Coexistent rheumatoid arthritis and systemic lupus erythematosus: clinical, serological, and phenotypic features

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Abstract

The clinical and serological features and HLA phenotypes are reported for 11 patients with coexistent features of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). All patients had a symmetrical small joint polyarthritis and features of SLE such as rash, photosensitivity, oral ulceration, serositis, cytopenia, and biopsy proved lupus nephritis. Eight had hypocomplementaemia. Autoantibodies were characteristic of the two diseases: all patients had rheumatoid factor and antibodies to double stranded DNA, eight (73%) had antibodies to collagen, and five (46%) had antibodies to Ro (SS-A). There was also an overlap of HLA phenotypes. Six patients were DR4 and seven were DR2 or DR3 positive, and of the five patients who were DR4 negative, four shared class I alleles often associated with DR4. If RA and SLE share a common autoimmune dysfunction, those patients who have the two diseases do so because they have genetic determinants of both.

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are considered to be separate diseases with defined criteria for diagnosis.^{1,2} Some patients, however, show features of both diseases.^{3,4} The course of RA may be complicated when drugs such as D-penicillamine induce autoantibodies associated with SLE.⁵ Alternatively, the two diseases may coexist by chance as RA affects about 1% and SLE 0.1% of the white population, or coexistent RA and SLE may be a separate autoimmune disease. In this report we describe the clinical, serological, and HLA findings in 11 patients with overlapping features of RA and SLE.

Patients and methods

PATIENTS

Eleven patients were identified as having overlapping features of RA and SLE (table 1). All were women, 10 were white and one (patient 4) was Chinese. All fulfilled the American Rheumatism Association (ARA) revised criteria for RA.¹ Ten fulfilled the 1982 revised ARA criteria for SLE² and the remaining patient (patient 11) fulfilled three criteria for SLE. The mean duration of symptoms was 12.7 years (range 3.5-28 years).

Each patient was assessed by a rheumatologist (CB) and radiographs of the hands and feet were graded according to the severity of loss of cartilage and the degree of erosive change.

Following informed consent, blood was taken for tests for autoantibodies and for determination of HLA phenotypes. The highest titres of rheumatoid factor and antibodies to double stranded DNA (dsDNA) during the course of illness are reported.

ANTINUCLEAR ANTIBODIES

These were detected by immunofluorescence using HEp-2 cells as the substrate and the serum sample diluted 1:40. Positive serum samples were titrated in quadrupling dilutions to 1:640.

ANTIBODIES TO EXTRACTABLE NUCLEAR ANTIGENS

Serum samples were tested for precipitating antibodies by countercurrent immunoelectrophoresis using a saline extract of lyophilised rabbit thymus (Pel Freez Biologicals, Rogers, AR) (protein concentration 30 mg/ml) and a freeze dried extract of human spleen; the specificity of the precipitins was established using control serum samples calibrated against reference serum samples obtained from the Centers for Disease Control (Atlanta, GA, USA).

ANTIBODIES TO COLLAGEN

Antibodies to native and denatured type II human collagen were measured in a solid phase radioimmunoassay.⁶ Serum samples were tested at 1:100 dilution, in duplicate, in the presence and absence of antigen. Bound antibody was detected using protein A from *Staphylococcus aureus* labelled with iodine-125. Counts bound in the absence of antigen were subtracted from those obtained with antigen, and the results were expressed as counts per minute of radioactivity. Levels of collagen antibodies in the patients were compared with those in three contrasting groups, comprising 20 healthy subjects, 19 patients with unequivocal SLE, and 105 patients with RA studied previously.⁶ As levels for collagen antibodies were not normally distributed, these were compared using the two tailed non-parametric Mann-Whitney U test. *p* Values ≤ 0.05 were regarded as significant.

HLA TYPING

Typing for HLA-A, B, and DR antigens was performed by standard microlymphocytotoxicity procedures.⁶

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Table 3 HLA phenotypes of 11 patients with overlapping features of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). For each patient the diagnosis which best fits the HLA phenotype is shown

Patient No	HLA phenotype*			HLA disease profile
	A	B	DR	
1	1, 2	8, 44	3, 4	RA and SLE
2	2, 24	7, 62	2, 4	RA and SLE
4	ND	ND	4, 5	RA
6	2, 28	63	4	RA
8	2	35, 37	1, 4	RA
9	2, 28	14, 44	4, 5	RA
3	1, 2	8, 44	2, 3	SLE
5	1, 2	8, 44	1, 3	SLE
7	2, 28	7, 8	2, 3	SLE
10	11, 28	8, 44	2, 3	SLE
11	1, 2	8, 60	3, 10	SLE

*ND=Not done.

cartilage loss as four of five patients (Nos 1, 2, 3, 10) with severe deforming non-erosive arthritis had high levels of antibodies to denatured collagen, whereas those patients with erosive disease and less cartilage loss (Nos 4, 5, 8, 9) had low levels. Patient 7, who had erosive disease and marked cartilage loss of the small joints of the hands, also had high levels of antibodies to denatured collagen. In three patients high levels of antibodies to native and denatured collagen were associated with low levels of rheumatoid factor.

HLA TYPING

HLA typing identified three genetic groups among the 11 patients: those who were RA-like, characterised by DR4 (four patients); those who were SLE-like, characterised by DR2 or DR3 (five patients); and those who had features of both RA and SLE, characterised by a combination of DR2 or DR3 and DR4 (two patients). Table 3, gives the phenotypes of the patients. Of the four RA-like patients, three had erosive changes, two of which were typical of RA and one (patient 4) atypical. Of the five SLE-like patients, three had mild erosive changes, and four (three of whom were DR2/DR3) had antibodies to Ro(SS-A). The two patients with phenotypic features of both SLE and RA had severe deforming arthritis without erosive change. Three other patients had similar arthritis; one was DR4 and the other two were DR2/DR3 positive.

Examination of the class I alleles in the five patients who were DR2 or DR3 positive revealed interesting associations in two patients (Nos 3, 10). If the haplotype B8; DR3 is assumed to be present in these patients, the other haplotype is B44; DR2. These B and DR alleles are in negative linkage disequilibrium in normal subjects and include a class I antigen, B44, which is usually associated with DR4 and occurs frequently in patients with RA. Two of the three remaining patients in this group also share class I alleles which are often seen in DR4 positive patients with RA.

Discussion

Rheumatoid arthritis and SLE are considered to be separate autoimmune diseases with defined

clinical features, serological markers, and HLA phenotypes. In our group of 11 patients, overlapping features exist such that the ARA criteria for diagnosis of both RA and SLE are fulfilled. These patients have autoantibodies characteristic of each disease and prominent in this profile are high levels of antibodies to collagen and a high frequency of antibodies to Ro(SS-A). The patients also share the HLA phenotypes of the two diseases.

One of the major clinical features differentiating RA and SLE is the nature of the polyarthritis. In the two diseases it is characterised by symmetrical involvement of the small and medium joints. Typically in RA there is a progressive deforming arthritis associated with erosive radiological changes, whereas in SLE the arthritis is usually non-erosive and non-deforming. Up to 10% of patients with SLE develop a deforming arthritis,⁷ and in these patients there is a higher frequency of rheumatoid factor than in those with non-deforming arthritis.⁸ The expression of arthritis in our patients varied: four had typical erosive changes, with severe deformities in one patient, five had Jaccoud's-like arthritis, and two had non-deforming arthritis with atypical erosive change.

The profile of autoantibodies was consistent with overlapping RA and SLE: all patients were rheumatoid factor positive and all had high titres of antinuclear antibodies, mainly specific to dsDNA. In addition, these patients had significantly higher levels of autoantibodies to collagen than patients with RA alone. Type II collagen, against which the antibodies are directed, is primarily found in hyaline cartilage and this may explain why in these patients there is cartilage damage rather than bone erosion. Autoantibodies to Ro(SS-A) were present in 46% of the patients. Antibodies to Ro(SS-A) are associated with SLE, being present in about 70% of patients with subacute cutaneous lupus. However, they occur rarely in patients with RA,⁹ although they have been previously reported in overlapping RA and SLE.¹⁰

Genetic predisposition to RA and SLE has been linked to the major histocompatibility complex. For SLE, the alleles most consistently reported include HLA-B8, DR2, DR3, and DQw1, and the null alleles of HLA linked components of complement.^{11 12} How the class II genes confer susceptibility to disease is not known, although peptide presentation to the responding T cell may be involved and these peptides may be derived from exogenous antigen (possibly viral) or autoantigen. It is of interest that a strong association between antibodies to Ro(SS-A) and DR2/DR3 heterozygosity has been observed.¹² This suggests that SLE is a clinical syndrome in which a particular class II molecule, which may be combinatorial, leads to the aberrant production of autoantibodies and the clinical expression of the disease is controlled by other genetic determinants.

The primary HLA association in RA appears to be with DR4 or extended haplotypes of DR4.¹¹ These HLA associations have also been linked to clinical features of the disease.¹³ The reported associations between autoantibodies to

type II collagen and DR4^{6 14} may be analogous to the association of antibodies to Ro(SS-A) with DR2/DR3 heterozygosity.

A striking feature of the 11 patients with coexistent RA and SLE is that they share the genetic features of the two diseases. Of the 10 patients for whom tissue typing was available, five (50%) were DR4 and seven (70%) were DR2 or DR3 positive. Four of the five patients who were DR4 negative shared the B locus antigens B44, B60, and B62 which occur most often in haplotypes with DR4. Thus, in these patients the presence of the class I antigens usually found associated with DR4 in combination with the class II antigens DR2 and DR3 which are found more often in patients with SLE, suggests firstly that the group has in common genetic as well as clinical features of the two diseases, and secondly that HLA genes and class II antigens are involved in the disease process. If RA and SLE share a common autoimmune dysfunction, those patients who have the two diseases do so because they have genetic determinants of both diseases.

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- 1 Arnett F C. Revised criteria for the classification of rheumatoid arthritis. *Bull Rheum Dis* 1989; **38**: 1-6.
- 2 Tan E M, Cohen A S, Fries J F, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271-7.
- 3 Panush R S, Edwards L, Longley S, Webster E. "Rhupus" syndrome. *Arch Intern Med* 1988; **148**: 1633-6.
- 4 Cohen M G, Webb J. Concurrence of rheumatoid arthritis and systemic lupus erythematosus: report of 11 cases. *Ann Rheum Dis* 1987; **46**: 853-8.
- 5 Chalmers A, Thompson D, Stein H E, Reid G, Patterson A C. Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. *Ann Intern Med* 1982; **97**: 659-63.
- 6 Rowley M J, Tait B, Doran T, Emery P, Mackay I R. Associations between the HLA and antibodies to collagen in rheumatoid arthritis. *Ann Rheum Dis* 1990; **49**: 578-81.
- 7 Bywaters E G L. Jaccoud's syndrome. A sequel to the joint involvement of systemic lupus erythematosus. *Clin Rheum Dis* 1975; **1**: 125-48.
- 8 Alarcon-Segovia D, Abud-Mendoza C, Diaz-Jouanen E, Inglesias A, de los Reyes V, Hernandez-Ortiz, J. Deforming arthropathy of the hands in systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 65-9.
- 9 Bernstein R M, Bunn C C, Hughes G R V, Francouer A M, Mathews M B. Cellular protein and RNA antigens in autoimmune disease. *Mol Biol Med* 1984; **2**: 105-20.
- 10 Menard H A, Boire G, Lopez-Longo F J, Masson C, Lapointe S. Rupus: an RA subset predicted and defined by the presence of anti-native Ro antibody. *Arthritis Rheum* 1989; **32** (suppl):S16.
- 11 Dawkins R L, Christiansen F T, Kay P H, *et al*. Disease associations with complotypes, supratypes, and haplotypes. *Immunol Rev* 1983; **70**: 5-22.
- 12 Hamilton R G, Harley J B, Bias W B, *et al*. Two Ro (SS-A) autoantibody responses in systemic lupus erythematosus. *Arthritis Rheum* 1988; **31**: 496-505.
- 13 Jaraquemada D, Ollier W, Awad J, *et al*. HLA and rheumatoid arthritis: a combined analysis of 440 British patients. *Ann Rheum Dis* 1986; **45**: 627-36.
- 14 Banerjee S, Luthra H S, Moore S B, O'Fallon W M. Serum IgG anti-native type II collagen antibodies in rheumatoid arthritis: association with HLA DR4 and lack of clinical correlation. *Clin Exp Rheumatol* 1988; **6**: 373-80.