Synovitis score: discrimination between chronic low-grade and high-grade synovitis

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Aims: To standardize the histopathological assessment of synovial membrane specimens in order to contribute to the diagnostics of rheumatic and non-rheumatic joint diseases.

Methods and results: Three features of chronic synovitis (enlargement of lining cell layer, cellular density of synovial stroma, leukocytic infiltrate) were semiquantitatively evaluated (from 0, absent to 3, strong) and each feature was graded separately. The sum provided the synovitis score, which was interpreted as follows: 0–1, no synovitis; 2–4, low-grade synovitis; 5–9, high-grade synovitis. Five hundred and fifty-nine synovectomy specimens were graded by two independent observers. Clinical diagnoses were osteoarthrosis (n = 212), post-traumatic arthritis (n = 21), rheumatoid arthritis (n = 246), psoriatic arthritis (n = 22), react-

ive arthritis (n = 9), as well as controls (n = 49) from autopsies of patients without joint damage. Median synovitis scores when correlated with clinical diagnoses were: controls 1.0, osteoarthritis 2.0, post-traumatic arthritis 2.0, psoriatic arthritis 3.5, reactive arthritis 5.0 and rheumatoid arthritis 5.0. The scores differed significantly between most disease groups, especially between degenerative and rheumatic diseases. A high-grade synovitis was strongly associated with rheumatic joint diseases (P < 0.001, sensitivity 61.7%, specificity 96.1%). The correlation between the two observers was high (r = 0.941).

Conclusion: The proposed synovitis score is based on well-defined, reproducible histopathological criteria and may contribute to diagnosis in rheumatic and non-rheumatic joint diseases.

Keywords: grading, histopathology, osteoarthritis, rheumatoid arthritis, synovitis

Abbreviations: OA, osteoarthritis; PsA, psoriatic arthritis; PtA, post-traumatic arthritis; RA, rheumatoid arthritis; ReA, reactive arthritis

Introduction

Only a few diseases manifest themselves in the synovial membrane, the majority being different forms of synovitis in the context of degenerative, metabolic or inflammatory/autoimmune diseases. The histopathological picture of synovitis shows a variety of forms, some with clearly defined, disease-specific features and others with uncharacteristic findings.[1–3]

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In recent years, histopathological scores for the evaluation of synovitis have been developed with the following aims: (i) to contribute to standardized histopathological diagnosis,[4,5] (ii) to objectify the effects of drug treatment in rheumatoid arthritis (RA),[6,7] (iii) to identify subtypes of RA[8] and (iv) to correlate the degree of severity of arthritis with synovitis by the quantification of the inflammatory infiltrate in synovial biopsy specimens.[8–12] Most of the grading systems cited above are used for the characterization of RA, so the histopathological criteria include RA-characteristic alterations, such as palisading or ulceration of the lining cell layer and rheumatoid granulomas. As the main focus of these systems is on the early diagnosis

of the initial inflammation in rheumatoid diseases, the typical synovitis biopsy specimens obtained by arthroscopy have been used as research material.

The purpose of the present study, on the other hand, was to draw up a histopathological synovitis score that is a semiquantitative transcription of the entire spectrum of rheumatic and degenerative diseases and that is related to cellular and quantifiable changes in the synovial membrane. This score should also be applicable to long-term synovitis and provide a basis for the assessment of synovectomy specimens. Synovectomy specimens obtained, for example, during therapeutic synovectomies and total joint replacement operations are frequently sent to the pathologist for histopathological diagnosis. The diagnosis of joint diseases is not only the rheumatologist's but also the orthopaedic surgeon's task. Although both evaluate rheumatic diseases clinically according to the American College of Rheumatology (ACR) criteria, synovectomy specimens and synovial biopsy specimens are sent to the pathologist. The orthopaedic surgeon frequently asks if a rheumatic disease, especially RA, can be diagnosed or excluded. A systematic evaluation of routinely surgically removed synovectomy specimens is lacking.

Furthermore, synovial tissue samples are used in experimental rheumatology, e.g. for the generation of gene expression profiles. A standardized histopathological evaluation of these samples according to a synovitis score could serve as a basis for further experimental use and could enhance the comparison of different specimens.

Synovial tissue can principally be divided into resident cell populations (fibrocytes, fibroblasts, endothelial cells, macrophages), non-resident cell populations (lymphocytes and plasma cells) and the lining cell layer. The latter can easily be identified by histopathology.[13] The immunological basis for the inflammatory infiltrate differs between degenerative and rheumatic diseases, and so does the histopathological picture.[14,15] These three compartments of synovial tissue show variable changes depending on the disease and are easily analysable. Therefore we propose to evaluate the enlargement of the synovial lining cell layer, the cellular density of the synovial stroma and the density of the inflammatory infiltrate in order to generate a synovitis score.

Materials and methods

PATIENTS

Synovectomy samples from 559 patients (14–88 years old, mean 61.6 years, SD 14.8 years; female $n = 347$,

62.1%; male $n = 212$, 37.9%) were analysed. Clinical diagnoses were based on defined criteria. Osteoarthritis (OA) was classified according to Altman *et al.*,[16] RA according to ACR criteria[17] and psoriatic arthritis (PsA) according to Moll und Wright.[18] Reactive arthritis (ReA) was diagnosed on the grounds of a urogenital or gastrointestinal infection confirmed up to 6 months before clinical and radiological symptoms of arthritis occurred.[19] Samples from patients with a history of joint injury such as lesions of the meniscus or ligaments were classified as post-traumatic arthritis (PtA). The numbers of samples analysed in each

Table 1. Scheme for the histopathological assessment of the three features of chronic synovitis

Enlargement of the synovial lining cell layer	
0 points	The lining cells form one layer
1 point	The lining cells form 2–3 layers
2 points	The lining cells form 4–5 layers, few multinucleated cells might occur
3 points	The lining cells form more than 5 layers, the lining might be ulcerated and multinucleated cells might occur
Density of the resident cells	
0 points	The synovial stroma shows normal cellularity
1 point	The cellularity is slightly increased
2 points	The cellularity is moderately increased, multinucleated cells might occur
3 points	The cellularity is greatly increased, multinucleated giant cells, pannus formation and rheumatoid granulomas might occur
Inflammatory infiltrate	
0 points	No inflammatory infiltrate
1 point	Few mostly perivascular situated lymphocytes or plasma cells
2 point	Numerous lymphocytes or plasma cells, sometimes forming follicle-like aggregates
3 points	Dense band-like inflammatory infiltrate or numerous large follicle-like aggregates
Sum 0 or 1	No synovitis
Sum 2–4	Low-grade synovitis
Sum 5–9	High-grade synovitis

category were as follows: OA $n = 212$, PtA $n = 21$, RA $n = 246$, PsA $n = 22$ and ReA $n = 9$. Analysis was carried out on 49 control samples (Co) obtained at autopsy of patients with normal joints. Biopsies from at least two ($n = 112$) or up to five ($n = 23$) separate areas of the same joint were available. Informed consent for the use of tissue samples in this study was given in all cases.

STATISTICAL EVALUATION

The values of this score are on an ordinal scale of measurement. Frequencies and median values were chosen for descriptive statistics and Pearson's correlation coefficient was used to investigate the correlation between the grading results of the two observers. The Mann–Whitney test was used to answer the question as to whether the scores differed in terms of diagnoses.

The sensitivity of the synovitis score for the diagnosis of an inflammatory joint disease was calculated as the ratio of correctly identified patients with a rheumatic disease (synovitis score at ≥ 5) to all of these patients. The specificity was assessed as the quotient of correctly allocated patients with non-rheumatic diseases (score < 5) to all of these patients.

With regard to the scores for different samples from the same patient, Spearman's ρ was used to calculate the correlation coefficient.

HISTOLOGICAL CHARACTERISTICS OF THE SYNOVITIS SCORE

The grading of the synovial membranes was carried out on routine haematoxylin and eosin (H&E)-stained slides, according to the three synovial membrane features (synovial lining cell layer, stroma cell density
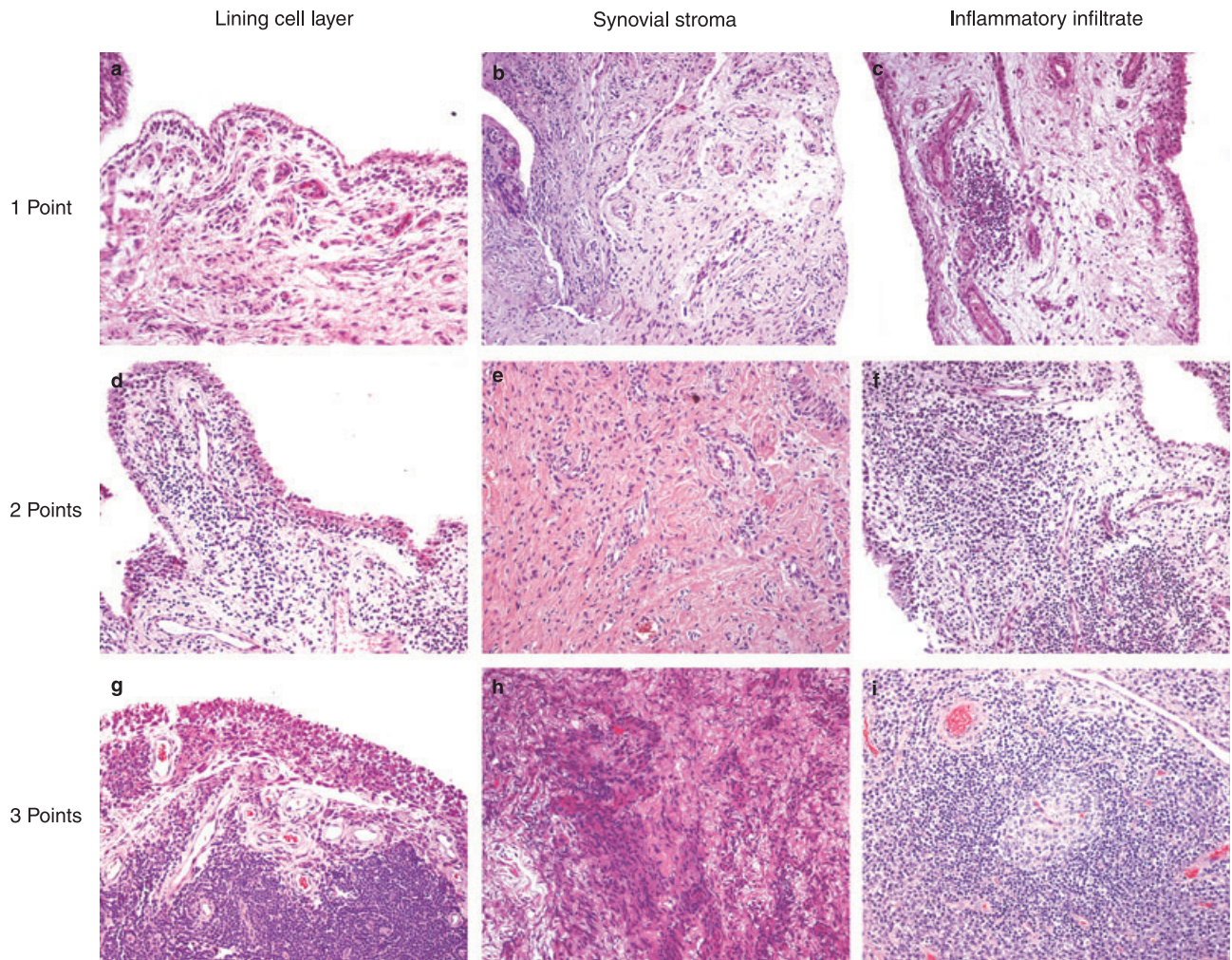

Figure 1. Examples of the histomorphological aspects of the enlarged lining cell layer (left column, **a,d,g**), the cellular density of the synovial stroma (centre column, **b,e,h**) and the inflammatory infiltrate (right column, **c,f,i**), gradually increasing from top to bottom (H&E).
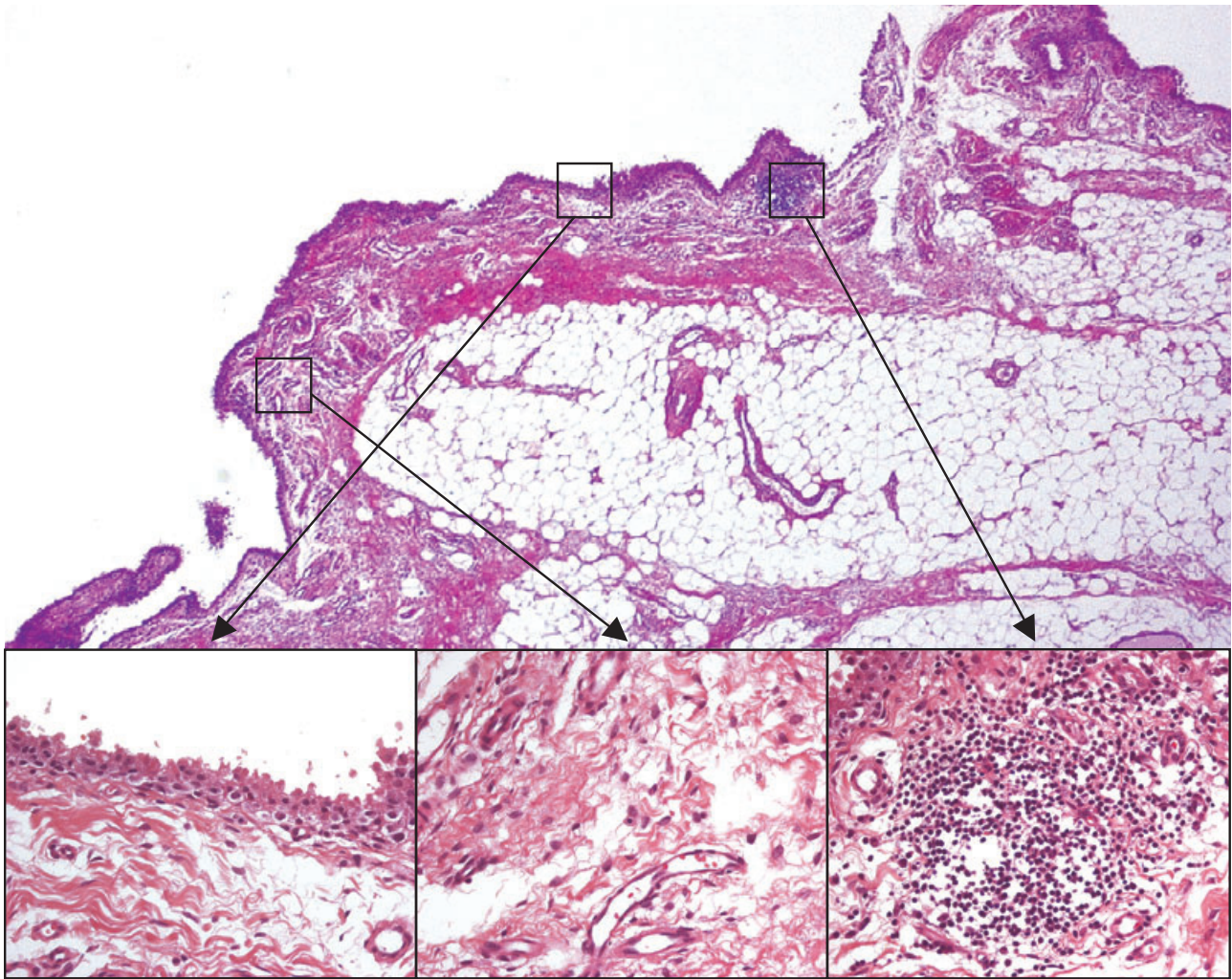
Figure 2. Post-traumatic arthritis. The synovial lining cell layer is slightly enlarged (1 point, left insert), the density of the synovial stroma is slightly increased (1 point, central insert) and there is a small follicle-like lymphocytic inflammatory infiltrate (1 point, right insert). Altogether, a slight synovitis (1 + 1 + 1 = 3 points) can be diagnosed (H&E).

and inflammatory infiltrate), the ranking of alterations being on a scale from none (0), slight (1) and moderate (2) to strong (3) (Table 1, Figure 1). The values of the parameters were summarized and interpreted as follows: 0–1, no synovitis; 2–4, low-grade synovitis; and 5–9, high-grade synovitis (Figure 2). This grading system is based on and resembles an advancement of the grading system first proposed at the 18th European Congress of Pathology.[20]

THE PROBLEM OF INFLAMMATORY HETEROGENEITY IN SYNOVECTOMY SPECIMENS

As inflammatory changes are heterogeneous by nature, analysis was done at the site showing the strongest histopathological alterations, analogous to the estab-lished assessment of the differentiation grade of neoplasms. It is advisable to analyse the inflammatory infiltrate under low magnification ($\times$ 50–100); on the other hand, the view of the enlarged synovial lining cell layer as well as the cell density of the synovial stroma is better at higher magnification ($\times$ 200–400).

Results

Both observers analysed the samples according to the grading system mentioned above. Analysing the synovitis score, the median values for individual clinical diagnoses were as follows: control 1.0, OA 2.0, PtA 2.0, PsA 3.5, ReA 5.0, RA 5.0 (Table 2, Figure 3).

In most of the cases, the synovitis score was ± 1 around the respective median value, but almost all
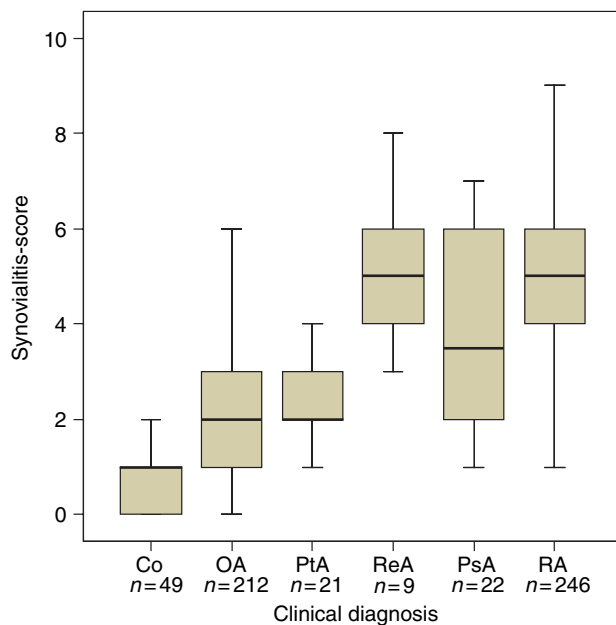
Figure 3. Box plot of the synovitis scores, separated according to clinical diagnoses. The median synovitis scores differentiate most of the diagnoses. However, the range of values is fairly wide so that overlapping is possible. Broad line, median; box, 25th and 75th percentile, respectively; whisker, 5th and 95th percentile, respectively.

diagnoses showed outlying values. So the range of OA was 6 (between 0 and 6), PsA 6 (between 1 and 7) and the range of RA was 9 (between 0 and 9).

Nevertheless, with regard to the synovitis score there were significant differences between controls and all other diagnoses and among many other disease groups. The probability values P (Mann–Whitney test) are given in Table 3. They demonstrate that, only with exception of the comparisons between OA and PtA,

PsA and ReA as well as RA and ReA, the synovitis scores were significantly different between the clinical diagnoses. As well as scoring systems for other diseases, this synovitis score was not totally specific for certain joint diseases. For example, there were cases of OA with a rather high synovitis score of 6, whereas some cases of RA had a score of only 2, 1 or even 0 points (Table 2).

Altogether, 277 samples could be regarded as belonging to rheumatic diseases (RA + ReA + PsA). Of these, the synovitis score was between 0 and 4 in $n = 106$ cases and between 5 and 9 in $n = 177$ cases. Two hundred and eighty-two samples came from patients with degenerative diseases or controls (Co + OA + PtA). Of these, a synovitis score between 0 and 4 was diagnosed in 271 cases and between 5 and 9 in 11 cases. This gives a sensitivity of 61.7% and a specificity of 96.1% for the histopathological diagnosis of a high-grade synovitis as an indicator of a rheumatic joint disease.

Of 112 patients, there were between two and five samples from different parts of the same joint, giving up to 10 different combinations of correlations. These correlation coefficients were between 0.861 and 0.949. The correlation between the samples was always at least significant ($P < 0.05$), and frequently highly significant ($P < 0.01$).

Grading of the cases by two independent observers showed a marked correlation (Pearson's correlation coefficient $r = 0.941$, $P < 0.001$).

Discussion

The synovitis score suggested here has proved to be clearly and easily applicable in the evaluation of 559

Table 2. Scoring profile for each particular disease

Synovitis Score Diagnosis	None 0	None 1	Low 2	Low 3	Low 4	High 5	High 6	High 7	High 8	High 9
Co, *n*	19	22	8	0	0	0	0	0	0	0
OA, *n*	12	37	84	39	28	10	2	0	0	0
PtA, *n*	0	3	10	6	2	0	0	0	0	0
ReA, *n*	0	0	0	1	2	2	2	1	1	0
PsA, *n*	0	1	5	5	4	4	2	1	0	0
RA, *n*	2	3	7	19	36	96	43	21	11	8

Co, Control; OA, osteoarthritis; PtA, post-traumatic arthritis; ReA, reactive arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Table 3. Probability values for the differences of the synovitis score between each particular disease

	OA	PtA	ReA	PsA	RA
Co	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
OA		$P = 0.587$	$P < 0.001$	$P = 0.001$	$P < 0.001$
PtA			$P < 0.001$	$P = 0.008$	$P < 0.001$
ReA				$P = 0.147$	$P = 0.774$
PsA					$P = 0.049$

Co, Control; OA, osteoarthritis; PtA, post-traumatic arthritis; ReA, reactive arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

samples. Two independent observers graded the samples with a high correlation ($r = 0.941$). Various joint diseases—degenerative and primarily inflammatory—were assessable by this score. The synovitis scores frequently turned out to be significantly different between degenerative and rheumatic joint diseases, even though the samples showed no characteristic findings of diseases such as rheumatoid granulomas. The result of a high-grade synovitis (synovitis score ≥ 5 points) was an indicator of a rheumatic joint disease. A minor drawback was the fact that some cases of degenerative joint disease displayed synovitis scores of ≥ 5 points and some cases of rheumatic joint disease appeared as low-grade synovitis, leading to a sensitivity of 61.7% and a specificity of 96.1% for this scoring system. Therefore, one might regard the proposed synovitis score as a feasible tool for the standardized histopathological evaluation of synovectomy specimens with diagnostic implications.

In inflammatory diseases the degree of diagnostic reliability and thereby the relevance of histopathological diagnostics depends on the organ system. Diagnostic efficacy ranges widely from definite disease classification, as for example lupus-glomerulonephritis according to the World Health Organization,[21] to only subsidiary diagnoses, as for example in chronic sialadenitis.[22]

There is a considerable number of inflammatory and non-inflammatory diseases within the histological diagnostics of synovitis, given the general acceptance that few diseases show pathognomonic changes in the synovial membrane. The histopathological diagnosis of synovitis is thus subject to inconsistency,[1,3,8] which is why it has long since presented a challenge to pathologists.

In recent years histopathological scores have been established with the purpose of correlating the clinical grades of severity of RA and synovitis[5,12] and objectifying the inflammatory infiltration and the effects that medical therapy has on synovitis.[6,7,9–11] However, they have only confirmed that the majority of histological characteristics show no good correlation with clinical results, although the Larsen grade, the rheumatoid factor titre and the number of joints affected correlate well with the histopathological score of Koizumi.[23]

All of the histopathological scores that have been published to date obviously focus on the grading of the inflammatory activity of RA synovitis in synovial biopsy specimens.[7,9–11] However, histopathological diagnosis requires the type of score that allows for histopathological grading independent of the aetiology of the joint disease. Besides, this score should also be useful in long-term, chronic diseases and equally valid in the evaluation of larger-sized synovectomy samples. The synovitis score presented here considers these requirements and focuses on histological changes that can be easily identified in routine H&E-stained slides.

A major problem in the diagnosis of inflammatory alterations in large tissue samples is the heterogeneity of the inflammatory reaction. So this study recommends selecting for analysis those areas with the greatest alterations, a method that, by analogy, has proven successful in histopathological tumour diagnosis, particularly for the grading of sarcomas.[24]

Due to this score, the assessment of numerous synovectomy tissue samples was reproducible when the analysis of the same tissue sample was repeated by different observers. Thus it is qualitatively comparable to other grading schemes used in tumour pathology, e.g. the Gleason grading system for prostatic carcinoma or the classification of breast carcinoma.[25,26]

Application of the synovitis score has revealed a significant difference between the inflammation grade of rheumatic and degenerative joint diseases, especially between OA and RA. These findings correspond to the results of Koizumi[23] whose, by comparison, elaborate evaluation system included 11 important histological characteristics on a semiquantitative scale with a maximum value of 20. A further significant difference has been recealed between post-traumatic synovitis and synovitis of rheumatoid type. All post-traumatic

synovitis cases showed slight inflammatory lesions, partly with a regular lining cell layer, which have been described in the literature.[27]

The result that is most important for histopathologists is that a synovitis score of ≥ 5 (high-grade synovitis) indicates a rheumatic joint disease with a sensitivity of 61.7% and a specificity of 96.1%. So in serologically and clinically non-specific inflammatory joint diseases, histopathological assessment of the synovial membrane may provide further diagnostic information.

Acknowledgements

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