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Histopathological Phenotyping of Rheumatoid Gonarthritis: Toward a Morphology-Based Classification of Synovial Tissue Patterns and Their Clinicopathological Significance

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ABSTRACT

Background. Rheumatoid gonarthritis is characterized by chronic synovial inflammation leading to progressive cartilage destruction, bone erosion, and irreversible joint dysfunction. Although histopathological evaluation plays an important role in assessing rheumatoid synovitis, conventional microscopic assessment primarily focuses on individual histological features rather than the overall architectural organization of synovial tissue. A practical morphology-based classification applicable to routine hematoxylin and eosin (H&E)-stained sections remains insufficiently explored.

Objectives. To identify predominant histopathological patterns in routine H&E-stained surgical synovial specimens from patients with rheumatoid arthritis of the knee and to explore their associations with disease duration, systemic inflammatory activity, and structural joint damage.

Methods. A cross-sectional clinicopathological study was performed on 21 formalin-fixed paraffin-embedded synovial tissue specimens obtained from patients with rheumatoid gonarthritis undergoing surgical treatment. Clinical and laboratory data, including disease duration, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide antibody (anti-CCP) status, and treatment history, were collected retrospectively. Histopathological evaluation was performed using routine H&E-stained sections. Synovitis severity was assessed using the Krenn Synovitis Score, and specimens were categorized into distinct histopathological patterns based on their predominant microscopic architecture. Statistical analysis was performed using non-parametric methods, with $p<0.05$ considered statistically significant.

Results. Routine histopathological examination demonstrated substantial morphological heterogeneity among rheumatoid synovial specimens. Four predominant histopathological patterns were provisionally identified: inflammatory (19.0%), fibro-inflammatory (23.8%), fibrotic-destructive (28.6%), and lymphoid-rich (28.6%). High-grade synovitis was present in 95.2% of cases. Significant differences were observed among the identified tissue patterns regarding disease duration, systemic inflammatory markers, Krenn Synovitis Score, and structural joint damage. The inflammatory pattern was characterized by pronounced lining hyperplasia and vascular proliferation, whereas the fibrotic-destructive pattern demonstrated extensive stromal remodeling associated with advanced structural damage. The lymphoid-rich pattern exhibited prominent lymphoid aggregates, germinal-center–like structures, and abundant plasma-cell infiltration. These findings suggest that routine H&E evaluation identifies distinct synovial tissue architectures that are associated with different clinicopathological characteristics.

Conclusions. In this exploratory cohort, routine H&E examination permitted provisional categorization of rheumatoid synovial specimens into four predominant architectural patterns. These patterns showed preliminary associations with selected clinicopathological variables. However, their reproducibility, external validity, prognostic significance, and relationship to established molecular synovial pathotypes remain to be determined in larger independent cohorts.

Keywords. Krenn Synovitis Score; Rheumatoid arthritis; Rheumatoid gonarthritis; Synovial tissue; Synovitis.

DOI:

BACKGROUND

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovitis, progressive cartilage destruction, bone erosion, and irreversible joint dysfunction.[1,2] Affecting approximately 0.5–1% of the adult population worldwide, RA remains one of the leading causes of chronic disability despite significant advances in disease-modifying antirheumatic drugs (DMARDs) and biologic therapies.[3] Although modern treatment strategies have substantially improved disease control, considerable heterogeneity persists in clinical presentation, therapeutic response, and the extent of

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structural joint damage among patients with apparently similar clinical characteristics.

The synovial membrane represents the principal site of pathological alterations in RA and plays a central role in disease initiation and progression.[4] Under physiological conditions, the synovium consists of a thin lining layer supported by a sparsely cellular sublayer stroma. In rheumatoid arthritis, however, the synovial membrane undergoes profound remodeling characterized by lining hyperplasia, stromal activation, angiogenesis, chronic inflammatory cell infiltration, fibrin deposition, and formation of invasive pannus tissue. These pathological changes ultimately contribute to cartilage degradation, bone destruction, and progressive loss of joint function.[5]

Histopathological examination of synovial tissue has become an increasingly valuable tool for understanding the biological mechanisms underlying rheumatoid arthritis. Conventional microscopic assessment typically focuses on individual morphological parameters such as synovial lining thickness, inflammatory infiltrates, vascular proliferation, fibrosis, and the presence of lymphoid aggregates. The Krenn Synovitis Score has further standardized histological evaluation by providing a reproducible grading system based on synovial lining hyperplasia, stromal cellularity, and inflammatory infiltration. Nevertheless, these approaches primarily quantify isolated pathological features and do not fully reflect the complex morphological heterogeneity observed among patients with rheumatoid arthritis.[6]

Recent advances in synovial tissue research have shown that rheumatoid arthritis is not a morphologically homogeneous disease. Molecular and immunophenotypic investigations have identified biologically distinct synovial pathotypes characterized by different inflammatory and stromal compositions. However, these classification systems largely rely on immunohistochemistry, transcriptomic analyses, or advanced molecular techniques that are not routinely available in most pathology laboratories Rather than evaluating isolated microscopic variables independently, we aimed to investigate whether combinations of morphological features could define recognizable predominant synovial tissue patterns that may better represent the histopathological diversity of rheumatoid arthritis.

We hypothesized that rheumatoid gonarthritis exhibits distinct histopathological phenotypes identifiable on routine H&E examination and that these phenotypes are associated with different clinicopathological characteristics and degrees of structural joint involvement. Rather than evaluating isolated microscopic variables independently, we aimed to investigate whether combinations of morphological features define reproducible synovial tissue patterns that may better represent the histopathological diversity of rheumatoid arthritis.

Therefore, the objective of the present study was to identify H&E-based histopathological phenotypes of rheumatoid gonarthritis in surgical synovial specimens and to evaluate their associations with clinical characteristics, laboratory inflammatory markers, and structural joint damage. We further sought to explore whether morphology-based phenotyping could provide a practical framework for histopathological stratification of rheumatoid synovitis suitable for routine pathological practice.

METHODS

We conducted a retrospective cross-sectional clinicopathological study to investigate the histopathological heterogeneity of rheumatoid gonarthritis using routine hematoxylin and eosin (H&E)-stained surgical synovial specimens. The study aimed to derive predominant H&E-based histopathological tissue patterns and to explore their associations with clinicopathological characteristics, systemic inflammatory activity, and structural joint damage.

The study included 21 patients with clinically established rheumatoid arthritis of the knee who underwent total knee arthroplasty and for whom adequate archived synovial tissue and corresponding clinical and laboratory information were available. Formalin-fixed paraffin-embedded synovial tissue specimens were retrieved from the archives of the Department of Pathology. The diagnosis of rheumatoid arthritis was established according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria and confirmed by review of the available clinical documentation. The cohort therefore represents a selected surgical population with advanced knee involvement rather than the broader clinical spectrum of rheumatoid arthritis. All 21 included patients were anti-CCP positive. Anti-CCP positivity was not used as a histopathological criterion for pattern assignment. Accordingly, the findings of this study should be interpreted specifically in the context of a seropositive surgical cohort and should not be extrapolated to seronegative rheumatoid arthritis without further validation.

One patient-level surgical synovial specimen was included for each patient. Histological assessment was performed on representative routinely processed synovial tissue sections available from the corresponding surgical specimen. Because the study was retrospective and tissue sampling was part of

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routine pathological processing rather than a prospectively standardized multisite biopsy protocol, the number and anatomical distribution of sampled synovial regions were not standardized for this investigation.

Patients were eligible if adequate synovial tissue was available for complete histopathological evaluation and essential clinical and laboratory data could be retrieved from the medical records. Patients with septic arthritis, crystal-induced arthropathy, psoriatic arthritis, other inflammatory arthritis, infectious synovitis, insufficient tissue preservation, or duplicate surgical specimens were excluded from the analysis.

Clinical data collection

Clinical information was collected retrospectively from the patients' medical records. Demographic variables included age, sex, body mass index, and disease duration. Laboratory variables included anti-cyclic citrullinated peptide antibody (anti-CCP) status, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Radiographic reports were reviewed to document structural joint damage, erosive disease, and joint-space narrowing.

Available preoperative radiographic reports were retrospectively reviewed for documented erosive changes, joint-space narrowing, and other structural abnormalities. For this exploratory analysis, severe structural damage was defined, based on the available radiological documentation, as advanced destructive joint involvement characterized by marked joint-space loss and/or extensive erosive or destructive changes. Because imaging was evaluated retrospectively from routine clinical documentation rather than using a prospectively applied, validated radiographic scoring system, structural-damage classification should be regarded as an exploratory clinical variable.

Treatment information was extracted from the available medical records and included documented methotrexate exposure and use of other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Detailed information regarding cumulative treatment duration, dose modifications, adherence, biologic or targeted synthetic DMARD exposure, and systemic or intra-articular glucocorticoid exposure was not consistently available for all patients. It was therefore not used for comparative analyses.

All specimens were routinely fixed in 10% neutral-buffered formalin, processed according to standard laboratory protocols, embedded in paraffin, sectioned at approximately 4 µm, and stained with hematoxylin and eosin. Two experienced pathologists performed the histopathological evaluation independently and were blinded to all clinical and laboratory data. Cases demonstrating discrepant microscopic findings were reviewed jointly until consensus was achieved.

Routine microscopic assessment included evaluation of synovial lining hyperplasia, stromal cellularity, inflammatory infiltrates, inflammatory distribution, lymphoid aggregates, germinal-center–like structures, plasma-cell infiltration, stromal fibrosis, vascular proliferation, vascular congestion, fibrin deposition, pannus formation, cartilage involvement, bone involvement when present, multinucleated giant cells, and necrosis. All histopathological variables were evaluated using predefined semiquantitative criteria to ensure consistent assessment throughout the study.

Germinal-center–like structures were identified morphologically as organized lymphoid aggregates with a relatively pale central zone of larger activated lymphoid cells, surrounded by a more densely cellular peripheral lymphoid component. Because immunohistochemical confirmation of follicular organization was not performed, these structures are referred to conservatively as germinal-center–like rather than definitive germinal centers.

Krenn synovitis score

Synovitis severity was assessed using the Krenn Synovitis Score. Synovial lining hyperplasia, stromal activation, and inflammatory infiltrates were independently graded on a four-point scale ranging from 0 to 3. The total score ranged from 0 to 9, with scores of 0–4 classified as low-grade synovitis and scores of 5–9 as high-grade synovitis.

Semiquantitative assessment of morphological variables

In addition to the Krenn Synovitis Score, individual morphological features were evaluated using predefined semiquantitative criteria. Inflammatory density was graded as mild, moderate, or marked according to the overall density of inflammatory cells within the synovial stroma, and its distribution was recorded as diffuse, perivascular, nodular, or mixed. Stromal fibrosis was categorized as minimal/mild, moderate, or severe according to the proportion and architectural prominence of collagenized stroma. Vascular proliferation was categorized as mild, moderate, or marked according to the density and prominence of small vessels within the synovial stroma. Lymphoid aggregates were recorded by their presence and degree of organization, while plasma-cell infiltration was classified as mild, moderate, or marked. Fibrin deposition, pannus formation, cartilage involvement, bone involvement, multinucleated giant cells, and necrosis were recorded as present or absent where evaluable. These individual variables were assessed before assignment of the final predominant architectural pattern.

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Histopathological pattern classification

After assessing the individual morphological variables, each specimen was assigned to one of four predominant architectural patterns. Pattern assignment was based on the combination and relative predominance of inflammatory, stromal, vascular, lymphoid, and destructive features rather than on any single microscopic variable.

Inflammatory pattern

Marked inflammatory infiltration and prominent synovial lining hyperplasia, accompanied by conspicuous vascular proliferation, with minimal or mild stromal fibrosis and without a dominant organized lymphoid or fibrotic architecture.

Fibro-inflammatory pattern

Coexistence of persistent inflammatory infiltration and substantial stromal remodeling, with moderate-to-marked fibrosis but without the extensive destructive architecture characteristic of the fibrotic-destructive pattern.

Fibrotic-destructive pattern

Extensive collagenized stromal remodeling constituting the dominant architectural feature, accompanied by one or more features of chronic tissue injury/remodeling, including fibrin deposition, vascular congestion, pannus formation, and involvement of adjacent articular structures where represented.

Lymphoid-rich pattern

Nodular lymphoid organization constituting the dominant inflammatory architecture, characterized by prominent organized lymphoid aggregates, frequently accompanied by Germinal-center–like structures and prominent plasma-cell infiltration.

In specimens showing features of more than one category, classification was based on the dominant architectural component. Cases dominated by organized lymphoid aggregates were assigned to the lymphoid-rich pattern even when background fibrosis or diffuse inflammation was present. Cases with substantial fibrosis but persistent inflammatory activity were classified as fibro-inflammatory unless extensive collagenized remodeling and destructive changes predominated, in which case they were assigned to the fibrotic-destructive pattern. Cases lacking dominant lymphoid organization or substantial fibrosis and showing predominantly active diffuse inflammation with vascular proliferation were classified as inflammatory. The classification therefore represents predominant morphological phenotypes rather than mutually exclusive individual histological abnormalities.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 29.0; IBM Corp., Armonk, NY, USA). Because of the small sample size and unequal number of cases across the four histopathological groups, all statistical analyses were considered exploratory. Continuous variables are presented as median and interquartile range (IQR), and categorical variables as absolute numbers and percentages. Overall comparisons of continuous variables among the four histopathological patterns were performed using the Kruskal–Wallis test. Categorical variables were evaluated using Fisher's exact test where appropriate because of the small expected cell frequencies. Variables that directly contributed to the definition of the histopathological patterns were analyzed descriptively and were not subjected to inferential testing as evidence of classification validity. All tests were two-sided, and p-values were interpreted as exploratory rather than confirmatory. Given the limited cohort size, emphasis was placed on the direction and distribution of observed differences rather than on statistical significance alone. No formal claims of independent validation were based on these analyses.

Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Research Ethics Committee approved the investigation (TSMU/20.02.2020/A), and all patient information was anonymized before analysis to ensure confidentiality.

RESULTS

Patient characteristics

Twenty-one patients with histologically confirmed rheumatoid gonarthritis who underwent surgical synovial tissue sampling were included in the study. The study population consisted predominantly of women, reflecting the known epidemiological distribution of rheumatoid arthritis. The median patient age was 61.0 years (IQR 56.0–66.5 years), and the median disease duration before surgery was 6.5 years (IQR 5.0–8.0 years). The majority of patients demonstrated seropositive rheumatoid arthritis with anti-cyclic citrullinated peptide antibody positivity and had received disease-modifying antirheumatic therapy before surgery, most commonly methotrexate. Baseline demographic, laboratory, and clinical characteristics are summarized in **Table 1**.

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Table 1. Demographic and clinical characteristics of the study cohort

Variable	Total (n = 21)
Age, years, median (IQR)	61.0 (56.0–66.5)
Female sex, n (%)	16 (76.2)
Male sex, n (%)	5 (23.8)
BMI, kg/m², median (IQR)	31.0 (29.0–33.0)
Disease duration, years, median (IQR)	6.5 (5.0–8.0)
Anti-CCP positive, n (%)	21 (100.0)
CRP, mg/L, median (IQR)	72.0 (27.0–108.0)
ESR, mm/h, median (IQR)	38.0 (28.0–52.0)
Methotrexate therapy, n (%)	17 (81.0)
Other csDMARD therapy, n (%)	9 (42.9)
Radiographic erosions, n (%)	16 (76.2)
Severe structural damage, n (%)	11 (52.4)
High-grade Krenn synovitis, n (%)	20 (95.2)

Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; IQR, interquartile range; kg/m², kilograms per square meter; mg/L, milligrams per liter; mm/h, millimeters per hour; n, number of patients.

Overall histopathological findings

Routine examination of hematoxylin and eosin-stained synovial sections demonstrated chronic synovitis in all cases. Synovial lining hyperplasia, increased stromal cellularity, chronic inflammatory infiltrates, vascular proliferation, and variable degrees of stromal fibrosis were consistently identified, although their extent differed markedly among individual specimens.

High-grade synovitis according to the Krenn Synovitis Score was present in 20 of 21 cases (95.2%), indicating that most surgical specimens represented advanced inflammatory disease. The median total Krenn score for the entire cohort was 7.0 (IQR 6.0–8.0). Synovial lining hyperplasia ranged from mild to marked, whereas inflammatory infiltration represented the dominant microscopic abnormality in most specimens. Stromal remodeling varied considerably, with some tissues demonstrating only minimal fibrosis while others exhibited extensive collagenization and architectural distortion.

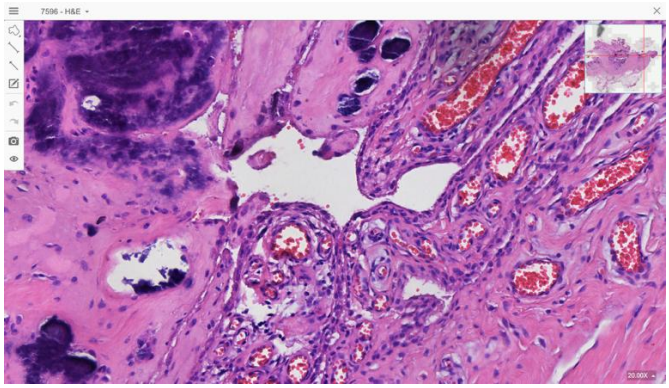
Lymphoid aggregates were observed in approximately half of the cases, whereas germinal center formation was confined to a smaller subgroup. Plasma-cell infiltration ranged from mild to marked, and vascular proliferation was a frequent finding throughout the cohort. Pannus formation, fibrin deposition, and cartilage involvement were predominantly observed in specimens demonstrating advanced structural remodeling.

Histopathological pattern recognition

Comprehensive assessment of the microscopic architecture demonstrated that rheumatoid synovitis was morphologically heterogeneous rather than uniformly distributed across the study population. Based on the predominant combination of inflammatory activity, stromal remodeling, vascular alterations, and lymphoid organization, four predominant histopathological patterns were provisionally recognized within this exploratory cohort.

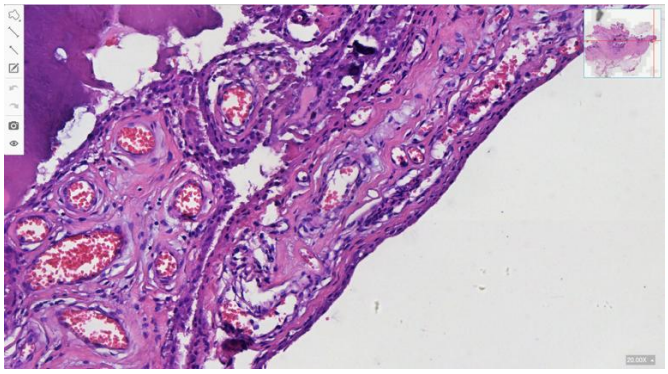
The inflammatory pattern accounted for four cases (19.0%) and was characterized by marked synovial lining hyperplasia, diffuse inflammatory infiltration, conspicuous vascular proliferation, and minimal stromal fibrosis (**Fig.1**).

FIGURE 1. Representative H&E photomicrograph demonstrating prominent angiogenesis within rheumatoid synovium, characterized by numerous newly formed capillary-sized vessels embedded in inflamed fibrovascular tissue. Original magnification ×200



The fibro-inflammatory pattern was identified in five cases (23.8%). These specimens demonstrated simultaneous active inflammation and progressive stromal remodeling, with moderate inflammatory infiltrates accompanied by increasing collagen deposition and fibrosis (**Fig.2**).

FIGURE 2. Representative H&E photomicrograph demonstrating chronic synovial remodeling with increased microvascular density, vascular wall thickening, and surrounding fibro-inflammatory stromal changes. Original magnification ×200



The fibrotic-destructive pattern was present in six cases (28.6%). When present, it demonstrated extensive stromal fibrosis associated with architectural distortion, fibrin deposition, vascular congestion,

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pannus formation, and destructive changes involving adjacent articular structures.

The remaining six cases (28.6%) showed a lymphoid-rich pattern characterized by prominent lymphoid aggregates, germinal center formation, abundant plasma cells, and nodular inflammatory organization.

Comparison of clinicopathological variables demonstrated significant differences among the identified histopathological patterns.

Patients with fibro-inflammatory synovitis had the longest disease duration, whereas those assigned to the fibrotic-destructive pattern generally had a shorter documented disease duration despite advanced tissue remodeling (**Tab.2**).

TABLE 2. Clinicopathological characteristics according to histopathological pattern

Variable	Inflammatory (n=4)	Fibro-inflammatory (n=5)	Fibrotic-destructive (n=6)	Lymphoid-rich (n=6)	p-value
Age, years	66.5 (63–68)	65.0 (61–67)	56.5 (54–60)	61.0 (57–65)	0.098
Disease duration, years	6.5 (6–7)	9.0 (8–10)	4.5 (4–5)	6.5 (6–7)	0.009
CRP, mg/L	110.0 (95–126)	35.0 (20–44)	102.5 (86–118)	22.5 (18–30)	0.008
ESR, mm/h	39.5 (34–46)	25.0 (22–29)	56.5 (51–63)	31.5 (28–36)	0.002
Krenn total score	7.5 (7–8)	5.0 (5–6)	7.0 (6–8)	6.0 (6–7)	0.025
Severe structural damage, n (%)	4 (100)	2 (40)	5 (83.3)	0 (0)	0.002

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; mg/L, milligrams per liter; mm/h, millimeters per hour; n, number of patients; p, probability value (statistical significance).

Systemic inflammatory activity also differed among the tissue patterns. Median CRP and ESR values were highest in inflammatory and fibrotic-destructive specimens, while lower inflammatory marker levels were generally observed in fibro-inflammatory and lymphoid-rich tissues.

Structural joint damage varied significantly among the identified histopathological patterns. Severe structural destruction and advanced joint-space narrowing were observed predominantly in inflammatory and fibrotic-destructive specimens, whereas moderate structural alterations predominated within fibro-inflammatory and lymphoid-rich tissues.

These findings suggest that comparable degrees of clinical joint destruction may arise through different microscopic patterns of synovial remodeling.

Morphological characteristics of the identified tissue patterns

Although all specimens demonstrated chronic inflammatory synovitis in the clinical context of established rheumatoid arthritis, each histopathological pattern showed a characteristic architectural profile.

Inflammatory specimens were dominated by diffuse inflammatory infiltration, prominent synovial lining hyperplasia, and marked vascular proliferation.

Fibro-inflammatory specimens demonstrated balanced coexistence of persistent inflammatory activity and progressive stromal fibrosis.

Fibrotic-destructive tissues exhibited extensive collagenized remodeling, vascular congestion, fibrin deposition, multinucleated giant cells, and focal necrotic changes, representing the pattern with the most extensive structural tissue remodeling observed within the cohort.

Lymphoid-rich specimens were distinguished by organized lymphoid aggregates with germinal center formation and abundant plasma-cell infiltration while demonstrating comparatively less extensive stromal fibrosis.

The complete comparison of clinicopathological variables and histopathological findings by tissue pattern is presented in **Tables 2** and **3**.

TABLE 3. Descriptive histopathological characteristics of the derived synovial tissue patterns

Feature	Inflammatory (n=4)	Fibro-inflammatory (n=5)	Fibrotic-destructive (n=6)	Lymphoid-rich (n=6)	p-value
Lymphoid aggregates present	0 (0%)	2 (40%)	2 (33.3%)	6 (100%)	0.013
Germinal centers present	0 (0%)	0 (0%)	0 (0%)	6 (100%)	0.001
Severe fibrosis	0 (0%)	4 (80%)	6 (100%)	1 (16.7%)	<0.001
Severe vascular proliferation	4 (100%)	3 (60%)	2 (33.3%)	1 (16.7%)	0.015

Abbreviations: p, probability value (statistical significance).

The morphological variables presented in Table 3 are shown descriptively to characterize the architectural profiles of the derived histopathological patterns. Because several of these features contributed directly to pattern assignment, between-group inferential testing of these variables would be circular and was therefore not used as evidence of the classification's independent validity.

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DISCUSSION

The present study investigated the histopathological heterogeneity of rheumatoid gonarthritis using routine hematoxylin and eosin-stained surgical synovial specimens. Rather than evaluating isolated microscopic features independently, we examined the overall architectural organization of the synovial membrane. We identified four predominant histopathological patterns defined by different combinations of inflammatory activity, stromal remodeling, lymphoid organization, and tissue destruction. Although all specimens demonstrated histological features of chronic inflammatory synovitis in the clinical context of established rheumatoid arthritis, substantial interindividual morphological variability was observed.

Synovial tissue has increasingly become recognized as an important source of biological information in rheumatoid arthritis. Previous studies have demonstrated considerable variation in the composition of inflammatory infiltrates, stromal activation, angiogenesis, and fibroblast behavior among patients with apparently similar clinical disease.[7,8] Consequently, several investigators have proposed molecular and immunophenotypic classifications of rheumatoid synovium, including lymphoid, myeloid, diffuse inflammatory, and pauci-immune or fibroid pathotypes.[9] Click or tap here to enter text. However, most of these classification systems rely on immunohistochemistry, multiplex immunofluorescence, or transcriptomic profiling, techniques not routinely available in diagnostic pathology laboratories. Our findings suggest that conventional H&E evaluation may allow recognition of predominant tissue patterns that share selected structural characteristics with previously described synovial phenotypes.

The inflammatory pattern identified in our cohort was characterized by diffuse chronic inflammatory infiltration, marked synovial lining hyperplasia, and prominent vascular proliferation, representing active synovitis with limited stromal remodeling. In contrast, the fibro-inflammatory pattern combined persistent inflammatory activity with progressive collagen deposition and stromal reorganization, suggesting coexistence of active inflammation and chronic tissue repair. The fibrotic-destructive pattern demonstrated extensive stromal fibrosis, vascular congestion, fibrin deposition, and destructive architectural changes, reflecting pronounced structural tissue remodeling within the examined specimens. Finally, the lymphoid-rich pattern was distinguished by organized lymphoid aggregates, germinal-center–like structures, and prominent plasma-cell infiltration, consistent with tertiary lymphoid organization previously described in rheumatoid synovium.

An important observation of the present study was that systemic inflammatory markers differed among the identified histopathological patterns. Patients demonstrating inflammatory and fibrotic-destructive tissue architecture generally exhibited higher CRP and ESR values than those assigned to fibro-inflammatory and lymphoid-rich patterns. Although interpretation should be cautious because of the limited sample size and potential influence of ongoing therapy, these findings suggest that microscopic tissue architecture may reflect different biological states of synovial inflammation. Interestingly, the fibrotic-destructive pattern combined severe structural remodeling with persistent systemic inflammatory activity, indicating that advanced tissue destruction does not necessarily occur without active inflammation.

Disease duration also differed between the identified patterns. Patients assigned to the fibro-inflammatory pattern had the longest disease duration, whereas the fibrotic-destructive pattern had comparatively shorter disease duration despite extensive structural remodeling. This observation suggests that the extent of microscopic tissue damage cannot be explained solely by disease duration and may instead reflect differences in the biological behavior of synovial inflammation, treatment response, or individual susceptibility to tissue destruction. Similar variability has been reported in previous studies demonstrating discordance between clinical disease duration and histopathological severity.[10,11]

The present study also emphasizes the limitations of evaluating individual histological variables in isolation. Conventional histopathological assessment frequently reports lining hyperplasia, inflammatory infiltrates, fibrosis, or vascular proliferation separately. However, rheumatoid synovitis represents a complex interaction between inflammatory and reparative processes occurring simultaneously within the same tissue. Evaluating the overall architectural organization of the synovium may therefore provide a more comprehensive representation of tissue pathology than isolated microscopic parameters alone. From a practical perspective, morphology-based tissue stratification may be readily incorporated into routine pathological examination without additional laboratory costs or specialized molecular techniques.

The findings of this study should be interpreted in light of several limitations. First, the study included a relatively small number of surgically treated patients from a single institution, limiting statistical power and generalizability. Second, the cross-sectional design precludes assessment of longitudinal disease

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progression or prediction of future structural damage. Third, all specimens were obtained during surgery and therefore represent advanced rheumatoid gonococcal arthritis rather than the full spectrum of disease severity. Finally, the proposed histopathological patterns were derived from conventional morphological assessment and require validation in larger independent cohorts.

In addition, synovial tissue in rheumatoid arthritis is spatially heterogeneous, and tissue sampling was based on archived material obtained during routine surgical pathology processing rather than prospectively standardized multisite sampling. Consequently, the assigned predominant pattern may not capture the complete within-joint histological heterogeneity of an individual patient. Future studies should evaluate multiple anatomically defined synovial samples per joint and assess within-patient spatial concordance of pattern assignment.

Despite these limitations, the present study provides a practical framework for morphology-based assessment of rheumatoid synovium using routine H&E sections. The proposed classification is intentionally based on histopathological features that are readily recognizable during routine diagnostic practice and therefore may facilitate standardized reporting of rheumatoid synovitis across pathology laboratories. Future investigations should evaluate the reproducibility of these tissue patterns, validate them in larger multicenter cohorts, and determine their relationship with immunophenotypic characteristics, digital pathology metrics, therapeutic response, and long-term structural outcomes. Integration of routine morphology with immunohistochemistry and whole-slide digital image analysis may further refine synovial tissue stratification and contribute to the development of clinically applicable pathology-based biomarkers in rheumatoid arthritis.

Overall, our findings support the concept that rheumatoid arthritis of the knee demonstrates substantial histopathological heterogeneity that can be recognized using conventional H&E examination. In this exploratory cohort, morphology-based assessment allowed provisional categorization of specimens by predominant synovial architecture. Whether independent observers can identify these patterns reproducibly remains to be established through formal interobserver reliability studies. The present findings therefore provide a foundation for future studies integrating histopathological, immunophenotypic, molecular, and digital pathology data.

Treatment exposure represents an additional potential confounder. Although we recorded available DMARD information, detailed longitudinal data on treatment intensity, duration, adherence, glucocorticoid exposure, and changes immediately preceding surgery were incomplete. The observed relationships between synovial morphology and systemic inflammatory markers therefore cannot be interpreted independently of potential treatment effects.

CONCLUSIONS

This exploratory retrospective study identified four predominant H&E-based architectural patterns in synovial tissue from patients with surgically treated rheumatoid arthritis of the knee: inflammatory, fibro-inflammatory, fibrotic-destructive, and lymphoid-rich patterns. These categories differed descriptively in their inflammatory, fibrotic, vascular, lymphoid, and destructive morphological features and showed preliminary associations with selected clinical and laboratory variables.

Because the classification was derived from a small cohort of patients with advanced surgically treated disease, the observed associations should be considered hypothesis-generating. Temporal progression between the identified patterns, prognostic significance, prediction of treatment response, and equivalence to previously described molecular synovial pathotypes were not assessed. Independent validation in larger cohorts using prespecified classification criteria, formal interobserver reliability analysis, comprehensive tissue sampling, and integration with immunophenotypic and molecular data is required before the proposed approach can be considered for routine clinical application.

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REFERENCES

1. Yamanishi Y, Firestein GS. Pathogenesis of rheumatoid arthritis: the role of synoviocytes. *Rheum Dis Clin North Am*. 2001;27(2):355-371. doi:10.1016/S0889-857X(05)70206-4.
2. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res*. 2018;6(1):15. doi:10.1038/S41413-018-0016-9.
3. Put S, Westhovens R, Lahoutte T, Matthys P. Molecular imaging of rheumatoid arthritis: emerging markers, tools, and techniques. *Arthritis Res Ther*. 2014;16(2):208. doi:10.1186/AR4542.
4. Kinne RW, Bräuer R, Stuhlmüller B, Palombo-Kinne E, Burmester GR. Macrophages in rheumatoid

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arthritis. *Arthritis Res*. 2000;2(3):189-202. doi:10.1186/AR86.
5. Alam J, Jantan I, Bukhari SNA. Rheumatoid arthritis: recent advances on its etiology, role of cytokines and pharmacotherapy. *Biomed Pharmacother*. 2017;92:615-633. doi:10.1016/J.BIOPHA.2017.05.055.
6. National Library of Medicine. Synovitis score: discrimination between chronic low-grade and high-grade synovitis. PubMed. Accessed July 13, 2026.
7. Townsend MJ. Molecular and cellular heterogeneity in the rheumatoid arthritis synovium: clinical correlates of synovitis. *Best Pract Res Clin Rheumatol*. 2014;28(4):539-549. doi:10.1016/J.BERH.2014.10.024.
8. Townsend MJ. Molecular and cellular heterogeneity in the rheumatoid arthritis synovium: clinical correlates of synovitis. *Best Pract Res Clin Rheumatol*. 2014;28(4):539-549. doi:10.1016/J.BERH.2014.10.024.
9. Sutton S, Clutterbuck A, Harris P, et al. The contribution of the synovium, synovial derived inflammatory cytokines and neuropeptides to the pathogenesis of osteoarthritis. *Vet J*. 2009;179(1):10-24. doi:10.1016/j.tvjl.2007.08.013.
10. van de Sande MG, Baeten DL. Immunopathology of synovitis: from histology to molecular pathways. *Rheumatology (Oxford)*. 2016;55(4):599-606. doi:10.1093/RHEUMATOLOGY/KEV330.
11. Krenn V, Morawietz L, Burmester GR, et al. Synovitis score: discrimination between chronic low-grade and high-grade synovitis. *Histopathology*. 2006;49(4):358-364. doi:10.1111/J.1365-2559.2006.02508.X.

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