1971) found in rheumatoid joints submitted for synovectomy a direct correlation between the degree of synovial lining cell hyperplasia and joint damage and an inverse correlation between the degree of lymphocytic infiltration and joint damage. Lymphocytes might play a helpful role in protecting the rheumatoid joint. Muirden (1970) has also reported a significant relationship between histological estimates of the extent of the iron deposits with the grades of x-ray changes in biopsied joints.

These findings are obviously of importance and suggest that methods of determining the prognosis of RA and the choice of appropriate therapy could be based on the histological appearances of synovial biopsies.

Precise quantification of the degree of synovial inflammation and the amount of articular damage in the joints of patients with RA is difficult. Physical examination and radiology provide information which is useful but indirect. For example, the degree of damage to articulating surfaces seen at arthrotomy may far exceed that suggested by x-rays. Arthroscopy of the knee allows direct inspection of much of the synovium and articulating surfaces. It also enables direct biopsy of selected sites without

recourse to arthrotomy (Jayson and Henderson, 1973).

The present study was directed towards confirming the findings of Muirden and Mills (1971). Clinical parameters, arthroscopic findings, and x-ray changes were quantified and used to determine the activity of the inflammatory process and the degree of joint damage. These have been compared with the graded histological changes in synovial biopsies.

Materials and methods

Studies were performed on patients with definite or classical RA (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) and significant involvement of at least one knee. The clinical assessments were performed by one of us (D.H.) before arthroscopy, and the following data were noted: age, sex, duration of disease, treatment with gold or corticosteroids, duration of morning stiffness, presence of nodules, grip strength, haemoglobin, ESR, rheumatoid factor, functional capacity (Steinbroker, Traeger, and Batterman, 1949).

The involved knees were assessed for the extent of inflammatory changes and the degree of joint damage, and the following clinical features were noted: duration of knee involvement, synovial thickening, effusion, tenderness or pain on movement, range of movement, fixed flexion deformity (measured in degrees with a goniometer). When appropriate the information was graded 0 = normal; 1 = doubtful or minimal abnormality; 2 = definite abnormality; 3 = gross abnormality.

X-rays of the knees were coded and read simultaneously by two of us (M.I.V.J. and D.H.) without knowledge of the clinical and arthroscopic findings, and these features examined: osteoporosis, surface erosions, geodes (bone

cysts), osteophytes, loss of joint space in (a) patellofemoral, (b) medial tibiofemoral, (c) lateral tibiofemoral compartments.

The observations were scored 0 = normal; 1 = possible change; 2 = definite change; 3 = gross change. The total of these scores was calculated by adding up the various scores. The maximum and worst possible radiological score was, therefore, 21.

Arthroscopy of the knee was performed under local anaesthesia using the Stortz Arthroscope (Jayson and Henderson, 1973). Particular attention was paid to degree of synovial erythema, extent of synovial proliferation, contact bleeding, fibrin, and cartilage damage. Each of these observations was again graded on a 0 to 3 scale.

Multiple synovial biopsies were obtained under direct vision. These were mainly taken from the medial tibiofemoral compartment where synovial proliferation is usually most obvious, but also were obtained from the suprapatellar pouch.

The biopsies were fixed in formol saline and sections were stained with haematoxylin and eosin and by Perls's Prussian Blue reaction for iron. On occasions, step sections were taken to obtain adequate amounts of tissue for histological examination.

The sections were coded and assessed without knowledge of their identity by all three authors. Standard sections were kindly provided by Dr. K. D. Muirden and the biopsies were graded with frequent reference to those sections. Features quantified were synovial lining-cell proliferation and lymphocytic infiltration, and gradings were established between 1 = normal or slight change to 4 = gross change, in a similar fashion to that used by Muirden and Mills (1971).

In addition, the following features were noted and graded on the same scale: total mononuclear cell infiltration, degree of plasma cell infiltration, synovial surface cell pleomorphism, vascular proliferation, thickening of vessel walls, iron deposition.

Results

The general characteristics of the patients are shown in Table I and the clinical, radiological, and arthroscopic changes in the involved knees in Table II. No correlations could be found between the severity of any of the clinical parameters for general disease and the severity of the process within the knee.

Of 22 patients, adequate biopsies for histological grading were obtained from 21, and the data presented are restricted to these patients.

Table I *Systemic features of 21 patients*

Age	57.0 yrs (21–74 yrs)
Sex	Male 10, female 11
Duration of RA	7.5 yrs (0–15–25 yrs)
Duration of morning stiffness	2.4 h (0–12 h)
Nodules	Present 5, absent 16
Functional capacity	I 1, II 11, III 9, IV 0
Blood sedimentation rate	62 mm/h (10–108 mm/h)
Haemoglobin	12.4 g/dl (9.8–17.1 g/dl)
RA latex test	Positive 20, negative 1

Table II *Data on 21 knees examined*

Assessments	Mean	Range
<i>Clinical</i>		
Duration of knee involvement (yrs)	5.7	(0–15–22)
Synovial thickening (yrs)	2.1	1– 3
Effusion (yrs)	1.6	0– 3
Tenderness or pain on movement (yrs)	1.6	0– 3
Fixed flexion deformity (degree)	6.7°	0°–20°
<i>Radiological</i>		
X-ray score	8.7	0–17
<i>Arthroscopic score</i>		
Erythema	1.6	1– 3
Synovial proliferation	2.2	1– 3
Contact bleeding	1.2	0– 3
Fibrin	2.1	0– 3
Cartilage damage	1.7	0– 3

FIG. 1 Synovial biopsy from a patient showing severe synovial lining-cell proliferation with some pallisading associated with a marked mixed cellular infiltration in the underlying tissue consisting of both lymphocytes and plasma cells. This illustrates that high grades in the two histological criteria studied by Muirden and Mills (1971) can, and frequently do, occur in the same biopsy. H. & E. $\times 264$

Histological grading often proved extremely difficult because of marked variation in the degree of cellular reaction within any specimen and between different specimens. Two photomicrographs of synovial biopsies (Figs 1 and 2) are included to illustrate the difficulties in histological assessment. The specimens were considered as a whole, however, and an attempt was made to assess the best overall grading with the proviso that the features of the specimens from the tibiofemoral compartments were weighted more heavily than those from the suprapatellar pouch.

Fig. 3 shows the comparison between lymphocytic

infiltration and synovial lining-cell hyperplasia. Although there was a tendency for synovial lining-cell hyperplasia to be worse in the patients with the least lymphocytic infiltration, this change did not reach statistical significance. None of the pathological specimens showed grade 4 lymphocytic infiltration as shown by Muirden and Mills (1971). Table III lists the comparisons between histological features which were undertaken. No significant correlations emerged.

Table IV lists the comparisons made between the degrees of lymphocytic infiltration (a) and the clinical, radiological, and arthroscopic evidence of synovial inflammation and joint damage. No

FIG. 2 Synovial biopsy from a patient showing two contrasting synovial villi. On the left, the villus shows marked synovial lining-cell hyperplasia with some palisading and only a scanty underlying cellular infiltration. In contrast, the villus on the right has a thinner, more indistinct synovial lining with an intense underlying lymphocytic and plasma cell infiltration. This illustrates the difficulties of grading histological features within different areas of one biopsy. H. & E. $\times 436$

FIG. 3 Comparison of lymphocytic infiltration and synovial lining cell hyperplasia

Table III Comparisons between histological features

Lymphocytic infiltration	Synovial surface cell hyperplasia Iron deposition Lining cell pleomorphism Giant cells
Synovial surface cell hyperplasia	Lymphocytic infiltration Total mononuclear cell infiltration Plasma cell infiltration Iron deposition Pleomorphism Giant cells
Iron deposition	Lymphocytic infiltration Total mononuclear cell infiltration Plasma cell infiltration Synovial surface cell hyperplasia Lining cell pleomorphism Giant cells Vascular proliferation Vessel wall thickness

Table IV *List of features compared with (a) lymphocytic infiltration, (b) synovial lining cell proliferation*

Systemic	Age Duration of RA Duration of morning stiffness Blood sedimentation rate Treatment with gold or corticosteroids
Knee-clinical	Duration of knee involvement Synovial thickening Effusion Tenderness or pain on movement Fixed flexion deformity
Knee-radiological	X-ray score
Knee-arthroscopic	Erythema Synovial proliferation Contact bleeding Fibrin Cartilage damage

significant correlations were found. Figs 4 and 5 illustrate comparisons of lymphocytic infiltration with the arthroscopic evidence of cartilage damage and with the x-ray score.

Table IV also lists the comparisons between lining-cell proliferation (b) with the grades for inflammation and articular damage. Again, there were no significant correlations. Figs 6 and 7 illustrate comparisons of synovial lining-cell proliferation with the arthroscopic evidence of cartilage damage and with the x-ray score. Comparisons were drawn between the other histological features, including the extent of iron deposition and the degrees of synovial inflammation and joint damage. No significant correlations were found.

FIG. 4 *Comparison of lymphocytic infiltration with the arthroscopic estimate of articular cartilage damage*

FIG. 5 *Comparison of lymphocytic infiltration and knee x-ray score*

FIG. 6 *Comparison of synovial lining cell hyperplasia with arthroscopic estimate of cartilage damage*

Discussion

This study failed to confirm any relationship between the histological pattern of rheumatoid synovitis and the extent of disease activity or joint damage. This failure may be interpreted in different ways. Quantification of clinical parameters of a disease is exceedingly difficult and most of the conventional methods of assessment which were used in this study are more useful for assessing the status of a single patient when seen on a number of occasions

FIG. 7 Comparison of synovial lining cell hyperplasia and knee x-ray score

than for making comparisons between groups of patients. The variation of reporting between different observers is well recognized and, indeed, the same observer may report the same material in a different fashion on separate occasions. In particular, the appearances at arthroscopy can be altered considerably by varying the physical conditions such as the

intensity of lighting, the pressure and temperature of the irrigating fluid, and the distance from the telescope tip to the observed surface. Despite these provisos, in experienced hands, arthroscopy provides considerable additional information, and in particular makes direct vision biopsies of involved areas available.

The biopsies were small and not comparable with the large amounts of synovium obtained at synovectomy. However, whenever possible multiple specimens were obtained from different parts of the joint so as to obtain representative samples. The changes of the synovium in RA are many and varied (Gardner, 1972) and it was disappointing that no correlations were found between the various features nor between the histological changes and the extent of the disease. It is still possible that with a larger series and perhaps with the use of more sophisticated techniques, such as electron microscopy and immunofluorescence, useful correlations giving some guidance to the likely prognosis of the disease may emerge.

It is also possible that there was some selection in the cases documented by Muirden and Mills (1971) in that the histological specimens were obtained at synovectomy so that only those patients suitable for this procedure were examined. In contrast, a broad spectrum of disease activity was included in the present study.

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