Sonography and subclinical synovitis

B Bresnihan, D Kane

Evaluating the sound of silence

The approach to the treatment of rheumatoid arthritis (RA) has changed substantially in recent years.¹ Firstly, it is now common practice to introduce conventional disease modifying antirheumatic drugs (DMARDs) such as methotrexate, and even targeted biological therapies, within months of the onset of symptoms.² One reason for this change is the growing appreciation that irreversible structural damage can occur very early in the course of inflammatory arthritis.³ Secondly, the establishment of dedicated early arthritis clinics facilitates early referral of patients with recent onset inflammatory arthritis for specialist evaluation and management.⁴ Thirdly, rheumatologists now have access to targeted therapies that greatly reduce the rate of progressive joint damage.⁵⁻⁷ Finally, it has been established that DMARDs reduces the rate of progressive joint damage most effectively when introduced within 6 months of symptom onset.⁸ In this context, the achievement of a sustained clinical remission in RA, the complete and permanent resolution of synovial inflammation, could become a realistic therapeutic goal. The same should be true of other inflammatory arthropathies.

CLINICAL CRITERIA AND SYNOVITIS

Ultrasonography demonstrates subclinical synovitis

The advances in rheumatology practice have depended on carefully validated measures of the clinical course and outcome. Rheumatologists employ clinical criteria that include quantifying the number of inflamed joints to define diagnostic categories,⁹ disease activity,¹⁰ response to treatment,¹¹ and remission.¹² In addition, it has been proposed that distinctive clinical patterns of arthritis, including monarthritis, oligoarthritis, and polyarthritis, may have important diagnostic and outcome implications.¹³ A study using ultrasound (US) to detect synovitis, published in this issue of the *Annals*, highlights the relative insensitivity of routine clinical examination in identifying inflamed joints, and suggests that subclinical synovitis may be common.¹⁴ Eighty patients with

oligoarthritis (≤ 5 clinically affected joints) for less than 1 year were studied. Sonographic synovitis was defined as an abnormally hypoechoic joint space reflecting synovial hypertrophy. Synovial fluid was demonstrated by the presence of an anechoic space within the joint which was compressible by the transducer. The presence of tenosynovitis and bone erosions was also documented. In total, 1470 joints were evaluated: 44% were symptomatic and 56% were asymptomatic. Thirteen per cent (107/826) of the clinically unaffected joints had evidence of sonographic synovitis. Eighty five (79%) of the asymptomatic joints with sonographic synovitis were metatarsophalangeal joints, 16% were metacarpophalangeal joints, and 5% were knee joints. Twenty six patients had a monarthritis based on clinical examination. Thirty five per cent of these had sonographic synovitis in more than one joint, and 23% had sonographic polyarthritis (≥ 6 affected joints). It is not clear if any of the patients with subclinical sonographic synovitis had evidence of associated bone erosion.

The development of high frequency, high resolution, real time musculoskeletal US, and of magnetic resonance imaging (MRI) has revolutionised imaging of the rheumatic diseases.^{15, 16} High resolution US readily demonstrates soft tissue inflammation such as joint and bursal effusion, synovial and enthesal thickening, and oedema. Sonographic synovitis correlates with MRI detection of synovitis,¹⁷ and with macroscopic synovial inflammation visualised at arthroscopy.¹⁸ The application of power Doppler technology now allows microvascular changes in soft tissue inflammation to be detected with equal sensitivity to MRI.¹⁹ Studies show that US is better than clinical examination in detecting soft tissue inflammation and effusion, even in large joints that are easily examined,^{20, 21} and in detecting enthesitis in patients with spondyloarthropathy.²² There is also evidence that MRI measurement of synovial inflammation in RA is better than clinical examination in predicting radiological outcome.²³

As musculoskeletal US becomes of increasing relevance to rheumatologists, it will be more widely applied in daily clinical practice. In the study reported by Wakefield *et al*, an average of 35 minutes was required to systematically scan each patient.¹⁴ Clinical rheumatologists may reasonably argue that this is impractical. However, in a previous study that employed a more targeted approach, US detected extensive subclinical synovitis that led to altered management in 12% of patients.²⁴ The enhanced sensitivity of US will probably lead to a re-adjustment of the "synovitis thermostat", with more patients classified as polyarthritis, and fewer as remission. The concept of remission in inflammatory arthritis will be re-examined. In rheumatic diseases such as osteoarthritis, which was previously thought to manifest little or no synovitis, US provided evidence of a significant inflammatory component.²⁵ In polymyalgia rheumatica, US demonstrated shoulder or hip synovitis in two thirds of patients, altering our understanding of a disease that was once believed to be non-articular.²⁶ The excellent reproducibility of US in detecting small joint synovitis²⁷ suggests that it may have advantages over clinical examination in assessing disease activity in RA, possibly leading to the inclusion of US as an outcome measure in clinical trials.

"Ultrasound challenges current classifications of polyarthritis, oligoarthritis, and remission"

Immunohistology confirms subclinical synovitis

Clinically undetectable synovial inflammation has also been highlighted in immunohistological studies. Thus, in a study of patients with established RA without knee joint involvement, synovial tissue from the clinically unaffected knee joints demonstrated lining layer hyperplasia and mononuclear cell infiltration in 69% and 31%, respectively, compared with 13% and 0% of control synovial tissue.²⁸ In another study of patients with established RA, synovial tissue was obtained from paired knee joints, one of which was clinically unaffected and the other overtly inflamed.²⁹ Histological features of inflammation were present in all of the clinically unaffected joints, characterised particularly by macrophage infiltration and by the expression of macrophage derived cytokines. Finally, in a study of early arthritis (symptoms for <1 year), synovial tissue samples from 55% of clinically unaffected knee joints demonstrated histological

inflammation, including lining layer hyperplasia, increased vascularity, and mononuclear cell infiltration.³⁰ In this study the diagnostic categories that demonstrated subclinical synovitis included RA and undifferentiated arthritis. In contrast, the asymptomatic knee joints of patients with reactive arthritis were histologically normal.

CONCLUSION

The observation that subclinical synovitis may be relatively common in both early and established inflammatory arthritis challenges current classifications of polyarthritis, oligoarthritis, and remission, as well as disease activity, and outcomes. However, it is too soon to conclude that widely accepted clinical categories should be reclassified, or that validated criteria should be redefined. It is not yet clear, for example, whether subclinical synovitis is associated with progressive joint damage and functional impairment. Longitudinal studies will be required to determine if the presence of subclinical polyarthritis will impact on early diagnosis and long term outcomes. Moreover, it is not known if the pathophysiological mechanisms that are activated in asymptomatic joints differ from those in overtly inflamed joints. Possibly, anti-inflammatory pathways predominate over proinflammatory pathways in the asymptomatic joints. This intriguing possibility supports the suggestion that joints with subclinical synovitis should be a target for further mechanistic studies, which might identify regulatory pathways with important therapeutic implications.

Ann Rheum Dis 2004;**63**:333–334.
doi: 10.1136/ard.2003.015982

Authors' affiliations

B Bresnihan, Department of Rheumatology, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland

D Kane, Department of Rheumatology, Cookson Building, The Medical School, University of Newcastle, Framlington Place, Newcastle upon Tyne NE2 4HH, UK

Correspondence to: Professor B Bresnihan;
b.bresnihan@svpc.ie

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