Systemic Lupus Erythematosus Features in Rheumatoid Arthritis and Their Effect on Overall Mortality

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ABSTRACT. ***Objective.*** Features of systemic lupus erythematosus (SLE) are commonly observed in patients with rheumatoid arthritis (RA). However, their frequency and clinical significance are uncertain. We examined the frequency of SLE features in RA and their effect on overall mortality.

Methods. We assembled a population-based incidence cohort of subjects aged ≥ 18 years first diagnosed with RA [1987 American College of Rheumatology (ACR) criteria] between 1955 and 1995. Information regarding disease characteristics, therapy, comorbidities, and SLE features (1982 ACR criteria) were collected from the complete inpatient and outpatient medical records. Cox regression models were used to estimate the mortality risk associated with lupus features.

Results. The study population comprised 603 subjects with incident RA (mean age 58 yrs, 73% women) with a mean followup time of 15 years. By 25 years after RA incidence, ≥ 4 SLE features were observed in 15.5% of the subjects with RA. After adjustment for age and sex, occurrence of ≥ 4 SLE features was associated with increased overall mortality [hazard ratio (HR) 5.54, 95% confidence interval (CI) 3.59–8.53]. With further adjustment for RA characteristics, therapy, and comorbidities, the association weakened but remained statistically significant (HR 2.56, 95% CI 1.60–4.08). After adjustment for age, sex, RA characteristics, therapy, and comorbidities, thrombocytopenia (2.0, 95% CI 1.2, 3.1) and proteinuria (1.8, 95% CI 1.3, 2.6) were significantly associated with mortality.

Conclusion. SLE features were common in RA, given sufficient observation time. Subjects with RA who developed ≥ 4 SLE features had an increased risk of death. Proteinuria and thrombocytopenia were individually associated with an increased mortality risk. (First Release Nov 1 2008; J Rheumatol 2009;36:50–57; doi:10.3899/jrheum.080091)

Key Indexing Terms:
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Clinicians have long recognized that features of systemic lupus erythematosus (SLE) occur sporadically in patients with rheumatoid arthritis (RA). It has been debated whether this reflects the presence of a single disease with features of both, or the occurrence of 2 distinct diseases in an individual subject[1-7]. Recent genetic studies have identified various loci associated with increased risks for both RA and SLE[8-11], along with candidate genes associated with predisposition to autoimmune diseases in general[12,13], supporting the hypothesis of "shared autoimmunity." These findings suggest a common genetic susceptibility underlying the clustering of systemic and organ-specific autoimmune disorders among members of the same family, or sometimes in the same person[14]. Therefore, we postulated that patients with RA who develop SLE features over the course of their disease represent a high-risk subset with a worse longterm prognosis. To date, most studies of SLE features in patients with RA are cross-sectional and provide little information as to the occurrence of these features and their effect over the entire lifespan[3,15,16].

Our purpose was to examine the frequency of SLE features in an incidence cohort of subjects with RA and their effect on overall mortality.

MATERIALS AND METHODS

We studied a previously described[17] inception cohort of 603 Rochester, Minnesota, residents ≥ 18 years of age, who fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA[18] between January 1, 1955, and January 1, 1995. The entire inpatient and outpatient medical records of study subjects from all healthcare providers in Olmsted County, Minnesota, were reviewed using the medical records-linkage system of the Rochester Epidemiology Project[19].

Data collection was performed longitudinally starting at 18 years of age (or date of migration into Rochester) and continuing until death, migration from Olmsted County, or date of abstraction (conducted between 2001 and 2003). Medical records were reviewed for RA disease characteristics, RA therapy, comorbidities, and SLE disease features, as described below.

Data regarding RA characteristics included rheumatoid factor (RF) seropositivity, radiographic erosions, and/or destructive changes of the joints, as well as evidence for any of the following: rheumatoid vasculitis, rheumatoid nodules, Felty's syndrome, rheumatoid myocarditis, rheumatoid lung disease, Sjögren's syndrome, and other RA complications. Data were also collected regarding use of disease modifying antirheumatic drugs (DMARD), biologic therapies, and corticosteroids for RA. Start and stop dates for all therapies were collected.

Comorbidities were ascertained using the Charlson comorbidity classification[20] and included cardiovascular disease, chronic pulmonary disease, peptic ulcer disease, and all grades and complications of diabetes mellitus, cancer, cancer chemotherapy, renal disease, liver disease and dementia.

We also reviewed the medical records for the presence and the dates of all the first occurrences of clinical and laboratory features of SLE as defined in the 1982 ACR criteria for SLE classification[21], with the exception of urinary cell casts, as it was not feasible to reliably abstract the cellular composition of the casts from the urinalysis reports. SLE features included malar rash, discoid rash, photosensitivity, oral or nasopharyngeal ulcers, pleuritis (defined by a history of pleuritic pain or rub heard by a physician or evidence of pleural effusion), or pericarditis (defined by electrocardiogram or rub, or evidence of pericardial effusion), neurologic disorders (seizure or psychosis as recorded by physician, in the absence of offending drugs or known metabolic derangements), renal disorders (proteinuria, defined as urine protein level > 500 mg/24 h or > 3+ on a dipstick), hematological disorders (hemolytic anemia defined as documented physician diagnosis of hemolytic anemia, with the presence of elevated reticulocytes; leukopenia defined as white blood cell counts < 4000/ml on 2 or more occasions; lymphopenia defined as lymphocyte counts < 1500/ml on 2 or more occasions, thrombocytopenia defined as platelet counts < 100,000/mm^3 in the absence of offending drug), antinuclear antibodies (ANA; depending on the laboratory, reported as positive at a titer of either 1:40 or 1:80), and immunologic disorders [anti-double-stranded (ds)DNA antibody, anti-Sm antibody, false-positive syphilis serology, and lupus erythematosus (LE) cells].

Various methods were used over the years for testing for autoantibodies. ANA were detected by indirect immunofluorescence on mouse liver substrates since 1965, and on human epithelial (HEp2) cell lines since the mid-1980s, and more recently by enzyme immunoassay methods. Anti-dsDNA was detected by immunoprecipitation of radiolabeled DNA since 1975, by enzyme immunoassays on microtiter plates starting in the early 1980s, and later by commercial ELISA kits. Anti-Sm antibodies were detected by immunoprecipitation on agar gel since 1975 and with commercial ELISA kits since the early 1990s. LE cell detection was performed after 1955. As most of these laboratory tests required assays not available during the entire study period, subjects were only considered "at risk" for laboratory criteria during those time periods when the tests for these criteria were clinically available. In each case, we recorded whether the laboratory tests had been performed, as well as the result. Percentages of subjects who developed immunological features were calculated in 2 ways: by considering only subjects in whom the laboratory tests were performed, and by considering all subjects under observation irrespective of whether testing was performed.

Statistical methods. Descriptive statistics including percentages, means, and standard deviations (SD) were used to summarize the data. Kaplan-Meier methods were used to compute the cumulative incidence of SLE features, including SLE features present at or before RA incidence date (baseline), as well as those that developed during followup. Cox models were used to examine the risk of mortality associated with SLE features. These models used an age timescale and were stratified by sex. Dichotomous time-dependent covariates were used to model the SLE features, RA disease characteristics, therapy exposures, and comorbidities that developed during followup. The potential adjustment variables for each group of adjustors (RA disease characteristics, RA therapy, and comorbidities) were examined univariately to determine their association with mortality risk. Then a subset of significant adjustors was selected from each group using backward selection, removing any variables with p values > 0.10. These subsets of variables were then used as adjustors in the models reported in Tables 2 and 3. For laboratory SLE features, subjects who never received the test were excluded from these analyses. Describing mortality following SLE features that develop throughout followup is complex. We used landmark analyses to obtain the results displayed in Figure 2. In these analyses, patients with RA were categorized by the number of SLE features they have developed at the start of the curves (in this case, at 1, 2, 5, or 10 years after RA incidence) and survival of these groups was then estimated and compared using Kaplan-Meier methods.

RESULTS

The study population comprised 603 incident RA subjects (mean age 58.0 ± 15.2 yrs, 73.1% women) diagnosed between 1955 and 1995 and followed for a mean duration of 15.0 years (total 9066 person-yrs). Table 1 shows occurrence of SLE characteristics at baseline and during the followup period in the cohort. The most common clinical SLE feature observed in the RA cohort was pleuritis/pericarditis (6.5%) and the most common laboratory features were lymphopenia (79.8%) and ANA (47.1% of all tested subjects and 32.3% of all subjects observed after the test was available). Of the 481 subjects with RA who developed lymphopenia, 38 had Sjögren's syndrome (SS) and 55 had keratoconjunctivitis sicca only. Of the 189 RA subjects with ANA positivity, 22 had SS and 26 had keratoconjunctivitis sicca only. A total of 266 subjects (44.1%) had at least 1 SLE feature (in addition to arthritis) and 2 (0.3%) subjects had physician diagnosis of SLE at RA incidence.

Figure 1 shows the cumulative incidence of 2, 3, 4, and 5 SLE features involving different organ systems as defined in the 1982 ACR criteria in the RA cohort after RA incidence. The percentage of subjects with RA estimated to have developed a second SLE feature (in addition to arthritis) was 87.8% at 20 years and 89.5% at 25 years. Over 25 years of followup, an estimated 54.5% of the subjects with RA developed 3 SLE features, 15.5% developed 4 features, and 5.0% developed 5 SLE features. During this period, only 9 (1.5%) subjects had a physician diagnosis of SLE, of whom 2 had a physician diagnosis of SLE at the RA incidence date

Table 1. Occurance of SLE features at baseline and over followup (9066 person-years) in 603 subjects with RA.

SLE Features	Baseline (RA incidence date), n (%)	Ever, n (%)
Clinical features		
Malar or discoid rash	4 (0.7)	8 (1.3)
Photosensitivity	5 (0.8)	10 (1.7)
Oral/nasopharyngeal ulcers	1 (0.2)	10 (1.7)
Pleuritis/pericarditis	15 (2.5)	39 (6.5)
Neurological disorder (seizure, psychosis)	4 (0.7)	11 (1.8)
Total no. patients	28 (4.6)	69 (11.4)
Laboratory features		
Renal disorder (proteinuria)	11 (1.8)	72 (11.9)
Hematological disorder	198 (32.8)	488 (80.9)
Hemolytic anemia	2 (0.3)	8 (1.3)
Leukopenia	29 (4.8)	119 (19.7)
Lymphopenia	189 (31.3)	481 (79.8)
Thrombocytopenia	6 (1.0)	35 (5.8)
Antinuclear antibodies*	79 (22.1/17.4)	189 (47.1/32.3)
Immunologic disorder*	32 (6.0/5.5)	54 (10.1/9.0)
Anti-dsDNA antibody*	5 (5.9/1.6)	12 (10.5/2.3)
Anti-Sm antibody*	1 (3.1/0.3)	2 (4.6/0.4)
False-positive syphilis serology*	10 (2.1/1.7)	10 (2.1/1.7)
LE cells*	16 (5.2/2.6)	35 (11.4/5.8)
RA subjects with at least 1 SLE criterion in addition to arthritis	266 (44.1)	
MD diagnosis of SLE	2 (0.3)	9 (1.5)

* These laboratory tests were not available over the entire span of the study (ANA available after 1965; anti-dsDNA and anti-Sm after 1975; lupus erythematosus (LE) cell detection after 1955). First value in parentheses shows percentage of positive results among those subjects tested. Second value is the percentage of positive results among all subjects observed after the test became available, assuming untested subjects as negative.

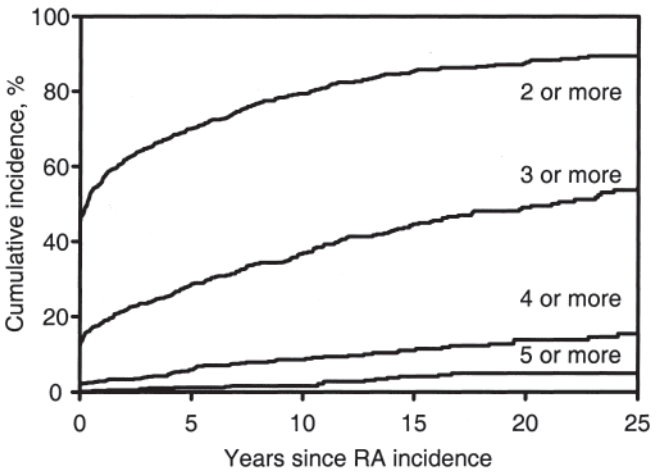

Figure 1. Cumulative incidence of developing 2, 3, 4, and 5 or more features of SLE over the course of RA. Arthritis is considered as one feature and is assumed to be present in all subjects with RA.

(baseline). We also examined whether subjects with RA diagnosed in recent years were more or less likely to develop SLE features than those diagnosed in earlier years. Although the development of SLE clinical features did not change over time ($p = 0.62$), overall SLE features, including laboratory features, were more likely to be detected in subjects with RA diagnosed in later years than in earlier years. In age and sex-adjusted models, subjects with RA first diagnosed after 1975 were 58% more likely [hazard ratio (HR) 1.58, 95% confidence interval (CI) 1.33, 1.89] to develop 2 and 79% more likely to develop 3 (HR 1.79, 95% CI 1.39, 2.30) SLE features, suggesting that increased availability of laboratory testing over time may have resulted in a higher likelihood of detection of SLE features in subjects with RA. However, subjects with RA diagnosed after 1975 were not significantly more likely to develop 4 (HR 1.07, 95% CI 0.65, 1.77) or 5 SLE features (HR 0.73, 95% CI 0.28, 1.87).

We then examined the mortality risk according to the number of SLE features. The association with the number of SLE features and mortality was examined using Cox proportional hazards models, adjusting for age, sex, RA therapy, RA characteristics, and comorbidities (Table 2). The age and sex-adjusted HR for mortality in subjects with 2–3 and 4 or more SLE features compared to those having only arthritis were 1.85 (95% CI 1.37, 2.49) and 5.54 (95% CI 3.59, 8.53), respectively. A statistically significant increase in mortality risk persisted after further adjustment for use of RA therapy in subjects with 2–3 SLE features (HR 1.67, 95% CI 1.23, 2.26) and 4 or more SLE features (HR 4.74, 95% CI 3.04, 7.39). Occurrence of 2–3 features was no longer associated with mortality after further adjustment for RA disease characteristics (HR 1.29, 95% CI 0.94, 1.78). However, occurrence of 4 or more SLE features remained significantly associated with a 2.56-fold (95% CI 1.60, 4.08) higher risk of mortality, even after further adjustment for comorbidities. Figure 2 illustrates the mortality risk of subjects who had 2, 3, or ≥ 4 SLE features at 1, 2, 5, and 10 years after RA incidence. At each timepoint (landmark), increasing number of SLE features was associated with higher mortality risks.

We then examined the mortality risk associated with individual SLE features. Table 3 shows the mortality risk associated with individual SLE features, after adjustment for age, sex (column 1), RA therapy (column 2), RA characteristics (column 3), and comorbidities (column 4). All SLE features except for photosensitivity and false-positive syphilis serology were individually associated with mortality, after adjusting for age and sex. Features most strongly associated with mortality in age and sex-adjusted analyses were neurologic disorders (HR 5.9, 95% CI 3.1, 11.5), hemolytic anemia (HR 4.1, 95% CI 1.8, 9.3), lymphopenia (HR 2.8, 95% CI 2.1, 3.7), oral/nasopharyngeal ulcers (HR 2.9, 95% CI 1.4, 6.2), and thrombocytopenia (HR 2.3, 95% CI 1.5, 3.5). The significant associations between individual

Table 2. Association between the number of SLE features and the risk of mortality in the RA cohort.

No. of SLE Features	Hazard Ratio (95% CI) Adjusted for Age and Sex	Age, Sex, RA Therapy	Age, Sex, RA Therapy, RA Characteristics	Age, Sex, RA Therapy, RA Characteristics, Comorbidities
1 (arthritis)	1	1	1	1
2–3	1.85 (1.37, 2.49)	1.67 (1.23, 2.26)	1.29 (0.94, 1.78)	1.13 (0.82, 1.57)
4	5.54 (3.59, 8.53)	4.74 (3.04, 7.39)	3.29 (2.08, 5.21)	2.56 (1.60, 4.08)

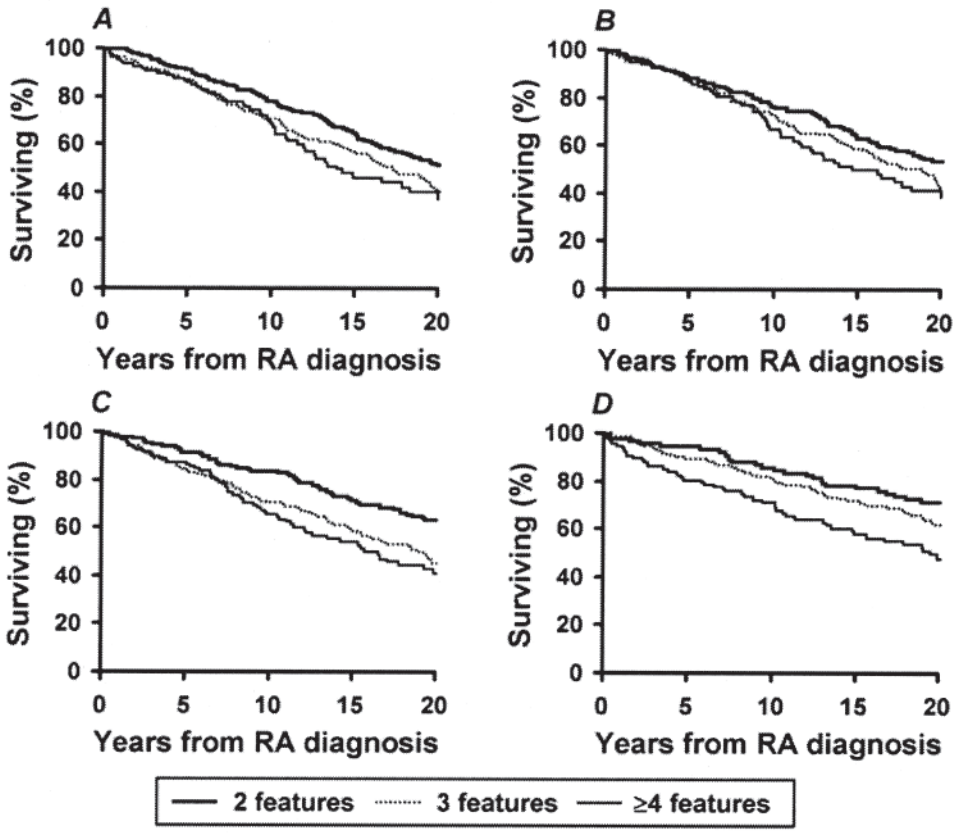

Figure 2. Mortality risk associated with 2, 3, or ≥ 4 features of SLE at 1 (A), 2 (B), 5 (C), and 10 (D) years after RA incidence.

SLE features and mortality were sustained following further adjustment for RA therapy and characteristics, except for malar/discoid rash, oral/nasopharyngeal ulcers, and leukopenia. After further adjustment for comorbidities, proteinuria (HR 1.8, 95% CI 1.3, 2.6) and thrombocytopenia (HR 2.0, 95% CI 1.2, 3.1) remained as statistically significant predictors of mortality.

DISCUSSION

Our study provides a comprehensive description of the incidence of SLE features over a followup period exceeding 40 years in a population-based inception cohort of subjects with RA. We extend the findings of previous cross-sectional studies by describing the overlap between features of RA and SLE and, for the first time, report the potential effect of SLE features on mortality in RA. Our findings demonstrate that SLE features are common in the lifetime course of RA and are significantly associated with an increased mortality risk, even after adjusting for well described RA-specific predictors of mortality. Indeed, for some SLE features (e.g., neurological features, hemolytic anemia), the risk may be as high as 6-fold. These findings emphasize the overlap between RA and SLE and provide further evidence for a common autoimmunity background in these diseases.

There are at least 4 possible explanations for the high incidence of individual SLE features in subjects with RA.

Table 3 Association between the individual SLE features and risk of mortality in the RA cohort.

No. of SLE Features	Hazard Ratio (95% CI) Adjusted for			
	Age and Sex	Age, Sex, RA Therapy	Age, Sex, RA Therapy, RA Characteristics	Age, Sex, RA Therapy, RA Characteristics, Comorbidities
Malar/discoid rash	2.2 (1.0, 4.9)	2.5 (1.1, 5.6)	0.8 (0.3, 2.0)	0.8 (0.3, 2.1)
Photosensitivity	1.1 (0.4, 2.6)	1.2 (0.5, 2.8)	1.0 (0.4, 2.6)	0.6 (0.2, 1.5)
Oral/nasopharyngeal ulcers	2.9 (1.4, 6.2)	2.3 (1.1, 5.0)	1.5 (0.7, 3.5)	1.1 (0.5, 2.4)
Pleuritis/pericarditis	1.9 (1.3, 2.8)	1.9 (1.3, 2.8)	1.9 (1.3, 2.9)	1.3 (0.9, 2.1)
Neurologic disorders	5.9 (3.1, 11.5)	6.4 (3.3, 12.4)	4.7 (2.2, 10.1)	2.1 (0.9, 4.9)
Proteinuria	2.1 (1.5, 2.8)	2.0 (1.5, 2.7)	1.8 (1.3, 2.5)	1.8 (1.3, 2.6)
Hemolytic anemia	4.1 (1.8, 9.3)	4.6 (2.0, 10.7)	4.0 (1.6, 9.9)	1.4 (0.5, 3.6)
Leukopenia	1.3 (1.0, 1.7)	1.2 (1.0, 1.6)	0.9 (0.7, 1.3)	0.6 (0.5, 0.9)
Lymphocytopenia	2.8 (2.1, 3.7)	2.6 (1.9, 3.5)	1.8 (1.3, 2.5)	1.4 (1.0, 1.9)
Antinuclear antibody	1.8 (1.4, 2.3)	1.6 (1.3, 2.1)	1.4 (1.1, 1.8)	1.3 (1.0, 1.7)
False-positive syphilis serology	1.7 (0.9, 3.3)	1.6 (0.9, 3.1)	1.6 (0.8, 3.1)	1.0 (0.5, 1.9)
Lupus erythematosus cells	2.2 (1.5, 3.3)	2.3 (1.5, 3.3)	1.7 (1.2, 2.6)	1.6 (1.0, 2.4)

First, SLE features may simply be coincidental occurrences in RA subjects. After RA incidence and throughout the course of the disease, individual SLE features occurred sporadically and the number rose continuously over time. More than three-quarters of the subjects in the RA cohort experienced at least 1 SLE feature (besides arthritis) and 15% experienced 4 SLE features by 25 years after RA diagnosis. Theoretically, 15% of subjects with RA who experienced 4 or more SLE features fulfilled criteria for SLE, as the 1982 SLE criteria clearly state that "a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation"[21]. Yet the number of subjects in our cohort who received a physician's diagnosis of SLE was only 9 (1.5%), indicating a large difference between the number of subjects fulfilling the criteria and those having a clinical diagnosis. The dispersed occurrences of these features over a long period may prevent easy recognition of these symptoms as a constellation. Even if they were recognized, the physician may be reluctant to consider an additional diagnosis in a subject with established RA and interpret the symptoms as extraarticular manifestations. Another explanation for the large discrepancy between the number of subjects fulfilling the criteria and receiving clinical diagnosis may be the arbitrary and nonspecific nature of classification criteria, which were developed in cross-sectional analysis of subjects with established disease. Our study highlights the limitations of the classification criteria when assessing symptoms collected over a long timeframe, considering the dynamic nature of the autoimmune disorders. Although only 9 subjects in the RA cohort received a physician's diagnosis of SLE, this rate was considerably more than what would be expected based on the incidence of SLE[22] alone. The incidence of SLE in this community has been reported to be 5.56 per 100,000; thus ≤ 1 new case would have been expected in this RA cohort if members of the cohort were at the same risk of SLE as the general population. A similar observation was also reported by Cohen and Webb in their case series, where the 11 subjects having the diagnosis of both RA and SLE comprised 3.6% of the SLE cohort whereas the predicted prevalence of RA in this SLE cohort was 1% or less[6]. Therefore, it is unlikely that these are coincidental occurrences.

Second, it is possible that SLE features represent extraarticular manifestations of RA, or they are associated with DMARD, glucocorticoid, or nonsteroidal antiinflammatory drug (NSAID) therapy, and thus should not be interpreted as features of SLE. Proteinuria may be the result of drug-induced nephropathy and thrombocytopenia may be due to drug-induced immune reactions. Although leukopenia and lymphopenia were associated with seropositivity and exposure to DMARD (all $p \leq 0.01$), we observed quite substantial numbers of leukopenia and lymphopenia cases occurring among patients with seronegative RA or patients who were never exposed to DMARD or glucocorticoids. Therefore, although therapy might have contributed to the occurrence of some SLE features, it does not appear to account for all features.

A third possible explanation is that these subjects represent a particular subset of subjects with SLE or RA , or even a distinct clinical entity, such as "rhupus syndrome"[2]. It is long recognized that features of RA and SLE may coexist in individual patients, reflecting either the presence of a single disease with features of both, or the occurrence of 2 distinct diseases in an individual patient[1-4,6,7]. It remains controversial whether rhupus is a true overlap between SLE and RA[16,23], or a variant of either condition (e.g., lupus arthropathy)[3,4,7,15,23], or corresponds to a clinically and immunologically distinctive entity[3,24]. In our study, although the number of patients who fulfilled the diagnostic

criteria for SLE were much higher, subjects with RA who had a physician's diagnosis of SLE composed only a small proportion of the cohort (1.5%). It is quite likely that physicians are reluctant to consider the diagnosis of SLE as a second disease in patients with established RA, and instead, view the disease features of SLE in these patients as part of the disease spectrum of RA (e.g., extraarticular manifestations) or therapy. Further, the long time interval between the occurrence of individual SLE features makes physician recognition of SLE in the clinical setting difficult.

Finally, the presence of SLE features in subjects with RA may support the hypothesis of "shared autoimmunity," i.e., that RA is not a specific, independent disease construct, but rather part of a broad clinical spectrum of autoimmune disease[12]. Shared autoimmunity is defined as occurrence of various forms of autoimmune disorders in several members of the same family, coincidence of autoimmune rheumatic and nonrheumatic diseases in the relatives of patients, presence of autoantibodies in the healthy relatives of subjects, and the occurrence of more than one autoimmune disorder in the same subject[25]. For instance, family members of patients with SLE are as likely to develop RA as family members of patients with RA[26]. Both RA and SLE patients frequently have other autoimmune diseases. Indeed, in a recent study, 33% of the subjects in a retrospective SLE cohort had at least one other autoimmune disorder (3.49% of the cohort had RA)[27]. Sjögren's syndrome is reported to occur in 11% to 31% of patients with RA[28]. In our cohort, 58 subjects had SS, with a cumulative incidence of 11.4% over 30 years[29]. Several studies have reported that positive RF and anticitrullinated peptide antibodies are found commonly in patients with SLE[30].

Genetic studies also support the concept of shared autoimmunity. The genetic risk in RA is associated with the shared epitope HLA-DRB1 on chromosome 6p21.3, especially in populations of European ancestry. In addition to the shared epitope, Anaya, *et al*[31] demonstrated that gene variants TAP2*0201 (RA and SLE) and TNF-308A (RA, SLE, and SS) on the same chromosomal region increased the susceptibility risk for multiple autoimmune disorders. A genome-wide scan of multiplex RA families found that the risk of RA was significantly associated with genes implicated in other autoimmune disorders including D1S235 (SLE), D4S1647, D5S1462, D16S516 (inflammatory bowel disease), D12S1052 (multiple sclerosis), and D16S516 (ankylosing spondylitis)[32]. Various other candidate genes have also been proposed as the underlying predisposing factor for the development of multiple autoimmune disorders. Among these genes, PDCD1[8], PTPN22[11], FCRL3[10], and STAT4[9] have been associated with both RA and SLE. Our clinical findings are clearly supported by these genetic studies and provide further evidence for the shared autoimmunity hypothesis.

These 4 possibilities can only be disentangled with a deeper understanding of the common and distinctive pathologies in these autoimmune diseases, and with prospective studies designed specifically to examine these hypotheses. Our study, taking advantage of the extended timespan, where not all DMARD therapies were available, provides some indication that RA-related therapy and/or RA severity may not completely explain the occurrence of SLE features found in subjects with RA. Altogether, our observations do not support the possibility that the coexistence of RA and SLE may simply be the coincidental occurrence of 2 independent diseases, or even a rare phenomenon.

We also examined the association of SLE features with overall mortality in subjects with RA. Our findings underscore the significance of SLE features as predictors of mortality in RA. Indeed, previous mortality studies in SLE populations have identified neurologic involvement, thrombocytopenia, hemolytic anemia, and renal involvement among the strong risk factors for mortality[33-36]. Some of the laboratory features we investigated are rather nonspecific findings. Proteinuria is a predictor of cardiovascular disease and mortality in the general population[37], similar to our findings in subjects with RA. Proteinuria may be functional (due to fever, strenuous exercise, exposure to cold, and pregnancy), or it may develop related to various disease processes including urinary tract infections, hypertension, congestive heart failure, diabetes mellitus, plasma cell dyscrasias, and SLE[38]. In subjects with RA, amyloidosis, NSAID or DMARD-related nephropathy, and mesangial glomerulonephritis resulting from immune complex deposition are other potential causes of proteinuria[39-41]. In our RA cohort, there were 7 subjects who had renal disease at baseline and 49 additional subjects who developed renal disease during the course of RA. Even though our definition of proteinuria is consistent with the 1982 ACR criteria for SLE diagnosis, information on the potential causes of proteinuria or renal biopsy results is not available. Our findings also indicate that thrombocytopenia is another nonspecific feature associated with mortality. Thrombocytopenia is not a common feature of RA, but it generally develops as a result of drug-induced immune reaction. Similarly, we did not collect information about the possible immune reactions underlying thrombocytopenia in this cohort. Although proteinuria and thrombocytopenia are relatively nonspecific features, they may still be useful in identifying RA subjects with a higher risk of mortality.

Our study has several potential limitations that should be considered. First, this was a retrospective study and only SLE features that came to medical attention and were recorded in the medical records were ascertained. We were unable to consistently ascertain urinary cellular casts, which is an important feature of renal disorders in SLE, and we did not collect information on antiphospholipid antibodies, which are included in the 1997 revised criteria[42]. Further, subjects who had a single negative laboratory test result may

not have been retested to determine if they later had a positive test. These limitations may contribute to underestimation of the true number of SLE features in subjects with RA. Second, this is a historical study and the RA population was ascertained between 1955 and 1995 with a followup until 2001-2003. Although the long followup period allows comprehensive description of SLE features over time, these findings may not reflect the clinical characteristics of the contemporary RA patients. Third, we assumed that SLE features, once present, would identify that subject as "exposed" from that point forward, in agreement with the methodology for how SLE classification criteria were defined. However, as some of these manifestations may be transient and and/or modifiable by therapy (e.g., serositis), we may have overestimated the true number of SLE features in subjects with RA that are present at a particular timepoint. On the other hand, laboratory abnormalities such as leukopenia or lymphopenia may have been exacerbated by therapy in some RA subjects. Assays for anti-dsDNA and anti-Sm antibodies are more robust features of SLE. However, they were not available throughout the study period and methods to detect these antibodies changed over time. Although the use of these assays increased over time, data on these variables were available in only a small subset of the RA cohort, and therefore provided limited power to examine their role on mortality. Finally, the predominance of Caucasians in the Olmsted County population may limit the generalizability of our findings to more ethnically diverse RA populations.

Our results have important implications for future research. Longitudinal studies with extended followup are necessary to understand the overlap between autoimmune diseases. This overlap and the transient aspect of especially laboratory features should be taken into account in the future development of classification criteria for autoimmune diseases, in particular for RA and SLE. Longitudinal studies can provide a more robust and clinically meaningful approach than cross-sectional studies and can identify the dynamic nature of these 2 diseases. Finally, subjects who develop several features of apparently different autoimmune diseases such as RA, SLE, and SS may provide a better understanding of the underlying susceptibility for autoimmunity.

Our observations may also have implications for clinical practice. Physicians should remain alert to manifestations of autoimmunity and overlapping disease features, even well after the diagnosis of RA is established. Physicians should take into account the entire spectrum of RA disease manifestations as well as overlapping SLE features when considering therapeutic strategies, recognizing that the therapeutic approach may change as autoimmune manifestations evolve over time. Most importantly, SLE features may help to identify subjects with RA at a higher mortality risk.

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