Editorial

Overlap Syndromes: Exploring the Genetic Underpinnings

In this issue of *The Journal*, Mohammed, *et al*[1] describe a group of patients with erosive arthritis who have features of Sjogren's syndrome (SS) sufficient to meet American-European consensus criteria[2]. The same patients also meet 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis (RA)[3]. The initial reaction to this description might be to dismiss the importance of the relationship because the patients with arthritis can be labelled as RA with Secondary SS. But what role do classification criteria play?

Because of the lack of a single gold standard in most rheumatic diseases, including SS, development of criteria for diagnosis or classification has been of continuing interest to rheumatologists. The main purpose of classification criteria is to standardize clinical definitions for use in research studies[4]. Standardized definitions are needed to allow comparison of studies from different centers. Included in classification criteria will be findings that distinguish a given disease from another similar illness. But this requires selection of criteria with higher specificity, and lower sensitivity. For this reason, classification criteria differ from diagnostic criteria.

Classification criteria are established to clearly define groups. Diagnostic criteria are meant for application in an individual patient. The individual may have a given disease, even if he does not meet the classification criteria for the disease.

The European-American consensus criteria were meant for the classification of SS. They were not established for the purpose of diagnosis, even though many investigators use them this way. To be sure, consensus criteria work well for the establishment of diagnosis, but there may well be cases that satisfy the clinician without meeting criteria. We must be careful not to be blinded by the use of classification criteria for diagnosis, as this can prevent us from studying the exceptions that shed light on disease understanding.

Mohammed, *et al* further our insight into the role that immune response genes and autoantibody profile play in disease expression. In 2008, Iwamoto, *et al* opened this discussion in *The Journal* by describing a group of patients with SS and non-erosive arthritis who also had anticyclic citrullinated peptide antibodies (anti-CCP)[5]. The cohort they presented had nonerosive arthritis, but the presence of anti-CCP was seen more prominently in these patients than in the remaining SS patients without arthritis.

Mohammed, *et al* have moved this perspective along, demonstrating that the common epitope associates with expression of anti-CCP antibodies and erosive articular inflammation, that DRB1*0301 associates with production of anti-Ro antibodies and development of SS, and that both these processes can occur in the same patient. Further, there was some modification in the patients with arthritis that made them somewhat different from simple rheumatoids. The arthritis group had no deformities, and a smaller percentage had erosions. They reported rash with the same frequency as the patients with SS, as well as peripheral sensory neuropathy and Raynaud's phenomenon.

Is this a perspective unique to SS? No it is not. Recent studies have shown that the shared epitope containing HLA-DRB1 alleles is associated with the presence of anti-CCP antibodies in RA, and not with anti-CCP negative RA[6]. Further, only the progression of early arthritis into CCP positive erosive arthritis can be predicted by the presence of the shared epitope[7]. With univariate analysis, the shared epitope does not seem to correlate with the development of anti-CCP negative RA, even if rheumatoid factor is present[8].

What will we see if the shared epitope, with the production of anti-CCP, is expressed in other rheumatic diseases? In patients with systemic lupus erythematosus, HLA-DRB1 genes with the shared epitope result in anti-CCP leading to erosions[9]. Such SLE patients have overlap features of RA ("rhupus"), satisfying ACR classification criteria for both SLE and RA. Anti-CCP antibodies exert the same disease

Correction

Bookman AAM. Overlap syndromes: Exploring the genetic underpinnings [editorial]. J Rheumatol 2009;36:1856-7. References 6 to 11 should appear as follows. This correction applies to the printed edition only. We regret the error.

6. Huizinga TW, Amos CI, van der Helm-van Mil AH, Chen W, van Gaalen FA, Jawaheer D, et al. Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA–DRB1 shared epitope for antibodies to citrullinated proteins. Arthritis Rheum 2005;52:3433–8.
7. El-Gabalawy HS, Goldbach-Mansky R, Smith II D, Arayssi T, Bale S, Gulko P. Association of HLA alleles and clinical features in patients with synovitis of recent onset. Arthritis Rheum 1999;42:1696-705.
8. van der Helm-van Mil AHM, Verpoort KN, Breedveld FC, Huizinga TWJ, Toes REM, and de Vries RRP. The HLA–DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. Arthritis Rheum 2006;54:1117–21.
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10. Korendowych E, Owen P, Ravindran J, Carmichael C, McHugh N. The clinical and genetic associations of anti-cyclic citrullinated peptide antibodies in psoriatic arthritis. Rheumatology 2005;44:1056–60.
11. Salliot C, Gottenberg J, Bengoufa D, Desmoulins F, Miceli-Richard C, Mariette X. Anticentromere antibodies identify patients with Sjögren's syndrome and autoimmune overlap syndrome. J Rheumatol 2007;34:2253-8.