Analyzing Synovial Tissue Samples. What Can We Learn About Early Rheumatoid Arthritis, the Heterogeneity of the Disease, and the Effects of Treatment?

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ABSTRACT. The synovium is the key target of the disease process in rheumatoid arthritis (RA). Examination of synovial tissue samples may provide insight into the events that take place in different phases of the disease and may help to decipher the mechanism of action of antirheumatic treatment. This review describes the features of synovitis in early RA, which clearly represent chronic inflammation. There is marked interindividual variability, suggesting that RA consists of different pathogenetic subsets. Evaluation of serial synovial tissue samples has shown that effective treatment is associated with a reduction in synovial macrophages, independent of the specific mechanism of action of the compound. This suggests that these are key effector cells in the pathogenesis. In addition, it provides a biomarker that can be used in clinical trials. (J Rheumatol 2005;32:25-26)

Key Indexing Terms:
SYNOVIAL TISSUE
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Rheumatoid arthritis (RA) is considered primarily a disease of the joints, although a variety of extraarticular manifestations may occur. As RA first and foremost involves the synovium, it can be anticipated that examination of synovial tissue samples may provide insight into the pathogenesis of the disease and the mechanism of action of treatment. Developments in synovial biopsy techniques, especially arthroscopy, have resulted in easier access to human synovial tissue. This has provided new opportunities for those engaged in arthritis research. Synovial tissue can now be selected from many sites within large and small joints, even in the earliest phases of disease, enhancing studies of pathogenesis, differential diagnosis, prognosis, and response to treatment. This review will address some of the lessons that have been learned from the systematic examination of synovial tissue.

In our center we have performed about 2000 rheumatological arthroscopy procedures in various studies[1]. The procedure is performed under local anesthesia and is generally well tolerated. Complications like bleeding and infection occurred in less than 0.3%. The setup requires the appropriate equipment, well trained arthroscopists, nurses and technicians, as well as standardized operation procedures.

Synovial tissue analysis has been used to describe the features of synovial inflammation in the earliest stages of the disease, as defined by clinical signs and symptoms. Systematic comparison of the pathological changes in synovial tissue from RA patients with so-called early RA (< 1 year duration) and patients with longstanding disease (> 5 years duration), who were matched for disease activity and medication, revealed that infiltration by the major cell types is not dependent on disease duration[2]. These observations are consistent with other studies[3,4]. Similarly, the expression of cytokines[2,4-6a], chemokines[7], matrix metalloproteinases[7], and adhesion molecules[8] is generally similar when synovial tissue from patients with early RA is compared to that from patients with longstanding disease. Similar results were obtained when only patients with a disease duration of < 3 months were studied[2].

The observation that what clinicians define as early RA actually represents chronic synovial inflammation might be explained by the assumption that there is a preclinical phase characterized by asymptomatic synovial inflammation. This could also explain the fact that erosive lesions can be found early in the course of RA, sometimes even at the time of initial diagnosis[9]. Consistent with this hypothesis, synovial inflammation has been described in clinically uninvolved joints of RA patients, as a model of pre-arthritis[10-13]. Of importance, recent studies have shown that circulating autoantibodies, like rheumatoid factor and anti-cyclic citrullinated peptide antibodies, may be present in individuals several years before the clinical signs and symptoms of RA become manifest[14,15]. Together, these studies suggest that antirheumatic treatment should be initiated early after the development of clinical signs of inflammation, as the disease is already in a chronic stage when a patient notes pain and swelling.

Synovial tissue analysis has also shown marked variation between different individuals in all phases of RA[16-18]. It has been suggested that RA patients display reproducible pat-

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terns in the organization and activity of synovial infiltrates, which are associated with the level of cytokine expression in the tissue[19]. Recent work using complementary DNA microarray analysis to profile gene expression in rheumatoid synovial tissue also showed considerable variability, resulting in the identification of molecularly distinct subsets of RA tissues[20]. Thus, these studies using different methodologies have consistently indicated that RA may comprise different pathogenetic mechanisms leading to a common clinical syndrome. Conceivably, more insight into these distinct subsets may help to define homogeneous groups for clinical studies and evaluation of targeted therapies.

In addition to the use of synovial biopsies for pathogenetic studies, serial synovial biopsy has been used to evaluate the effects of novel treatments[21]. First, this approach may obviously help to decipher the mechanism of action of a specific therapy at the site of inflammation. Second, measurement of biomarkers in the synovium could be used as a screening method to test new compounds requiring relatively small numbers of subjects. It can be expected that in the future, clinical investigations will consist of small trials with a high density of data, including biomarkers[22]. Recently, we found that the number of synovial macrophages is the most sensitive immunohistologic variable to change after effective treatment of RA, and may be used as a biomarker when novel therapeutic agents for RA are screened for potential efficacy[23]. Other more sophisticated biomarkers, including gene-expression profiles, are likely to be developed and validated in the near future.

In conclusion, synovial biopsy and systematic tissue analysis can provide valuable insights into the pathophysiologic mechanisms associated with the pathogenesis of RA and will play an increasingly important role in future clinical trials.

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