Review

The challenge of early synovitis: multiple pathways to a common clinical syndrome

Hani El-Gabalawy

National Institutes of Health, Bethesda, MD, USA

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Introduction

Synovial inflammation involving one or more joints is the presenting feature, and often the predominant clinical manifestation of a spectrum of pathologic states, many of which continue to be incompletely understood. The outcome of early synovitis can range from rapid and complete resolution to a persistent inflammatory process associated with irreversible articular damage and progressive functional decline.

A rapidly expanding body of information generated from clinical, epidemiological, and basic research is providing a deeper understanding of how genetic susceptibility factors interact in complex ways with diverse environmental factors, resulting in seemingly related clinical syndromes. Such clinical syndromes can be thought of as 'phenocopies': in other words phenotypically similar, yet mechanistically distinct, states. Delineation of the specific molecular pathways that underlie disease expression is also linking highly distinct and seemingly unrelated clinical syndromes. These disorders are mechanistically similar, yet phenotypically distinct. These concepts are particularly relevant to understanding the spectrum of autoimmunity, chronic inflammation, and how they intersect to produce synovitis.

In attempting to understand more completely the mechanistic similarities and differences in patients with early synovitis, an increasing panoply of variables needs to be considered. Although, to date, no clear model has emerged upon which to classify early synovitis better, an understanding of how these variables interact and intersect will undoubtedly be of value in delineating the early synovitis phenocopies.

Clinical patterns and classification

In clinical practice, early synovitis is initially classified on the basis of the extent, location, and symmetry of the joint involvement. Although rheumatologists, as a group, are particularly skilled at this type of pattern recognition, the etiopathogenic mechanisms determining these patterns of joint involvement are unknown, and therefore the implications are empiric. Symmetrical involvement of the wrists and small joints of the hands and feet is highly characteristic of established rheumatoid arthritis (RA) and, when present at the onset of the synovitis, suggests the patient's symptoms will probably evolve into the typical RA phenotype, particularly if rheumatoid factor (RF) is present. The tendency for psoriatic arthritis to involve the distal interphalangeal joints of the hands, and to involve multiple joints of a single digit asymmetrically, is also used as an early classification feature, even in the absence of any obvious psoriatic plaques. The 'reactive arthritis' syndrome that in some individuals follows particular genitourinary and gastrointestinal infections typically features an asymmetric lower extremity oligoarthritis. Patients with this articular pattern are often labeled with this diagnosis, even if an antecedent infection cannot be identified. Features such as enthesitis, sacroiliitis, and dactylitis tend to cluster with this complex of articular inflammation, and collectively form an overall 'spondylarthropathy' pattern.

ACR = American College of Rheumatology; AFA = antifilaggrin; AGE-IgG = advanced-glycation-endproduct-modified immunoglobulin G; AKA = antikeratin; APF = antiperinuclear factor; CT = *Chlamydia trachomatis*; EBV = Epstein-Barr virus; ESSG = European Spondylarthropathy Study Group; IFN = interferon; IL = interleukin; LFA = lymphocyte function associated antigen; MCTD = mixed connective tissue disease; MHC = major histocompatibility complex; MRI = magnetic resonance imaging; RA = rheumatoid arthritis; RF = rheumatoid factor; RT PCR = reverse transcriptase polymerase chain reaction; SE = shared epitope; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

This informal pattern recognition has been formalized into criteria sets, which attempt to classify arthritis syndromes, although not necessarily on a mechanistic basis. The best validated and most widely used of these criteria sets are the 1987 American College of Rheumatology (ACR) RA criteria [1] and the 1991 European Spondylarthropathy Study Group (ESSG) spondylarthropathy criteria [2]. These criteria sets were developed as a consensus of expert opinion around patients with well-established and characteristic clinical features. They are not well suited for classifying cohorts of early synovitis patients, particularly if the aim is to identify uniform groups that have a common pathogenic mechanism and predictable prognosis. Indeed, even within the context of what is generally accepted to be 'typical' RA, there is considerable genetic, pathologic, and immunologic heterogeneity.

Published data from early synovitis cohorts, including our own at the NIH, indicate that a large percentage of patients can only be labeled as having 'unclassified' or 'undifferentiated' arthritis [3–6]. In our cohort, approximately one-third of the patients who were evaluated within one year of symptom onset fell into this category, and in some series this has been as high as 50% [4,7]. It has been stated [8] that the term 'undifferentiated' could have any of the following implications: 1) an early stage of a well defined rheumatic disease that will later become differentiated; 2) an abortive form, or forme fruste, of a well defined rheumatic disease; 3) an overlap syndrome; or 4) a truly unknown, undefined disease that may be differentiated in the future. Of note, none of these classifications imply a pathogenic mechanism. The follow-up data that are available from early synovitis cohorts suggest that most of the undifferentiated patients remain undifferentiated, but in general tend to have a favorable prognosis with frequent remission [4,6].

Imaging in the evaluation of early synovitis

Radiographic imaging of articular and periarticular structures may contribute information that defines specific phenocopies more precisely. However, many of the findings such as soft tissue swelling, periarticular bone loss, new bone formation, and bone erosion may be non-specific. Moreover, the radiographic findings in patients with early synovitis are often subtle, confounding diagnostic categorization. In particular, establishing the unequivocal presence of erosions is notoriously difficult within the first year of synovitis. The insensitivity of plain radiography in detecting early erosions is evident when these techniques are compared to magnetic resonance imaging (MRI) [9–12]. Furthermore, in addition to detecting early erosions with a high degree of sensitivity, MRI is currently the only modality that clearly images the synovium, allowing the generation of quantitative data regarding synovial volume and perfusion [13–17]. These parameters are broadly indicative of the degree of synovial hyperplasia, infiltration, and proliferation. Longitudinal studies of inflamed RA joints have shown that the measurement of synovial volume using gadolinium-enhanced MRI is of value in predicting the subsequent development and progression of articular erosions [17,18]. This result tends to confirm the clinical impression that RA joints with a 'boggy', thickened synovium often undergo progressive damage.

MRI has been applied to the task of defining subsets of early synovitis patients on the basis of the distribution pattern of the inflammation [19–21]. The data suggest two principal imaging patterns, one where the inflammatory changes are based primarily in the synovium, and another where the periarticular entheses are inflamed in association with intense edema of the adjacent bone. These two patterns are proposed to broadly classify patients with early synovitis into an 'RA' phenotype where synovitis is the primary process, and a 'spondylarthropathy' phenotype where enthesitis is the primary process, and synovitis occurs on a secondary basis. Although the simplicity of this paradigm is conceptually appealing, it remains to be seen whether such a 'tidy' model will be of value in classifying the heterogeneous spectrum of patients seen in early synovitis clinics. It is also not clear whether these MRI patterns are based on distinct pathogenic mechanisms, as has been suggested [21]. Interestingly, the limited data available regarding entheseal pathology suggest a relative paucity of inflammatory features histologically, a finding which may itself hint at a unique pathologic process in these structures.

Pathologic features

In view of the widely divergent outcomes associated with early synovitis, it has been assumed that specific pathologic features, or constellations of pathologic features, can be identified in early synovial tissue samples. Identification of these features would allow the definition of distinct pathogenic mechanisms, and in turn, the definition of unique phenocopies. The pursuit of this hypothesis has been facilitated by the more widespread use of closed needle biopsy and needle arthroscopy techniques. Several centers, including our own, have undertaken extensive studies of early synovial tissue samples, taken soon after the onset of the synovitis, which are analyzed using a variety of histological and molecular pathology techniques. The patients are then followed longitudinally, and the pathologic data is related to outcomes. Although many of these initiatives are still in progress, the published data do not suggest major differences between early RA synovitis and other forms of early synovitis, or even between early and late synovitis [22–24]. The prominence of plasma cells and macrophages at all stages of RA synovitis has been noted [25–27]. Indeed, recent data suggest that synovial macrophage infiltration may occur at a very early, possibly preclinical, stage in RA [28], and that the degree of macrophage infiltration may ultimately be an indicator of the erosive potential of the synovitis [26,27]. Consistent with this view is mounting evidence that osteoclasts, the precursors of which are myeloid cells, are likely to be

important mediators of bone erosion [29]. It can be speculated that the identification of synovial microenvironments which promote pathways leading to the differentiation of large numbers of myeloid cells into osteoclasts would be an important step towards defining an erosive synovial phenotype pathologically. At present there is little experimental evidence in this regard.

Infectious agents

Synovitis is clearly associated with a wide spectrum of infectious agents, and the mechanisms underlying this association are varied and complex. In the case of septic arthritis, arguably the best understood of these associations, a pathogen gains access to the usually sterile synovial cavity, precipitating an acute monoarticular synovitis which is predominated by polymorphonuclear leukocytes, and which is rapidly destructive. Viable organisms are directly demonstrable in the synovial fluid or tissue, and the inflammatory process usually resolves completely with the prompt and successful eradication of the organism. In general, genetic elements do not appear to play a major role in the susceptibility to most forms of septic arthritis, although this has not been extensively studied.

Lyme arthritis is frequently in the differential diagnosis in patients with early synovitis, particularly in endemic areas. This disorder has been a good model for understanding the mechanisms by which microorganisms can interact with the host's immune responses to precipitate and perpetuate synovitis. *Borrelia burgdorferi* spirochetes have been demonstrated in synovial tissue samples obtained early in the disease, and PCR techniques have further enhanced the early detection of this organism in synovial tissue and fluid [30–34]. The chronic arthropathy, typically affecting a single knee joint, is more suggestive of a persistent local immune response to bacterial antigens than of a chronic infectious process. Furthermore, this syndrome demonstrates an association with HLA-DR4. The histopathologic features of chronic Lyme synovitis can be indistinguishable from those of RA [35], although we have observed that Lyme synovitis tends to feature extensive stromal fibrin deposits. Of considerable scientific interest has been the recent observation that individuals with persistent, treatment-resistant Lyme arthritis demonstrate specific T cell responses to endogenous lymphocyte function associated antigen (LFA)-1 sequences that are homologous to sequences in the OSP-A outer membrane protein of *Borrelia burgdorferi* [36]. This apparent molecular mimicry illustrates the degree of complexity inherent in the mechanisms by which microorganisms interact with the host to cause a persistent inflammatory lesion in the synovium.

The complex interplay between pathogen and host, which can whimsically be termed 'the battle of the genomes', is particularly relevant to reactive arthritis. In this intriguing clinical syndrome, there is a clear association with specific pathogens…*sometimes*, a clear genetic predilection…*sometimes*, and complete resolution of the synovitis…*most of the time*. In well characterized cases, a lower extremity asymmetric synovitis, variably associated with enthesitis and sacroiliitis, typically follows a genitourinary or gastrointestinal infectious syndrome after 2–4 weeks. Yet only a minority of patients with this pattern of early synovitis have demonstrable organisms in their urogenital or gastrointestinal tract. Many are labeled as having undifferentiated arthritis. On the other hand, detailed studies of synovial samples from the NIH early synovitis cohort have demonstrated the presence of *Chlamydia trachomatis* (CT) DNA, RNA, and antigens, not only in the synovium of patients with 'typical' reactive arthritis, but also in a spectrum of other synovial tissues, including samples from patients with RF-positive RA, and even in apparently healthy individuals [37,38]. In this cohort, synovial cytokine expression profiles assessed using a nested reverse transcriptase polymerase chain reaction (RT PCR) technique [39] failed to confirm the comparatively high interleukin (IL)-4 levels in the synovium of reactive arthritis patients that were previously reported [40]. In agreement with the previous studies, they did indicate that the synovium of patients with early CT reactive arthritis, in contrast to that of undifferentiated arthritis patients with a similar clinical pattern but no synovial CT, exhibits high levels of both interferon (IFN)-γ and IL-10 [41,42]. Such a cytokine profile has been speculated to play a role in attenuating the expression of specific CT genes such as *MOMP*, while promoting the expression of other genes such as *hsp60* [43,44]. Ultimately, this may result in ineffective elimination of the pathogen.

Interest in a bacterial or viral etiology for RA continues to wax and wane. Particularly provocative have been recent studies indicating the presence of parvovirus B19 and Epstein-Barr virus (EBV) DNA, RNA, and antigens, specifically in the synovium of RA patients [45,46]. In the case of EBV, this was highly associated with DR4 encoding shared epitope alleles, suggesting an important immunogenetic link. As these studies were performed primarily on synovial samples from patients with long-standing disease, it would be quite instructive to verify the findings in heterogeneous early synovitis cohorts. It is possible that, rather than being specific etiologic agents, these viruses are involved in the persistence of the synovitis once it is established.

Autoantibodies

It has recently been recognized that, in addition to RF, a number of antigen–autoantibody systems are highly specific for RA, and may be of importance both pathogenetically and prognostically [47]. These systems include the antifilaggrin (AFA), antikeratin (AKA), antiperinuclear factor (APF) group, all of which appear to relate to the presence of citrulline residues in target antigens [48]. Anti-Sa antibodies, also highly specific for RA, identify an unknown 50 kDa antigen (called Sa) which is present in

the synovium, and may also be citrullinated [49]. Antibodies directed against the protease inhibitor calpastatin (Ra-1) have been shown to be common in RA sera [50], as have antibodies directed toward advanced-glycation-endproduct-modified immunoglobulin G (AGE-IgG) [51]. Ra-33 is directed towards a spliceosomal ribonucleoprotein, and is detectable in RA, systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD) patients [52]. Approximately 10–15% of RA patients demonstrate antibodies to native collagen II, although these antibodies are not specific to this arthropathy [53].

Several groups are currently evaluating the diagnostic and prognostic significance of these autoantibodies in cohorts of patients with early synovitis. The preliminary findings from our cohort confirm a strong association of antifilaggrin and anti-Sa antibodies with RF-positive polyarthritis, although we identified a number of patients with RF-negative synovitis, both poly and oligoarticular, who were also positive for these two antibodies. Moreover, it appears that anti-Sa antibodies may be associated with a subset of patients having more severe, erosive RA [54].

Genetics considerations

Studies evaluating genetic association with rheumatic diseases have generally been carried out in populations of patients with well established, well characterized clinical syndromes. In the case of RA, the association is based principally in the class II region of the major histocompatibility complex (MHC), a group of at least 50 genes on human chromosome 6 that encode cell-surface proteins and that are involved in the immune response to both self and nonself antigens. The genetic association has been best explained by the shared epitope (SE) hypothesis [55]. In this model, disease susceptibility and/or severity is based on the presence of a shared epitope, the QK(R)RAA amino acid residue sequence in the third hypervariable region of the DRβ1 molecule. The SE sequence is present in a number of DRB1 alleles, all of which have been individually and collectively associated with typical RF-positive RA. Furthermore, there appears to be an allele dosage effect, particularly in respect to disease severity [56]. We have found that the SE alleles, particularly DRB1*0401, are clearly over-represented in patients with early RF-positive polyarthritis compared to both other patients with early synovitis and normal controls [3]. Moreover, we detect a high degree of association between SE alleles and the presence of anti-Sa and antifilaggrin antibodies [54]. Interestingly, we were able to show an association between SE and the presence of early erosions in patients with RF-negative, but not RF-positive polyarthritis. Similar data have been generated from the Norfolk Arthritis Registry (Silman A, personal communication).

Based on elegant transgenic animal models [57], an alternative hypothesis has been proposed to explain the MHC class II RA association [58]. This hypothesis suggests that RA disease susceptibility actually relates to DQ locus alleles, and that this susceptibility is modified by the absence of protective (non-SE) DRB1 alleles. The model, which is harmonious with models of genetic susceptibility to type I diabetes, has recently been tested in two European RA populations and found to be a good fit with the epidemiologic data [59], but was not confirmed in another European study [60]. Analysis of the data from our early synovitis cohort supports this model, although issues of linkage dysequilibrium continue to be problematic in these analyses. These issues have been raised in the context of several other MHC associations, including those relating to the tumor necrosis factor (TNF)-α gene.

There is a high degree of association between specific subtypes of HLA-B27 and the heterogeneous clinical spectrum of the 'spondylarthropathies'. It is not yet clear how disorders such as ankylosing spondylitis, reactive arthritis, and psoriatic arthritis are related pathogenetically, and what role B27 plays in these mechanisms. The association with axial manifestations such as sacroiliitis and spondylitis is particularly strong in all of these conditions. Our own data indicate that B27 is increased in the entire spectrum of early synovitis, including up to 20% of patients with RF-positive polyarthritis, a finding that has been previously reported in a Finnish RA cohort [61,62]. Moreover, we identified a significant association between B27 and SE alleles in the patients but not in a control population. These observations point to complex genetic interactions potentially involving extended 'arthritogenic' haplotypes, rather than associations of individual MHC alleles with specific forms of arthritis. The complexity of the genetic associations has been recently pointed out in experimental arthritis models where disease susceptibility, severity, and chronicity were each shown to be determined by entirely different regions in the genome [63,64].

Towards a mechanistically based prognostic model

As data from longitudinal studies of early synovitis cohorts are gathered, the relative importance of candidate prognostic variables is being clarified. The initial clinical patterns, autoantibody profiles, synovial pathologic features, cytokine profiles, and gene polymorphisms, among many other variables, represent variables that are being tested in robust multivariate models. In addition, the underlying mechanisms which potentially link these diverse variables are being explored, both in humans and in animal models. Ultimately, both the biological and statistical models aim to define homogeneous patient subsets to which targeted therapeutic paradigms can be applied. The definition of meaningful outcomes continues to be challenging, and recently there has been a shift towards using ambitious outcome measures such as the achievement of complete remission, the prevention rather than retardation of erosive damage, and the maintenance of normal function.

Currently, there is general agreement that the majority of patients who present with RF-positive symmetrical polyarthritis will probably go on to have persistent, erosive synovitis associated with a variable degree of disability. These patients are being targeted for early aggressive therapies. On the other hand, there is less certainty about the prognosis of RF-negative polyarthritis. At present it is not known whether there are common risk factors for bone erosion that link RF-positive RA, psoriatic arthritis, and subsets of RF-negative polyarthritis. On the basis of our own data, and data from other early synovitis cohorts, it can be proposed that in patients with early RF-negative polyarthritis, the presence of an RA-associated autoantibody such as anti-Sa, antifilaggrin, or anticitrulline, and/or the presence of one or more SE alleles, is an important indicator of erosive potential and an unfavorable prognosis. These variables can be used to allocate subsets of RF-negative polyarthritis patients to the same aggressive therapeutic strategies proposed for RF-positive patients.

Patients who present with oligoarthritis, in general, have the highest rates of complete resolution of synovitis within the first months after symptom onset, irrespective of whether they are labeled as having reactive arthritis or undifferentiated arthritis. There has been some suggestion that the presence of HLA-B27 in this group of patients is associated with more persistent synovitis, although the risk factors for erosive disease remain entirely unclear. It is possible that the presence of bacterial antigens or bacterial DNA transcripts in the synovium is a persistence factor. If indeed this is the case, this group of patients is the best suited for early synovial biopsy and a broad-based search for microbial antigens and transcripts in the synovium [65,66]. Despite the fact that most antibiotic trials of chronic reactive arthritis have been disappointing so far, there are little data available regarding how the effects of antimicrobial therapy may relate to the presence of bacterial antigens and transcripts in the synovium.

Summary

There is an increasing recognition that patients with synovitis of recent onset have divergent pathogenic mechanisms underlying what appear to be relatively similar clinical phenotypes. There is also a recognition that there are major differences in the outcome of early synovitis. The challenge facing investigators in this area is clarifying how these mechanisms determine outcome and, in turn, which mechanisms are the most appropriate therapeutic targets.

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Author address: Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA

Correspondence: Hani El-Gabalawy, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA.
E-mail: elgabala@exchange.nih.gov