Rheumatoid synovitis and joint disease

Relationship between arthroscopic and histological changes

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Yates, D. B., and Scott, J. T. (1975). *Annals of the Rheumatic Diseases*, 34, 1. Rheumatoid synovitis and joint disease. Relationship between arthroscopic and histological changes. Arthroscopic and histological synovial features have been studied in forty-two patients with classical or definite rheumatoid arthritis. A total index of disease activity as judged arthroscopically correlates significantly with a total index of histological activity. In those patients who have dense, waxy looking villi, the intensity of the villus-proliferation is associated with lymphocyte infiltration of the synovium. No relationship between synovial lining cell proliferation and cartilage disease nor between sparsity of lymphocyte infiltration and cartilage disease could be established.

While direct examination of the knee joint by arthroscopy has been an established practice in Japan for many years (Watanabe, Takeda, and Ikeuchi, 1969), it is only recently that the technique has become more popular in the Western world. Jayson and Henderson (1973) have shown the value of arthroscopy for the diagnosis of inflammatory joint disease, and in particular the advantages of arthroscopy over arthrotomy for detailed examination of the synovium.

The value of synovial biopsy material in assessing the severity and prognosis of rheumatoid arthritis has been examined by many authors with mixed results. Some of the problems have arisen from the fact that blind biopsy techniques were used, but even with adequate material major variations in histology from area to area within any one joint have been reported in up to 89% of patients (Cruickshank, 1952). On the other hand, certain features of rheumatoid synovitis—synovial lining cell thickness and lymphocyte infiltration—are of importance in the development of subsequent damage to articular cartilage (Muirden and Mills, 1971). The present investigation examined the relationship in rheumatoid arthritis between arthroscopic appearances of the synovium of the knee and histopathological changes in sections of synovial biopsies obtained under direct vision; together with the relationships between histology and visible damage in articular cartilage.

Patients, materials, and methods

Forty-two patients (33 seropositive and 9 seronegative) who fulfilled the A.R.A. criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958) for classical or definite rheumatoid

arthritis have been studied. The duration of total disease activity ranged from 4 weeks to 30 years (mean 7 years; seropositive 8.1 years; seronegative 3 years). Patients were admitted to hospital for one day only; clinical assessment was carried out, after which arthroscopy and simultaneous synovial biopsy using a Stortz fibreoptic instrument was performed under local anaesthesia with full sterile precautions in an operating theatre. On the day of the investigation blood was taken for rheumatoid factor serology (Rose, Ragan, Pearce, and Lipman, 1948) and ESR.

A full visual survey was made of the synovium of the suprapatellar pouch, medial and lateral capsular walls, and over the infrapatellar fat pad. Normal synovium (Fig. 1a) appears as a pale yellow thin membrane through which small vessels and the underlying white fibrous tissue of the joint capsule may be seen. Abnormalities consisting of synovial hyperaemia (Fig. 1b), dense, waxy-looking 'active' villi (either squat, and appearing like cobblestones, or conical or pedunculated with clubbed ends—Fig. 1c), and white, avascular fibrous villi (Fig. 1d) were each scored 0, no change; 1, slight; 2, moderate; or 3, marked changes. A similar scoring system was applied to fibrin floating free within the joint space (Fig. 1e) and to cartilage disease (either erosion, cartilage thinning, or pannus encroaching on to the cartilage (Fig. 1f)). After photographs had been taken, multiple synovial biopsies were obtained. In order to minimize error due to sample variation, at least 6 biopsies (each measuring 0.1 cm × 0.2 cm × 0.4 cm) were taken from an area high on the medial capsular wall; only these biopsy specimens were used for subsequent statistical analysis.

Biopsy specimens were fixed in neutral phosphate buffered 10% formalin and sections stained with haematoxylin and eosin, Periodic Acid Schiff, and Lendrum's Martius Scarlet Blue trichrome. These sections were examined, without knowledge of the identity of the patient, in three ways.

FIG. 1 (a) Normal synovium. (b) Synovial hyperaemia. (c) 'Active' villus formation; pedunculated large and waxy looking villi arising from synovium. (d) Fibrous villus formation; white avascular villi arising from synovium. (e) Rice body; large mass of fibrin floating above hypertrophic synovium. (f) Cartilage disease; pitted, irregular surface of medial femoral condyle with loss of articular cartilage in the centre

A Histological features consistent with rheumatoid arthritis according to the A.R.A. criteria (surface fibrin deposition, synovial cell hyperplasia, subsynovial mononuclear cell infiltration, perivascular cellular infiltration, and perivascular oedema) were each graded 0-4 depending on the severity of each feature and the sum used as an index of total histological activity.

B Sections were assessed for the dominant phase of the four phases of synovitis categorized by Britton, Ruddy, Corson, Sosman, Schur, and Austen (1970). These phases are as follows.

- (i) *Exudative* Synovial congestion of vessels and oedema with some exudation of neutrophilic leucocytes and fibrin deposition.
- (ii) *Infiltrative and proliferative* Infiltration by lymphocytes, plasma cells, and histiocytes, proliferation of fibroblasts, synovial cell hyperplasia, and conspicuous capillaries.
- (iii) *Necrotic* Areas of necrosis of lining cells and also in subsynovial connective tissue together with some fibrin deposition.
- (iv) *Fibrotic* Predominant fibrosis without mononuclear cell infiltration or necrosis.

C Finally, in order to correlate cartilage damage with two specific histological features, the average thickness of the synovial lining layer was calculated in terms of numbers of cells; and the intensity of lymphocytic infiltration was graded 0-8 from a count of the average number of lymphocytes seen in three random high power fields of subsynovium.

Arthroscopy caused minimal discomfort only and there were no complications.

Results

Correlations between arthroscopic and histological features are summarized in Table I; correlations

between clinical features and arthroscopic and histological features are summarized in Table II. It can be seen (Fig. 2) that by comparing the total histological activity with the total visible synovitis (the score derived from the sum of the four arthroscopic synovial features but excluding cartilage disease) a significant ($P < 0.01$) relationship exists. However, if individual histological features are each assessed against the total visible synovitis, there are no significant correlations. Where 'active' villus formation is seen on arthroscopy, however, there is significant relationship ($P < 0.01$) between the severity of the villus formation and the intensity of lymphocyte infiltration (Fig. 3). No relationship, direct or inverse, is found between villus formation and the thickness of the synovial lining layer.

When the severity of cartilage disease is assessed against histological features, again there is no significant correlation. In particular, there is no relationship between cartilage disease and lymphocyte infiltration (Fig. 4), nor between cartilage disease and thickness of the synovial lining layer (Fig. 5).

From Table II it is seen that there is no relationship between any of the clinical or serological features measured and arthroscopic appearance. The dominant phase of synovitis histologically does however vary with the duration of activity within the joint (Fig. 6). In the majority of patients with an exudative synovitis the disease had been active for 6 months or less ($\chi^2 = 7.33$; $P < 0.01$), whereas a fibrotic histology was seen in synovium where the disease had been active for more than 18 months ($\chi^2 = 6.33$; $P < 0.025$).

Table I Correlations between arthroscopic and histological features

Total arthroscopic score	v.	Total histological score	$r = 0.46$	$P < 0.01$
Total arthroscopic score	v.	Lymphocytic infiltration	$r = 0.31$	NS
Total arthroscopic score	v.	Lining cell thickness	$r = 0.24$	NS
Active villus formation	v.	Lymphocytic infiltration	$r = 0.56$	$P < 0.01$
Active villus formation	v.	Lining cell thickness	$r = 0.12$	NS
Visible hyperaemia	v.	Lymphocytic infiltration	$r = 0.20$	NS
Visible hyperaemia	v.	Lining cell thickness	$r = 0.12$	NS
Cartilage disease	v.	Lymphocytic infiltration	$r = 0.07$	NS
Cartilage disease	v.	Lining cell thickness	$r = 0.05$	NS

Table II Correlations between clinical features and arthroscopic and histological features

Level of DAT	v.	Total arthroscopic score	$r = 0.01$	NS
Level of DAT	v.	Total histological score	$r = 0.03$	NS
Duration of disease activity	v.	Total arthroscopic score	$r = 0.12$	NS
Duration of disease activity	v.	Total histological score	$r = 0.04$	NS
Synovial fluid protein level	v.	Total arthroscopic score	$r = 0.02$	NS
Synovial fluid protein level	v.	Total histological score	$r = 0.12$	NS
Disease activity < 6 m	v.	Exudative synovitis	$\chi^2 = 7.33$	$P < 0.01$
Disease activity > 18 m	v.	Fibrotic synovitis	$\chi^2 = 6.33$	$P < 0.025$

FIG. 5 Correlation between severity of cartilage disease and the average number of cells in the synovial lining layer; $r = 0.05$: not significant

FIG. 6 Distribution of dominant phase of synovitis against duration of active disease in the joint studied

Discussion

Most pathological studies of patients with active or chronic rheumatoid synovitis have failed to show a significant association between synovial histopathological changes and clinical disease activity

(Schumacher and Kitridou, 1972). This may in part be due to problems in interpretation of synovial biopsy material which may vary from area to area in one joint. Similar variation has been observed in arthroscopic appearances (Robles-Gil, 1973; Watanabe and others, 1969). It is not uncommon, for example, to see relatively normal synovium in the suprapatellar pouch, with gross abnormalities in the synovium covering the medial and lateral capsular walls. In this study, therefore, multiple synovial biopsies were taken from a similar area of the medial capsular wall in all patients.

Since considerably more synovium can be examined with an arthroscope than with a microscope, useful details of severity and activity of synovial disease may be obtained by arthroscopy. The present study has shown a significant correlation between total visible synovial changes and those seen histologically, with a further association between 'active' villus formation and the number of lymphocytes present in the subsynovium, a finding in accordance with the arthroscopic study of Takeda (1960) of 384 cases of various knee joint disorders. The 'active' villi correspond with those described by Palmer (1967) as bulky and dense and characteristic of RA—being either squat and sessile or elongated and pedunculated—but nothing like the delicate form of normal villi.

There appears to be an overall correlation between 'active' villus formation, subsynovial lymphocyte infiltration, reduced synovial fluid complement level (Britton and others, 1970) and a severe clinical course with increased joint damage (Hedberg, 1963; Pekin and Zvaifler, 1964).

Variations in disease activity are not only found in different situations but also during the course of the disease. At any one time synovial membrane shows a mixed picture of acute and chronic changes together with signs of tissue repair and fibrosis. It has been shown that only in the very early stages of rheumatoid disease (Kulka, Bocking, Ropes, and Bauer, 1955) is there any one consistent histological pattern, namely congestion, oedema, and fibrin deposition without much cellular infiltration. It is of interest that exudative synovitis is now seen to occur relatively early in an involved knee joint while fibrosis is a later feature.

Much interest has recently been aroused by the report of Muirden and Mills (1971) who showed in a series of 42 surgical synovectomies that extensive joint damage as estimated by articular cartilage erosion and thinning or by pitted erosions along bone-cartilage junctions was associated with a histological picture of marked lining cell proliferation and a sparseness of subsynovial lymphocytes. The method of study carried out by these workers using surgical synovectomy specimens was different from the present arthroscopic study, and most of the patients in the latter had little or no cartilage disease

(Figs. 4 and 5). A direct comparison of results may not therefore be justified, but in so far as no relationship, either direct or inverse, has been found between cartilage damage observed at arthroscopy and either lining cell proliferation or lymphocyte infiltration,

the previous findings lack confirmation. Although slightly less articular cartilage is visualized arthroscopically than at arthrotomy, the correlation coefficients (both less than 0.1) are so low that any correlation seems highly unlikely.

References

- BRITTON, M. C., RUDDY, S., CORSON, J. M., SOSMAN, J. L., SCHUR, P. H., AND AUSTEN, K. F. (1970) 'The complement system in rheumatoid synovitis', in 'Immune Reactions and Experimental Models in Rheumatic Diseases. Proceedings of the 4th Canadian Conference on Research in the Rheumatic Diseases', Toronto, ed. D. Gordon, p. 40
- CRUICKSHANK, B. (1952) *Ann. rheum. Dis.*, **11**, 137 (Interpretation of multiple biopsies of synovial tissue in rheumatic diseases)
- HEDBERG, H. (1963) *Acta rheum. scand.*, **9**, 165 (Studies on the depressed haemolytic complement activity of synovial fluid in adult rheumatoid arthritis)
- KULKA, J. P., BOCKING, D., ROPES, M. W., AND BAUER, W. (1955) *Arch. Path.*, **59**, 129 (Early joint lesions of rheumatoid arthritis)
- JAYSON, M. I. V., AND HENDERSON, D. R. F. (1973) *Rheumatol. and Rehab.*, **12**, 195 (Arthroscopy in the diagnosis in inflammatory joint disease)
- MUIRDEN, K. D., AND MILLS, K. W. (1971) *Brit. med. J.*, **4**, 219 (Do lymphocytes protect the rheumatoid joint?)
- PALMER, D. G. (1967) *Arthr. and Rheum.*, **10**, 451 (Synovial villi: an examination of these structures within the anterior compartment of the knee and metacarpo-phalangeal joints)
- PEKIN, T. J., AND ZVAIFLER, N. J. (1964) *J. clin. Invest.*, **43**, 1372 (Hemolytic complement in synovial fluid)
- ROBLES-GIL, J. (1973) Arthroscopy monograph
- ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., AND JESSAR, R. A., (1958) *Bull. rheum. Dis.*, **9**, 175 (1958 Revision of diagnostic criteria for rheumatoid arthritis)
- ROSE, H. M., RAGAN, C., PEARCE, E., AND LIPMAN, M. O. (1948) *Proc. Soc. exp. Biol. (N.Y.)*, **68**, 1 (Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis)
- SCHUMACHER, H. R., AND KITRIDOU, R. C. (1972) *Arthr. and Rheum.*, **15**, 465. (Synovitis of recent onset)
- TAKEDA, S. (1960) *J. Jap. Orth. Ass.*, **34**, 373 (Relationship between arthroscopic and histological observations for the synovial membrane)
- WATANABE, M., TAKEDA, S., AND IKEUCHI, H. (1969) In 'Atlas of Arthroscopy', 2nd ed. Springer, Berlin