

EROSIVE ARTHRITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS: ANALYSIS OF A DISTINCT CLINICAL AND SEROLOGICAL SUBSET

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SUMMARY

Erosive arthritis (EA) in systemic lupus erythematosus (SLE) can be debilitating and deforming with uncertain factors for risk, although antibodies to the A2 hnRNP core protein, known as anti-RA33, have been associated with EA. Two hundred patients under long-term follow-up for SLE were evaluated for EA and associated clinical and serological abnormalities. In addition, sera were tested in a masked fashion for anti-RA33 antibodies in a total of 60 patients: 10 with EA and 50 age-, sex- and ethnically matched controls. Ten of 200 (5%) patients with SLE, mainly non-white women, had EA. There were trends for increased renal involvement ($P = 0.06$), Sjögren's syndrome ($P = 0.07$) and Raynaud's phenomenon ($P = 0.03$) in patients with EA compared to those without EA. Rheumatoid factor (RF) was increased in patients with EA ($P < 0.02$), as were antibodies to double-stranded DNA ($P < 0.05$), Sm ($P < 0.01$) and La/SS-B ($P < 0.001$). Anti-RA33 antibodies were present in 70% with EA compared to 28% without EA ($P < 0.05$). RF correlated with anti-RA33 antibodies in patients with EA, but not with the presence of anti-RA33 alone. Thus, anti-RA33 antibodies may identify those patients with SLE who are at risk for EA, and an association with RF suggests a common immune response or pathological mechanism in autoimmune erosive joint disease.

KEY WORDS: Systemic lupus erythematosus, Autoantibodies, Arthritis.

SYSTEMIC lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by a diversity of both clinical and immunological abnormalities. Prominent amongst the immunological abnormalities is the presence of autoantibodies to a somewhat restricted range of self-antigens [1]. There have been many attempts to link particular antibodies to clinical features or subsets of lupus [2-4]. Thus, it is accepted generally that patients with high anti-double-stranded (ds) DNA antibody levels are most likely to have renal disease, those with anti-Ro antibodies to have photosensitive skin rashes, subacute cutaneous lupus or the neonatal lupus syndrome, those with anti-U1snRNP to suffer frequently from myositis and Raynaud's phenomenon, and patients with anti-phospholipid antibodies to have arterial/venous thrombosis, recurrent miscarriages and livedo reticularis. In an earlier small study of 30 patients with lupus [5], we proposed that there might be a link between antibodies to the A2 hnRNP core protein, known as anti-RA33, and erosive joint disease in SLE.

Although joint pain and swelling are common features of SLE, erosive arthritis (EA) is reported generally in <5% of patients [2]. EA may be debilitating and deforming with uncertain factors for risk, although non-erosive arthritis in SLE has been associated with sicca syndrome [6] and a decreased frequency of concomitant renal disease [7]. Because anti-RA33 anti-

bodies may identify patients at risk for developing EA, the following study was undertaken to establish the frequency of anti-RA33 antibodies with EA in patients with SLE in a large group of patients, and the clinical and serological associations of the antibodies, if any.

PATIENTS AND METHODS

Patients

The clinical and laboratory data described are on the first 200 patients with SLE to be reviewed with a minimum follow-up of 2 yr or until death. Of these 200 patients, 24 have now died. Five additional patients, none of whom had EA, were followed for <1 yr and were not included in the study. A diagnosis of SLE was established in all patients by the revised ARA classification criteria [8]. None of the patients had drug-induced SLE. All patients with joint pains were X-rayed, and erosions were carefully sought. EA was defined by radiographic evidence of EA of the hands and/or feet on standard views.

Patients were classified into two groups: those with EA (Group 1; $n = 10$) and those without EA (Group 2; $n = 190$). Involvement of the central nervous system (CNS), heart, lungs, joints and kidneys, as defined by Morrow *et al.* [9], was recorded for the analysis, as well as secondary Sjögren's syndrome (SS) and Raynaud's phenomenon (RP). Renal involvement was defined as glomerulonephritis (GN) on biopsy or with diastolic blood pressure > 90 mmHg, oedema requiring diuretic therapy, proteinuria > 0.5 g/24 h, creatinine clearance < 60 ml/min, or raised serum creatinine level (> 124 $\mu\text{mol/l}$). In virtually all cases, however, renal biopsy evidence was obtained. SS was established by the criteria of Vitali *et al.* [10].

Antibodies to dsDNA were detected by ELISA

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(Cambridge Life Sciences). The presence of antibodies to Ro/SS-A, La/SS-B, Sm and RNP was established by ELISA (Shield Diagnostics). Rheumatoid factor (RF) was detected by the Rose-Waaler method. These serological tests were carried out in the same laboratory.

The medical literature from 1983 to the present was reviewed for SLE with EA and SLE with EA and GN.

RA33 antibody testing

Anti-RA33 antibody testing was performed using immunoblotting with soluble nuclear extracts from HeLa cells as previously described [11]. A total of 60 sera were tested in a masked fashion. Of these sera, 10 were from the patients with EA in addition to 50 sera from age-, sex- and ethnically matched patients selected from the 190 in Group 2.

Statistical analysis

Data were analysed by χ^2 test using Yates correction, except when $n < 10$, in which case Fisher's exact test was used. A P value of < 0.02 was considered statistically significant.

RESULTS

Erosive arthritis was present in 10 of 200 patients (5% of the total) and preceded or coincided with the diagnosis of SLE in 8/10. All patients with EA were women, and 50% were non-Caucasian (Table I). In comparison, patients without EA were mainly Caucasian women, with other ethnic groups comprising 26% of the study group. Table I compares the clinical features of patients without EA. As clinically suspected, there were trends for increased renal involvement ($P = 0.06$), SS ($P = 0.07$) and RP ($P = 0.03$) in patients with EA compared to those without EA. There was no significant increase in CNS disease or heart and lung involvement when comparing the two groups. The duration of disease did not appear to relate to the

TABLE I
Demographic and clinical characteristics of SLE patients with and without erosive arthritis (EA)*

Characteristic	SLE patients with EA $n = 10$ (%)	SLE patients without EA $n = 190$ (%)	P †
Demographics			
Female gender	10 (100)	179 (94)	> 0.5
Race			
Caucasian	5 (50)	140 (74)	< 0.5
Afro-Caribbean	3 (30)	26 (14)	
Asian	2 (20)	16 (8)	
Others	0	8 (4)	
Glomerulonephritis	6 (60)	52 (27)	0.06
Heart or lung involvement	4 (40)	98 (52)	> 0.5
CNS involvement	4 (40)	50 (26)	> 0.5
Sjögren's syndrome	4 (40)	27 (14)	0.07
Raynaud's phenomenon	6 (60)	44 (23)	0.03

*Values are the number (%). SLE, systemic lupus erythematosus; CNS, central nervous system.

† P value determined by χ^2 test using Yates correction.

development of SS or anti-RA33 antibodies in either patients with or without EA (data not shown).

In general, serological tests were significantly increased in patients with EA (Table II). Rheumatoid factor was more frequent in patients with EA ($P < 0.02$), as were antibodies to Sm ($P < 0.01$) and La/SS-B ($P < 0.001$). There was a trend for increased anti-dsDNA antibodies in patients with EA ($P < 0.05$). Antibodies to RNP were not significantly increased in a comparison of the two groups.

Seven of 10 patients (70%) with EA had anti-RA33 antibodies. Of the 50 patients without EA who were tested for anti-RA33 antibodies, 30 were Caucasian, 10 were Afro-Caribbean and 10 were Asian. Fourteen of these patients (28%) tested positive for anti-RA33. Thus, antibodies to RA33 were more frequent in patients with EA ($P < 0.05$). Serological tests were compared among all anti-RA33-positive patients for an association with EA (Table III). Rheumatoid factor alone was more frequent in those with anti-RA33 and EA ($P < 0.05$). Among these patients, five had antibodies to RA33 and were RF positive, two had antibodies to RA33 but no RF, and one was RF positive without antibodies to RA33. Thus, 80% of the EA patients had

TABLE II
Comparison of serological features in SLE patients with and without erosive arthritis (EA)*

Feature	SLE patients with EA $n = 10$ (%)	SLE patients without EA $n = 190$ (%)	P †
RF	6 (60)	39 (21)	< 0.02
Antibodies			
dsDNA	9 (90)	93 (49)	< 0.05
Sm	4 (40)	15 (8)	< 0.01
Ro/SS-A	5 (50)	66 (35)	0.5
La/SS-B	6 (60)	24 (13)	< 0.001
RNP	4 (40)	35 (18)	< 0.5
RA33	7 (70)	14 (28)‡	< 0.05

*Values are the number (%). SLE, systemic lupus erythematosus; RF, rheumatoid factor; dsDNA, double-stranded DNA.

† P value determined by χ^2 test using Yates correction.

‡Fifty sera tested.

TABLE III
Comparison of serological features among anti-RA33 + SLE patients with and without erosive arthritis (EA)*

Feature	Anti-RA33 + SLE patients with EA $n = 7$ (%)	Anti-RA33 + SLE patients without EA $n = 14$ (%)	P †
RF	5 (71)	2 (15)‡	< 0.02
Antibodies			
dsDNA	6 (86)	7 (50)	> 0.1
Sm	2 (29)	1 (7)	> 0.1
Ro/SS-A	2 (29)	8 (57)	> 0.1
La/SS-B	3 (43)	3 (21)	> 0.1
RNP	3 (43)	4 (29)	> 0.1

*Values are the number (%). SLE, systemic lupus erythematosus; RF, rheumatoid factor; dsDNA, double-stranded DNA.

† P value determined by Fisher's exact test.

‡Thirteen sera tested.

anti-RA33 and/or RF, compared to 44% of control patients without EA (anti-RA33 and RF, $n = 2$; anti-RA33, $n = 11$; RF, $n = 9$). Antibodies to dsDNA, Sm, La/SS-B and RNP appeared to be increased in the anti-RA33-positive patients with EA, but these did not reach statistical significance.

DISCUSSION

Arthralgia rather than arthritis occurs in the majority of patients with SLE. Joint deformities may resemble rheumatoid arthritis (RA) despite few erosions and dominant ligamentous laxity [2]. Erosive arthritis is unusual, estimated at <5% of patients [2]. Whereas non-erosive deforming arthritis has been associated with sicca syndrome and a decreased frequency of facial erythema and photosensitivity [6], risk factors remain uncertain for EA. Clinical impression suggests that concomitant EA and renal involvement is rare despite the considerable frequency of lupus nephritis. Indeed, the presence of serum RF has been implicated as 'protective' against nephritis, though unproven [12]. Furthermore, persistent rheumatoid-like arthritis rather than RF appears to be inversely correlated with renal abnormalities, based on clinical data or kidney biopsy [7].

As in most series, EA was unusual among our SLE population, being present in 5% of our patients and tending to occur in non-white women. Although the prevalence of GN in the total SLE population was relatively low (29%), perhaps a result of follow-up in a rheumatology clinic rather than a nephrology unit, kidney involvement appeared to be over-represented in the EA group compared to the non-EA group. Interestingly, there was a trend for increased SS among our patients with EA, an association which appears with variable frequency in the MRL/1 mouse model of SLE and may be due to local RF production or immune complex deposition [13].

Although this study was not designed to look at true polyclonal activation and epitope spreading, it is intriguing that our patients with EA appear to have had more widespread or severe disease than those without EA. The duration of disease, however, did not appear to relate to the development of SS or anti-RA33 antibodies in either patients with or without EA, and our data only give an approximate time when the joint disease became erosive. Therefore, the relative severity of disease in our patients with EA remains unclear.

With a prevalence similar to RA in the general population, it has been suggested that EA is not a feature of SLE, but concomitant RA [14]. Although the distinction between RA/SLE overlap and SLE with EA may be unclear in some cases, all patients with EA in the present series fulfilled at least four diagnostic criteria for SLE, 8/10 fulfilling ≥ 5 . Moreover, our patients with EA tested more frequently for circulating autoantibodies characteristic for SLE, in particular anti-dsDNA and anti-Sm, than did those without EA. While HLA-DR4 is significantly increased in patients with RA [15], this type was present in only one of our

patients with EA, while 23/174 (13%) patients tested without EA were DR4 positive. Indeed, the DR4 type may be decreased in patients with nephritis [16], an unusual feature in RA, but frequent in our patients with EA. Thus, it is unlikely that the patients with erosive joint disease had RA as well as SLE.

Initially, anti-RA33 antibodies were thought to be highly specific for RA, but have since been reported in 20–40% of patients with SLE [5, 17] and may identify the subset with EA. In the present series, 70% of all patients with EA and SLE had anti-RA33 antibodies compared to 28% of controls studied. In contrast, antibodies to RA33 have been identified in only 35% of patients with RA [17]. That 80% of our patients with EA had anti-RA33, RF, or both, compared to 44% of SLE patients without EA, suggests that anti-RA33 antibodies, like RF, are representative markers of erosive disease.

Antibodies to RA33 recognize a 33 kDa nuclear antigen that is present in the 40S hnRNP complex and is indistinguishable from the A2 hnRNP core protein [18]. Although the physiological role for RA33 is not fully known [17, 18], the hnRNP core proteins interact with heterogeneous nuclear RNA and constitute part of the spliceosome, a multimolecular structure which processes mRNA [19]. Antibodies to other spliceosomal proteins (Sm and RNP) target the small nuclear RNP complex (snRNP) and have been described in SLE, but not in RA. Anti-Sm and anti-RNP have been identified in association with anti-RA33 antibodies in a general population of patients with SLE [17], but there was no significant relationship in the present study of either anti-RA33-positive patients with EA or in the total anti-RA33-positive population (data not shown). However, since antibodies to the snRNPs as well as to the hnRNPs were much more frequent in SLE patients with EA compared to those without, it must be assumed that the autoimmune response to the spliceosome is related to erosive joint disease in SLE. The presence of RF, however, correlated with antibodies to RA33 in SLE patients with EA, but not with the presence of anti-RA33 alone, perhaps suggestive of a common pathomechanism in erosive joint disease.

In summary, anti-RA33 antibodies may define those patients with SLE, mainly non-white women, who are at risk for EA as well as renal disease. The presence of anti-RA33 antibodies appears to correlate with RF positivity in these patients, but not in a general population of SLE. Moreover, erosive joint disease in SLE, regardless of anti-RA33 positivity, may correlate with RF in association with particular autoantibodies. Perhaps future, prospective studies of patients with SLE may clarify the role of these autoantibodies in the immune response and pathogenesis of autoimmune erosive joint disease.

REFERENCES

1. Tan EM. Antinuclear antibodies: Diagnostic markers for autoimmune disease and probes for cell biology. *Adv Immunol* 1989;44:93–151.
2. Isenberg DA, Horsfall A. Systemic lupus eryth-

- ematosus—adult onset. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, eds. Oxford textbook of rheumatology, 2nd edn. Oxford: Oxford University Press, 1998:1145–80.
3. Vitali C, Bencivelli W, Isenberg DA *et al.* and the European Consensus Study Group for Disease Activity in SLE. Disease activity in systemic lupus erythematosus: Report of the Consensus Study Group of the European Workshop for Rheumatology Research. I. A descriptive analysis of 704 European lupus patients. *Clin Exp Rheumatol* 1992;10:527–39.
 4. Smolen JS, Morimoto C, Steinberg AD *et al.* Systemic lupus erythematosus: Delineation of subpopulations by clinical, serological, and T cell subset analysis. *Am J Med Sci* 1985;289:139–47.
 5. Isenberg DA, Steiner G, Smolen JS. Clinical utility and serological connections of anti-RA33 antibodies in systemic lupus erythematosus. *J Rheumatol* 1994;21:1260–3.
 6. Alarcon-Segovia D, Abud-Mendoza C, Diaz-Jouanen E, Iglesias A, De los Reyes V, Hernandez-Ortiz J. Deforming arthropathy of the hands in systemic lupus erythematosus. *J Rheumatol* 1988;15:65–9.
 7. Kaplan D, Ginzler EM, Feldman J. Arthritis and nephritis in patients with systemic lupus erythematosus. *J Rheumatol* 1991;18:223–9.
 8. Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
 9. Morrow WJW, Isenberg DA, Todd-Pokropek A, Parry HF, Snaith ML. Useful laboratory measurements in the management of systemic lupus erythematosus. *Q J Med* 1982;51:125–38.
 10. Vitali C, Bombardieri ST, Moutsopoulos HM *et al.* Preliminary criteria for the classification of Sjögren's syndrome: Results of a prospective concerted action supported by the European community. *Arthritis Rheum* 1993;36:340–7.
 11. Hassfeld W, Steiner G, Hartmuth K *et al.* Demonstration of a new antinuclear antibody (anti-RA33) that is highly specific for rheumatoid arthritis. *Arthritis Rheum* 1989;32:1515–20.
 12. Turner-Stokes L, Jones M, Addison I, Mansell M, Isenberg DA. Does rheumatoid factor protect lupus patients from the development of nephritis? *Ann Rheum Dis* 1989;48:14–6.
 13. Horsfall AC, Skarstein K, Jonsson R. Experimental models of Sjögren's syndrome. In: Isenberg DA, Horsfall AC, eds. Autoimmune diseases: focus on Sjögren's syndrome. Oxford: BIOS Scientific Publishers, 1994:67–88.
 14. Labowitz R, Schumacher HR. Articular manifestations of systemic lupus erythematosus. *Ann Intern Med* 1971;74:911–21.
 15. Karr RW, Rodey GE, Lee T, Schwarz BD. Association of HLA-DRw4 with rheumatoid arthritis in black and white patients. *Arthritis Rheum* 1980;23:1241–5.
 16. Fronek Z, Timmerman LA, Alper CA, Hahn BH, Kalunian KC, Peterlin BM *et al.* Major histocompatibility complex genes and susceptibility to systemic lupus erythematosus. *Arthritis Rheum* 1990;33:1542–53.
 17. Hassfeld W, Steiner G, Studnicka-Benke A *et al.* Autoimmune response to the spliceosome. *Arthritis Rheum* 1995;6:777–85.
 18. Steiner G, Hartmuth K, Skriner K *et al.* Purification and partial sequencing of the nuclear autoantigen RA33 shows that it is indistinguishable from the A2 protein of the heterogeneous nuclear ribonucleoprotein complex. *J Clin Invest* 1992;90:1061–6.
 19. Dreyfuss G, Matunis MS, Pinol-Roma S, Burd CH. hnRNP proteins and the biogenesis of mRNA. *Annu Rev Biochem* 1993;62:289–321.