Clinical, Serological, and Synovial Determinants of Early Remission in Patients with Synovitis of Recent Onset

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ABSTRACT

Background: Synovitis of recent onset can be self-limited or persistent, leading to progressive articular damage and requiring ongoing pharmacological suppression. We sought to determine clinical, serological and pathological findings that correlated with later remission in patients with early synovitis.

Methods: 124 patients with peripheral joint synovitis of less than one year duration were referred to NIH protocol 94-AR-0194. Clinical parameters, rheumatoid arthritis (RA) autoantibodies (rheumatoid factor (RF), anti-cylic citrillunated peptide (CCP), anti-Sa), and human leukocyteantigen (HLA) susceptibility alleles were measured at baseline. Patients underwent closed synovial needle biopsy of an affected joint and histopathological features seen on routine light microscopy were analyzed. Clinical, serological, and histopathological parameters recorded during the first year were examined for their relation to remission or disease persistence after one year of observation.

Results: After one year, 36/124 (29%) of the cohort was in remission off anti-rheumatic therapy. Compared to patients with persistent synovitis, patients in remission were younger (67% vs 34% age<40, $p=0.001$), were more likely to have presented with oligoarthritis (76% vs 38%, $p<0.001$), and had an overall lower prevalence of RA autoantibodies (17% vs 49%, $p=0.001$). Synovial histopathological findings correlating with persistence included lymphoid organization, microvascular damage with stromal fibrin deposition, and activated mesenchymal stromal cells. In a multivariate model, the absence of these unfavorable histopathological features were independently related to later remission both in the cohort as whole, and in patients presenting with oligoarthritis

(n=61), of whom 46% achieved remission.

Conclusions: Resolution of early synovitis is common after one year, particularly in younger patients who present with oligoarthritis and who lack RA associated autoantibodies. Routine light microscopic analysis of synovial samples obtained using closed needle biopsy adds further power to the association, and may be of particular value in patients presenting with oligoarthritis, where remission occurs in almost half of the cases.

Synovitis of recent onset often poses a challenge to clinicians, both from a diagnostic and a prognostic point of view (1-3). The outcome of synovial inflammation is known to vary considerably. In some cases the process is persistent and progressive, requiring ongoing suppressive therapy and leading to articular damage and functional disability. In others, there is complete resolution of the process over a period of months without any requirement for ongoing pharmacological suppression. It remains an important objective to discriminate between these divergent outcomes at an early stage of the process so that appropriate management is initiated in a timely manner.

It is well established that patients presenting with rheumatoid factor (RF) positive symmetrical polyarthritis are usually diagnosed as having rheumatoid arthritis (RA), and typically have persistent synovitis requiring ongoing drug therapy to suppress the articular inflammation and prevent damage. Although seropositivity for RF is an unfavorable prognostic marker in patients with early inflammatory arthritis (4-6), this autoantibody lacks specificity. More recently, it has been shown that the sera of RA patients contain antibodies that are directed towards a range of antigens containing the amino acid citrulline, which is formed as a result of post-translational modification of

arginine by the ubiquitous enzyme peptidyl arginine deiminase (7). These reactivities include anti-keratin antibodies (AKA), anti-perinuclear factor (APF), anti-filaggrin antibodies (AFA), anti-Sa antibodies, and antibodies directed towards cyclical citrullinated peptides (CCP). These antibodies have a high degree of specificity for RA (8-10), are detectable at an early stage of the process (11-13), and may be of prognostic significance in patients with early synovitis (14-16). Interestingly, it has been shown that these antibodies, along with IgA RF, can antedate the development of clinical disease, in some cases by years (17).

The outcome in adult patients presenting with oligoarthritis is unpredictable, irrespective of whether or not they are diagnosed as having a spondylarthropathy (18,19). Indeed, there is often considerable diagnostic uncertainty associated with this presentation. Reactive arthritis is diagnosed if there are features present such as sacroiliitis or enthesitis, if there is a temporally associated urogenital or gastrointestinal infectious process, and particularly if HLA-B27 is positive. In a substantial number of oligoarthritis cases, the patient is deemed as having "undifferentiated arthritis" (UA), this diagnosis having been shown to be quite prevalent in early arthritis clinics (11,20-22). Although it is known that a proportion of patients who are ultimately diagnosed as having RA present with oligoarthritis, to date, the diagnostic and prognostic value of autoantibodies such as RF, anti-CCP, and anti-Sa in this group of patients has not been well defined.

There is currently limited knowledge about the prognostic value of synovial pathology in early synovitis, in part because of a relative paucity of appropriately sized, biopsy-based studies of early synovitis patient cohorts. The Parker-Pearson closed

synovial biopsy technique is a low risk, cost effective method of obtaining synovial tissue samples, and is well suited for a study of synovitis of recent onset (23). We utilized this technique to study a large early synovitis cohort at the National Institutes of Health.

Patients with synovitis of less than 12 months duration, involving one or more peripheral joints were characterized clinically and pathologically at study entry. The patients were then followed and the outcome of the synovitis after one year of observation was documented. In this report we present data regarding the clinical, serological, and pathological predictors of remission in this cohort of patients.

METHODS

Patients

This study clinically and pathologically evaluated a cohort of 124 patients with synovitis of recent onset. The cohort described in the current study was recruited to a large, biopsy-based early synovitis protocol at the National Institutes of Health (protocol 94-AR-194). All study procedures were fully approved by the institutional review board of National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the patients participated in the study after informed consent. The clinical, HLA, and autoantibody features of this entire cohort have been previously described (2,16,20). The subset of patients described in the current study included all recruited patients having histologically adequate synovial tissue samples, and appropriate clinical follow-up for a full year following the initial clinical evaluation and synovial biopsy. This cohort did not differ significantly in terms of clinical features or outcome from the larger cohort previously published.

All study patients had persistent synovitis (> 6 weeks) of one or more peripheral

joints, which had been present for less than one year at the time of evaluation and synovial biopsy. Patients with traumatic, septic, and crystal induced arthritis were specifically excluded. In addition, patients with a clearly defined connective tissue disease such as systemic lupus erythematosus or scleroderma were also excluded for analysis. At the time of the initial evaluation, most of the patients had not had any form of disease modifying anti-rheumatic drugs. Patients underwent a complete clinical, radiographic, and laboratory evaluation at the time of the synovial biopsy procedure. A swollen joint count was determined by evaluating for the presence of effusion and/or synovial thickening in 66 peripheral joints (hips were excluded).

Following this initial clinical evaluation, patients were followed on four clinic visits over the subsequent year period, and a final diagnosis was made after the year of follow up. Treatment was undertaken by the referring physician, typically a rheumatologist or an internist, according to accepted clinical guidelines. Patients were assigned a diagnosis of RA if they met American College of Rheumatology criteria set for this disease (24).

Patients were classified as having a spondyloarthropathy, most commonly reactive arthritis, if they met the European Spondyloarthropathy Study Group (ESSG) criteria set (25). Other specific diagnoses were made on clinical grounds. Patients who could not be classified after the full year of observation were labeled as having undifferentiated arthritis (UA).

In this study, we were specifically interested in clinically and pathologically characterizing a subset of early synovitis patients destined to have a self-limited course, and differentiating these patients from those who will have persistent synovitis. The

definition of self-limited, or remittent, synovitis that was used in this study incorporated the following three criteria, all of which needed to be met at the end of the one year study period:

1) no swollen or tender joints

2) no elevation in acute phase reactants as detected by erythrocyte sedimentation rate (ESR) and C reactive protein

3) no requirement for ongoing corticosteroid or disease modifying antirheumatic drug therapy. Because of the difficulty of controlling for over-the-counter medication, use of non steroidal anti-inflammatory drugs (NSAID) did not preclude remission status at one year.

Synovial Biopsy procedure

Representative samples of the synovial tissue, primarily from actively inflamed knee joints, were obtained using the Parker-Pearson biopsy technique (HRS, RGM, HEG), as previously described (23). Typically, 15-20 samples were obtained from various parts of the joint by angling the needle in different directions. In total, 3-5 individual biopsy samples were allocated for detailed light microscopy. These representative samples were formalin fixed together, embedded in paraffin, and stained with hematoxylin and eosin (H&E) for histopathologic assessment. Other samples were used for polymerase chain reaction, in-situ hybridization, and electron microscopic studies reported previously ( ).

In addition to the patient cohort, synovial tissue samples were obtained from four normal healthy volunteers recruited to the same protocol using the same biopsy technique. These samples were used to define the normal spectrum of histological

features seen in this tissue, and were used as references for evaluating the presence or absence of specific pathological features seen in the patients with early synovitis.

Synovial tissue analysis

H&E sections of the synovial tissue samples were examined for the presence or absence of a spectrum of histopathological features. The definition and description of the specific histopathological features evaluated in the biopsy samples is summarized in Table 1. Examples of these features in the synovium of normal controls, and in samples from patients with self-limited and persistent synovitis are shown in Figure 1. All sections examined had several individual synovial biopsy samples available, with a clearly visible synovial lining layer.

Because the aim of the study was to differentiate self-limited from persistent synovitis, it was decided that an analysis based on the simple presence or absence of each histopathological feature was the most reproducible and clinically meaningful. Each pathological feature, as defined in Table 1, was deemed to be present in a synovial tissue if it was clearly identifiable in at least two non-adjacent medium low power fields (x200). If a feature was present in only one field, it was considered "marginal". An analysis of the data suggested that the inclusion of marginal scores did not impact on the overall results, and as a result, all marginal scores were considered as representing a feature to be present. The four normal synovial samples were used to establish the normal range of histological features found in the synovium. This reference to normal synovial histological features was particularly important when evaluating features related to vascularity, such as the presence of angiomatoid vessels and vascular occlusion/damage. Two experienced observers who were blinded to the clinical data (HEG, CAH)

independently evaluated the sections for the presence or absence of each of the pathological features. In cases where there was disagreement regarding the presence of a feature, a consensus was achieved by reviewing the sections together.

Statistical analysis

Comparisons between persistent synovitis and self-limited synovitis were made using student T test, and Mann Whitney U test for linear variables, and Chi squared test for categorical variables. Binary logistical regression was performed using a forward conditional method with probability of 0.05 and 0.1 respectively for entering and excluding variables. Probability values of less than 0.05 were considered significant.

RESULTS

Clinical Features

The clinical characteristics of the patient cohort at the time of the initial biopsy are shown in Table 2. The group with self-limited synovitis was considerably younger than the group with persistent synovitis (45.8 vs. 36.6 years, $p=0.001$), and had a lower number of swollen joints (4.0 vs. 11.2, $p<0.001$). There were no differences in the level of acute phase reactants as measured by ESR or CRP.

Three autoantibodies known to be highly associated with RA were evaluated in the cohort, these being RF, anti-CCP, and anti-Sa. As shown in Table 2, all three of these autoantibodies were significantly, although not exclusively, associated with persistent synovitis. Of the total of 42 RF positive patients, 7 (17%) had a self-limited outcome, whereas only one anti-CCP positive, and none of the anti-Sa positive patients had a self-limited outcome. These data suggest that the presence of CCP or Sa antibodies is more closely associated with persistent synovitis than is the presence of RF.

Table 3 summarizes the clinical diagnoses at the one year visit, and the details of disease modifying anti-rheumatic drug (DMARD) and corticosteroid therapy at the initial evaluation and after one year. These data indicate that after one year of observation, the majority of patients with self-limited synovitis had been classified as having spondylarthropathy or undifferentiated arthritis.

All but 3 spondylarthropathy patients had reactive arthritis. In contrast, the majority of patients in the persistent group were classified as having RA. Data regarding therapy in the two groups are also shown in Table 3. Both at baseline and at the completion of the one year study period, patients with persistent synovitis were significantly more likely to be receiving one or more DMARD and/or systemic corticosteroids. DMARD used included methotrexate, sulfasalazine, minocycline, and hydroxychloroquine. Of interest, only 22% of the self-limited group received DMARD therapy at any point during the course of the study, making this variable highly unlikely to account for the induction of remission in these patients.

Association of Pathological Features with Persistence/Remission

A comparison of the frequency of the pathological features in persistent and self limited synovitis is shown in Table 4. Fibrin deposits on the surface of the synovial lining cell layer were commonly seen in both groups. In contrast, fibrin deposits within the synovial stroma itself were rarely seen in self-limited synovitis and were highly predictive of persistence one year later (OR 6.0, CI:1.6-27, p=0.002). In the most severe cases, a dense fibrin cap was present on the surface of the lining, and the fibrin permeated in an uninterrupted manner deep into the synovial stroma. In these cases, the lining cell layer could not be clearly identified, and the sub-lining synovial stroma tended to be

hypovascular, and was populated by highly activated appearing stromal cells with large pale nuclei and prominent nucleoli (Figure 1). This cellular appearance has been termed "mesenchymoid transformation", and in the current study, was associated with persistent synovitis (OR 2.9, CI: 1.1-8.1, p=0.02). These activated appearing stromal cells were frequently in direct contact with mononuclear cells. Hyperplasia of the synovial lining cell layer was present in 31/124 (25%) samples, but did not differentiate persistent from self-limited synovitis. In 13/124 (11%) samples there were areas of overt synovial necrosis. In all cases, the presence of synovial necrosis was associated with persistence. Interestingly, the presence of stromal fibrosis was associated with self-limited rather than persistent synovitis.

There was little to distinguish the inflammatory cell infiltrates seen in self-limited and persistent synovitis. Small perivascular aggregates of mononuclear cells were often seen in both groups, and indeed were present in one of the normal synovial tissue samples. In contrast, large, well-developed lymphoid follicles and plasma cell infiltrates tended to be associated with persistent synovitis (OR 3.0, CI 0.8-14, p=0.08).
There were striking differences between persistent and self-limited synovitis in terms of the characteristics of the synovial microvasculature. The presence of microvascular damage and occlusion was highly predictive of persistence (OR 3.8, CI: 1.4-11, p=0.003). Swelling of the endothelial cells was the most commonly observed microvascular abnormality, although various degrees of vascular occlusion were also demonstrable in many samples, particularly in patients diagnosed as having RA (Figure 1). Overt vasculitis was rarely observed. Interestingly, there were no obvious differences between the two groups in terms of the presence of angiomatoid blood vessels, although

it should be stated that this feature was particularly difficult to evaluate strictly on the basis of analyzing H&E sections.

Particularly striking was the association between persistent synovitis and the presence of high endothelial venules in the synovial membrane (OR 9.3, CI: 2.0-60, $p=0.001$). This feature was only seen in 2/36 (6%) of cases with self-limited synovitis, whereas it was present in 31/88 (35%) of cases with persistent synovitis. Moreover, there was a high degree of association between the presence of HEV and the presence of well developed lymphoid follicles ($r=0.68$, $p<0.0001$) in the synovial stroma.

We performed an analysis to exclude the possibility that the histopathological differences between the persistent and remittent group could be partially accounted for by the use of DMARD at the time of synovial biopsy. In total 43/124 (35%) patients were receiving DMARD at the time of biopsy. The prevalence of each pathologic feature was compared in the patients taking DMARD and those not taking DMARD at the time of biopsy. This analysis did not reveal differences between these two groups with respect to any of the features (data not shown). These data indicate that there were no differences between on DMARD and no DMARD patients in terms of the discriminating histopathological features.

A multivariate logistic regression model was used to identify the best independent predictors of self limited synovitis. Variables inputted into the model included all clinical and pathological variables that were significantly associated with the outcome by univariate analysis. This list included age, presence of oligoarthritis, RF, anti-CCP, anti-Sa, and the histopathological variables stromal fibrin, stromal cell proliferation, lymphoid follicles, microvascular damage, high endothelial venules, necrosis, and fibrosis. These

data indicated that age (OR 0.95, p=0.003), oligoarthritis (OR 5.08, p=0.002) were positive predictors self-limited synovitis, while the presence of stromal fibrin (OR 0.13, p=0.005), and high endothelial venules (HEV) (OR 0.17, p=0.03) were independent negative predictors of this outcome.

Clinical and histopathological predictors of persistence/remission in patients presenting with oligoarthritis

The diagnosis and outcome of patients presenting with oligoarthritis (1-4 swollen joints) is often in doubt, although the presence of oligoarthritis was the strongest predictor of a self-limited outcome. As shown in Table 2, in the current cohort, 61/124 (49%) of the patients presented with oligoarthritis. Although only 28/61 (46%) of these oligoarthritis patients were actually in remission after one year, these 28 patients formed the majority of the patients in the self-limited synovitis group. We therefore attempted to identify the clinical and pathological features that differentiated persistent from self limited synovitis in patients presenting with oligoarthritis. The data are shown in Table 5.

The patients with self-limited remittent oligoarthritis were significantly younger than the patients with persistent oligoarthritis (36 vs. 45, p=0.01). The presence of RF did not predict persistence in these patients. In contrast, the presence of either anti-CCP or anti-Sa antibodies in this subset of oligoarthritis patients was associated with persistent synovitis (OR 6.5, CI 1.2-47, p=0.01). Moreover, the same pathologic features that predicted persistence in the overall cohort, namely stromal fibrin deposition, microvascular damage/occlusion, and high endothelial venules, also predicted persistence in this subset. A logistic regression model indicated that age and stromal fibrin were the most important independent predictors of persistence in this subset (data not shown).

Association of lymphoid organization with RA-associated autoantibodies

We attempted to define histopathological features that are most characteristic of early RA. Associations with the diagnosis of RA itself, and with the presence of RF, anti-CCP, anti-Sa, radiographic erosions, or the shared epitope alleles were sought. The analyses indicated the predictive histopathological were not specifically associated with a diagnosis of RA, the presence of radiographic erosions, or the presence of "shared epitope" HLA alleles. In contrast, the presence of any combination of RF, anti-CCP, or anti-Sa was highly associated with lymphoid follicles (OR 4.2, $p=0.005$), high endothelial venules (4.4, $p<0.001$), and microvascular damage (OR 3.5, $p=0.005$). None of the other histopathological features were significantly associated with these autoantibodies.

DISCUSSION

This study attempted to clinically, serologically and pathologically discriminate patients with early synovitis destined to have persistent arthritis from patients likely to have a self limited, remittent course. All patients had active synovitis at the time of biopsy defined as the presence of objective swelling of one or more peripheral joints, and an inflamed knee was typically the source of the synovial biopsy material. On average, the biopsy was performed within 6 months of symptom onset. We defined self-limited synovitis as the complete absence of joint swelling and systemic acute phase reactants one year after study entry, while being on no form of DMARD or corticosteroid therapy. Essentially all of the autoantibody positive polyarthritis patients ultimately had persistent synovitis, were diagnosed as having RA, and required ongoing use of DMARD and corticosteroids. In contrast, the outcome of oligoarthritis was more divergent, with

almost 50% of patients meeting the definition of complete remission after one year. Indeed, the group of 36 patients with self-limited synovitis was comprised primarily of young individuals presenting with oligoarthritis These data are consistent with the findings in a similar cohort in the United Kingdom (UK) where intra-articular corticosteroids were frequently effective in inducing rapid and lasting remission in a subset of oligoarthritis patients (18).

In total, 53% of the patients with self-limited synovitis group were diagnosed as having UA, while only 31% were diagnosed as having a spondylarthropathy on the basis of having met the ESSG criteria, the most widely accepted diagnostic criteria set in this heterogeneous group of disorders (25). The prevalence of HLA-B27 was 39% in this latter group, significantly higher than the 13% prevalence seen in both the RA and UA groups. HLA-B27 itself did not predict persistence, and RF was a weak predictor. In contrast, the presence of anti-CCP, anti-Sa, or both was a strong predictor of persistent synovitis in all patients, with only one anti-CCP positive patient remitting after a year. These data highlight the potential value of anti-CCP and anti-Sa RA in identifying patients who may be most likely to have persistent synovitis, particularly in patients with early oligoarthritis. These data are consistent with the finding of a predictive model of early arthritis (11).

In addition to the value of the clinical presentation and autoantibodies, we show that specific histopathological features that are evident in the synovium at an early stage predict persistence of the synovitis. These pathological features can broadly be categorized as the presence of lymphoid organization with follicle formation and high endothelial venules, microvascular damage with deep fibrin deposition, and the presence

of activated appearing stromal cells in the synovial stroma. These features are representative of related, but potentially independent processes. The presence or absence of any one of these features is by itself insufficient to predict persistence or resolution, but taken together several of these pathologic features independently add to a predictive model of persistence.

A number of previous studies have evaluated the histopathology and immunohistology of early synovitis, although not specifically with remission or persistence as endpoints (26-30). These studies have generally suggested that the differences between early RA synovitis and other forms of synovitis are quantitative rather than qualitative, with the former being characterized by higher numbers of plasma cells, macrophages, and increased protease levels. In the current study, the synovium of anti-CCP and anti-Sa positive patients frequently had evidence of lymphoid organization, irrespective of whether or not the RA clinical criteria were met. This included the presence of high endothelial venules specialized in lymphocyte trafficking, and large follicular structures comprised primarily of lymphocytes and plasma cells. Although an inflammatory infiltrate of lymphocytes, macrophages, and plasma cells could be seen in a high proportion of tissues, the organization of these elements into follicular structures was much more evident in patients with RA autoantibodies. This follicular organization is reminiscent of lymph nodes, and considerable investigative effort has centered around attempting to understand the cellular and molecular pathways that lead to synovial lymphoid neogenesis (31-34). It has been proposed that the propensity to develop ectopic germinal centers in the synovium is a property that is inherent to a specific subset of RA patients, and can be demonstrated longitudinally in these individuals. Moreover, this

process is characterized by a unique pattern of synovial cytokine and chemokine expression (32-34). In the current study, although lymphoid follicles were common, we did not identify germinal centers in association with these structures using routine light microscopy, but further immunohistologic studies may be needed to resolve this question. Irrespective of whether germinal centers are present or not, it is well known that autoantibodies are actively synthesized in RA synovium. This observation is well established in the case of RF. It has been shown recently that synovial B lymphocytes also produce antibodies directed against citrullinated antigens (35). Furthermore, citrullinated antigens were commonly detected in the synovium of RA patients (36,37). Interestingly, these citrullinated antigens were shown to be derived specifically from fibrin and fibrinogen, suggesting that post-translational modification of these proteins may be needed to render them antigenic. In support of this notion, the current study demonstrates a high degree of the association between the presence of stromal fibrin deposition, anti-CCP antibodies, and indeed the ultimate persistence of the synovitis. Additionally, anti-Sa antibodies were shown to recognize citrullinated vimentin, another potential synovial autoantigen (38). If taken together with the demonstration that RA patients appear to have a genetically determined propensity for increased citrullination (39), and that the RA associated HLA-DRB1*0401 allele preferentially presents citrullinated antigens to T cells (40), these data suggest that autoimmunity to citrullinated synovial antigens such as fibrin and vimentin may play a pivotal role in sustaining the immune responses that underlie the chronicity of RA synovitis.

The other important process underlying the chronicity of synovitis is the response of the synovium itself to inflammatory stimuli. This is most evident in RA pannus, where

the synovial lining layer and cellular elements of the sublining stroma proliferate exuberantly to form a hyperplastic, destructive lesion. The stimuli for this mesenchymal proliferation have been shown to include serum derived growth factors, cytokines such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα) that are derived from infiltrating synovial macrophages, and activation events that require cell to cell contact (41). Local tissue hypoxia from an imbalance of vascular perfusion and metabolic demand promotes the development of neovasculature, in an analogous manner to rapidly proliferating tumors (42,43). In our study, persistent synovitis was not predicted by the presence of angiomatoid blood vessels thought to represent neovascularization, but rather by the presence of microvascular damage, occlusion, and vessel wall proliferation. Although infrequent, areas of overt necrosis were seen only in patients with persistent synovitis. It can be speculated that the nature and extent of the synovial mesenchymal response may be genetically regulated, and that defects in some aspects of wound healing and response to injury may contribute to the persistence of the synovial lesion. Of interest, the finding of widespread fibrosis, indicative of resolution of the synovitis, was more associated with clinical remission.

The current study begins to define a set of histopathologic features seen on routine light microscopy that can potentially be used to predict the risk of persistence in early synovitis. Adequate sampling of the synovium was achieved in a large cohort of patients using a low risk, low cost procedure (23). Avoidance of complicated scoring methods in favor of simply making yes/no determinations regarding a core set of histopathological features makes this approach accessible to a wide spectrum of clinicians. Synovial tissue analysis obviously cannot be used in isolation, but as we

demonstrate in this study, can complement clinical and serological data in developing more robust prognostic models. In an age of early aggressive therapy, this approach may have its greatest value in identifying "undifferentiated" early synovitis patients with a favorable prognosis, in whom aggressive therapy would not be indicated. Our study demonstrates that available clinical parameters such as ESR or CRP levels do not serve to identify such patients. More predictive of a self-limited course is the absence of RA associated autoantibodies such as anti-CCP, and the absence of synovial microvascular damage/occlusion, stromal proliferation, and lymphoid organization. We therefore propose that the analysis of histopathological features present in synovial tissue samples obtained using closed needle biopsy will be of value in clinical decision making in patients with synovitis of recent onset, particularly if they present with an oligoarticular distribution of the synovitis.

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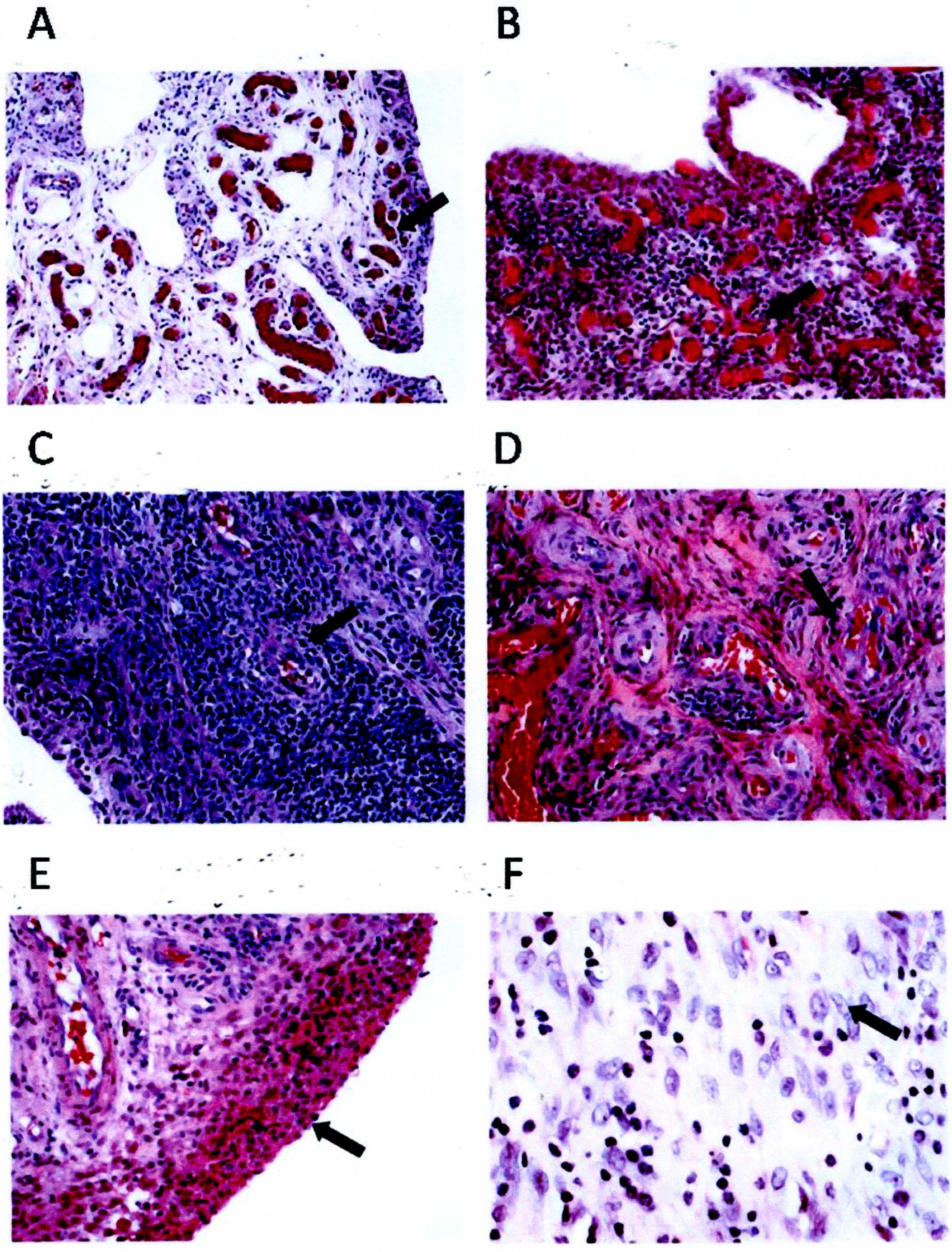
FIGURE 1: Histopathological features seen in **(A)** normal synovium, **(B)** self-limited synovitis, and **(C-F)** persistent synovitis. The normal synovium seen in **(A)** demonstrates an extensive network of small blood vessels immediately underlying a thin synovial lining cell layer (arrow). The stroma is hypocellular and uninfiltrated, athough occasional small perivascular infiltrates of mononuclear cells were seen in the normal samples. The synovial tissue shown in **(B)**, taken from a patient with undifferentiated arthritis that had a self-limited course, demonstrates a diffuse infiltrate of mononuclear cells, plasma cells, and occasional polymorphonuclear leukocytes. There is a rich "angiomatoid" vascular network in the stroma (arrow), but the vessels are not damaged. The synovial tissue shown in **(C)** is typical of RF, anti-CCP, anti-Sa positive patients, and demonstrates lymphoid follicular organization around well developed high endothelial venules (arrow). Microvascular damage and occlusion is demonstrated in **(D)**. This feature was a significant predictor of persistence. Hyperplasia of the lining layer demonstrated in the synovium of an early RA patient **(E)** tended to be associated with persistence, but was less predictive than proliferative stromal responses. "Mesenchymoid transformation" shown in **(F)** is characterized by the presence of large numbers of activated appearing stromal cells with large pale nuclei and several nucleoli (arrow). All sections stained with hematoxylin and eosin. Original magnifications: **(A)** x100; **(B-E)** x200; **(F)** x400


A
B
C
D
E
F

Table

SYNOVIAL HISTOPATHOLOGIC FEATURE	*DEFINITION*
surface fibrin deposits	deposits of fibrinoid material on the articular surface of the synovial lining cell layer
stromal fibrin deposits	deposits of fibrin in the immediate and/or deep sublining stroma
synovial lining layer hyperplasia	increased thickness of the synovial lining cell layer beyond 2-3 cells
stromal cell proliferation	presence of large numbers of stromal cells with pale nuclei and nucleoli
small perivascular lymphoid aggregates	small perivascular collections of <50 mononuclear cells
lymphoid follicles	large aggregates of >50 mononuclear cells with or without germinal centers
diffuse mononuclear cell infiltrate	a diffuse infiltrate of mononuclear cells without perivascular concentration
plasma cell infiltrate	typical appearing plasma cells with a dense, eccentrically placed nucleus
polymorphonuclear cell infiltrate	infiltration of the synovial stroma with neutrophils and/or eosinophils
angiomatoid vessels	collections of small blood vessels arranged in clusters suggestive of angiogenesis
microvascular occlusion/damage	vascular luminal occlusion, or endothelial swelling, or disruption of vessel walls
high endothelial venules	venules with tall columnar or cuboidal endothelium
necrosis of synovial stroma	areas of tissue necrosis generally lacking cellular and vascular elements
fibrosis of synovial stroma	areas where the stroma has been replaced by dense collagen fibers

TABLE 1 Definitions of histopathologic features evaluated in hematoxylin and eosin (H&E) sections of synovial biopsy samples. Each feature was considered to be present if visible in two or more non-adjacent medium power fields (x200).

	persistent synovitis (n=88)	*remittent synovitis (n=36)*	*P value*
females (%)	50 (57%)	24 (67%)	ns
age (yrs)	45.8 ± 15.0	36.6 ± 11.3	0.001
symptom duration (wks)	33.3 ± 27.1	22.8 ± 21.7	ns
ARTICULAR FEATURES			
swollen joint count	11.1 ± 11.0	4.0 ± 6.7	<0.001
oligoarthritis (%)	33 (38%)	28 (78%)	<0.001
polyarthritis (%)	55 (62%)	8 (22%)	<0.001
LABORATORY FEATURES			
ESR (mm/hr)	43.3 ± 30.3	38.6 ± 35.5	ns
CRP (mg/dl)	2.0 ± 2.3	2.0 ± 3.2	ns
RA AUTOANTIBODIES			
RF+ (%)	35 (40%)	7 (19%)	0.03
anti-CCP+ (%)	21 (24%)	1 (3%)	<0.01
anti-Sa+ (%)	12 (14%)	0 (0%)	0.02
HLA ASSOCIATIONS			
HLA-B27	15 (17%)	6 (17%)	ns
HLA-DR4/shared epitope	36 (41%)	14 (39%)	ns

TABLE 2 Clinical, serological, and HLA characteristics of early synovitis patient cohort.

	persistent synovitis (n=88)	*remittent synovitis (n=36)*	*P value*
CLINICAL DIAGNOSIS			
rheumatoid arthritis	54 (61%)	6 (17%)	<0.001
spondylarthropathy	7 (8%)	11 (31%)	0.001
undifferentiated arthritis	27 (31%)	19 (53%)	0.02
THERAPY AT TIME OF BIOPSY			
DMARD*	36 (41%)	7 (19%)	0.02
prednisone	31 (35%)	5 (14%)	0.02
THERAPY AT ONE YEAR FOLLOW UP			
DMARD*	62 (70%)	-	
prednisone	28 (32%)	-	
NEVER ON DMARD	18 (20%)	28 (78%)	<0.001

TABLE 3 Diagnosis at the end of the one year study period, and details of therapy. (*) DMARD used include methotrexate, sulfasalazine, and hydroxychloroquine

	persistent synovitis (n=88)	*remittent synovitis (n=36)*	*odds ratio (95% CI)*	*P value*
EXUDATE				
surface fibrin deposits	54 (61%)	16 (44%)	2.0 (0.8-4.7)	ns
stromal fibrin deposits	31 (35%)	3 (8%)	6.0 (1.6-27)	0.002
SYNOVIAL PROLIFERATION				
lining layer hyperplasia	25 (28%)	6 (17%)	2.0 (0.7-6.0)	ns
increased sublining stromal cells	36 (41%)	7 (19%)	2.9 (1.1-8.1)	0.02
INFLAMMATORY CELLS				
perivascular lymphoid aggregates	65 (74%)	24 (67%)	1.4 (0.6-3.5)	ns
lymphoid follicles	19 (22%)	3 (8%)	3.0 (0.8-14)	0.08
diffuse mononuclear cells	22 (25%)	6 (17%)	1.7 (0.6-5.1)	ns
plasma cell infiltrate	40 (46%)	10 (28%)	2.2 (0.9-5.5)	0.07
PMN infiltrate	6 (7%)	3 (8%)	0.8 (0.2-4.4)	ns
MICROVASCULATURE				
angiomatoid vessels	44 (50%)	14 (39%)	1.6 (0.7-3.7)	ns
microvascular occlusion/damage	42 (48%)	7 (19%)	3.8 (1.4-11)	0.003
high endothelial venules	31 (35%)	2 (6%)	9.3 (2.0-60)	0.001
NECROSIS	13 (15%)	0	NA	0.02
FIBROSIS	19 (22%)	16 (44%)	0.3 (0.1-0.9)	0.01

TABLE 4 Prevalence of the histopathological features described in Table 1 in synovial tissue samples from patients with early synovitis.

	persistent oligoarthritis (n=33)	*remittent oligoarthritis (n=28)*	*odds ratio (95% CI)*	*P value*
CLINICAL				
monoarthritis	10 (30%)	13 (46%)	0.5 (0.2-1.6)	ns
elevated CRP (> 0.7 mg/dl)	11 (33%)	10 (36%)	0.9 (0.3-3.0)	ns
female sex	18 (55%)	18 (64%)	0.7 (0.2-2.1)	ns
age>40	20 (61%)	6 (21%)	5.6 (1.6-21)	0.002
RA AUTOANTIBODIES				
rheumatoid factor	10 (30%)	6 (21%)	2.0 (0.6-7.5)	ns
anti-CCP or anti-Sa	11 (33%)	2 (7%)	6.5 (1.2-47)	0.01
HLA ASSOCIATIONS				
HLA-B27	8 (24%)	6 (21%)	1.2 (0.3-4.6)	ns
shared epitope	12 (36%)	12 (43%)	0.8 (0.2-2.4)	ns
PATHOLOGIC FEATURES				
stromal fibrin deposition	14 (42%)	3 (11%)	6.1 (1.4-32)	0.006
microvascular occlusion/damage	16 (49%)	5 (18%)	4.3 (1.2-17)	0.01
high endothelial venules	10 (30%)	2 (7%)	5.7 (1.0-42)	0.02
necrosis	6 (18%)	0	NA	0.02

TABLE 5 Clinical, serological, HLA, and pathological predictors of a self-limited course in patients presenting with oligoarthritis of recent onset.