Clinically Active Serologically Quiescent Systemic Lupus Erythematosus

DAFNA D. GLADMAN, NAUSHAD HIRANI, DOMINIQUE IBAÑEZ, and MURRAY B. UROWITZ

ABSTRACT. ***Objective.*** To identify the frequency and characteristics of clinical activity with serological quiescence (CASQ) in a large cohort of patients with systemic lupus erythematosus (SLE) followed prospectively at a single center.

Methods. Patients followed at the Lupus Clinic between 1991 and 1995 who on at least 3 consecutive visits had clinical activity in the absence of a low complement and elevated DNA binding were identified. Demographics, disease characteristics, and therapy for the CASQ periods, as well as prior and subsequent disease course until April 2002 were analyzed.

Results. Of 514 patients followed at the Lupus Clinic according to a standard protocol, 62 patients had at least one episode of CASQ lasting a 9.8 ± 6.4 months. During these periods, patients showed evidence of clinical disease activity with a SLEDAI-2K of 8.9 ± 5.3. Major organ involvement (central nervous system, renal, vasculitis) occurred in 43 patients. Forty-four patients were treated with prednisone 16.7 ± 11.4 mg/day, 21 were on immunosuppressive medication and 30 on antimalarials. Of the 58 patients who had followup after their last CASQ defining visit, 9 remained CASQ for 39 ± 23 months. Of the remaining 49 patients, 23 became inactive, 21 became clinically and serologically active, and 5 were serologically active but clinically quiescent (SACQ).

Conclusion. Clinical laboratory correlation in SLE is a heterogeneous relationship. The majority of patients have clinical-serological concordance. The minority have discordance between clinical and serological status, and are either SACQ or CASQ. Therefore, monitoring both clinical and serological features in patients with SLE is important. (J Rheumatol 2003;30:1960–2)

Key Indexing Terms:
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The relationship between serologic and clinical disease activity abnormalities of patients with systemic lupus erythematosus (SLE) has been a subject of study since the 1960s[1-7]. Most of this work has focused on deriving predictors or correlates of disease activity or disease flares, and a body of evidence has accumulated that suggests that a large proportion of SLE patients can be managed by considering their serologic activity state in clinical decision making[2,8,9]. The most useful correlates seem to be elevated anti-DNA antibody titers as predictors of renal disease flares[10,11], and normalization of hypocomplementemia with treatment of renal lupus nephritis[12,13]. The patients in whom these observations hold have been referred to as clinically and serologically concordant.

From The University of Toronto Lupus Clinic, Centre for Prognosis Studies in The Rheumatic Diseases, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada.

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D.D. Gladman, MD, FRCPC, Professor of Medicine University of Toronto, Deputy Director Centre for Prognosis Studies in The Rheumatic Diseases; N. Hirani, MD, Elective Student; D. Ibañez, MSc, Biostatistician; M.B. Urowitz, MD, FRCPC, Director, Centre for Prognosis Studies in The Rheumatic Diseases.

Address reprint requests to Dr. D. Gladman, Centre for Prognosis Studies in The Rheumatic Diseases, Toronto Western Hospital, 399 Bathurst St. EC 5-034, Toronto, Ontario, M5T 2S8.

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However, Lightfoot, *et al* found that anti-DNA antibodies persisted for over a year in some patients with SLE before clinical exacerbations occurred[3]. Furthermore, we have described a group of discordant patients and found that 12% of our clinic population manifested a significant period of serologic activity in the absence of clinical disease[14,15]. Almost half of these patients did not exhibit a flare during the entire followup period of 17 years, and no predictors of discordance were found[16]. The existence of this subset, in addition to factors such as older, varied serologic techniques used in some studies and non-uniform measures of disease activity, may account for the inability of several investigators to show good correlation between serology and flares[6]. Aside from the therapeutic implications, discordance has also challenged the presumed pivotal causal significance ascribed to circulating auto-antibodies in the pathogenesis of the various manifestations of SLE. An even greater challenge to this paradigm is the existence of patients with periods of clinical activity and serologic quiescence (CASQ).

We identified the frequency of CASQ in a large cohort of patients with SLE followed prospectively in a single center, described the clinical characteristics of CASQ, and described the disease course post-CASQ.

MATERIALS AND METHODS

Patient selection. Between January 1, 1991 and December 31, 1995, 524

patients were followed at the University of Toronto Lupus Clinic. Patients are followed at the clinic at 2-6 month intervals according to a standard protocol that includes a complete history and physical examination as well as a panel of laboratory tests[17]. All information is entered into a computer database.

Serologic studies. Anti-dsDNA antibodies were detected by the *Crithidia luciliae* and quantified by the ^{125}I Farr assay. Serum complement components C3 and C4 were measured by immunodiffusion plates and functional CH50 assays were also performed.

Assessment of disease activity. Clinical disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). This is a recent modification of the SLEDAI, and is a validated disease activity measure in SLE[18]. The standard protocol includes all items necessary to calculate the SLEDAI-2K at each visit. Patients with 3 consecutive clinic visits having a SLEDAI-2K > 0 in the absence of abnormal serology (anti-DNA antibodies or reduced complement levels) were identified. These periods of clinical/serologic discordance are referred to as CASQ. Patients were then followed to April 2002. If the patient either seroconverted, or entered into clinical remission on an assessment after the initial 3 qualifying assessments, the CASQ period was defined as ended. In addition to recording the SLEDAI-2K at each visit, we calculated the adjusted mean SLEDAI (AMS), which reflects the degree of disease activity over the study period[19].

The presence of major organ involvement, including central nervous system (CNS), renal manifestations, and vasculitis, was identified. The latter was defined by the presence of ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiographic proof of vasculitis.

Analysis. Descriptive statistics were used to describe the nature of the CASQ period, the disease pattern before the CASQ period, and the post-CASQ period.

RESULTS

Patient characteristics. Of the 514 patients seen in the Lupus Clinic during the specified period, 62 patients (12%) were identified as having CASQ periods. There were 54 women and 8 men, 55 Caucasians, with a median age at SLE diagnosis of 32.5 years, and disease duration of 7.3 years at the time of the first assessment of CASQ.

Clinical features during CASQ period (Table 1). A CASQ period lasting a median of 8 months during the followup period was identified for 62 of the 514 patients. During these periods, patients showed evidence of clinical disease activity with a mean SLEDAI-2K of 8.9 ± 5.3. Major organ involvement (CNS, renal, vasculitis) occurred in 43 patients, and 59 patients had minor organ involvement. These flares were treated with corticosteroids and immunosuppressive medications (IS) as necessary. Forty-four of the 62 patients (71%) were treated with prednisone at a mean dose of 16.7 ± 11.4 mg/day. Twenty-one patients were taking IS and 30 were on antimalarials (AM).

Table 1. Demographic and clinical features during and after the CASQ period.

	CASQ Period n = 62	Post-CASQ n = 58
Mean length of time in period, mo ± SD	9.8 ± 6.4	73.8 ± 40.5
Number active (SLEDAI-2K≠ 0)	62	57
Max SLEDAI-2K	8.9 ± 5.3	10.4 ± 5.9
AMS	6.5 ± 3.3	4.6 ± 3.2
Major organ involvement	43	44
CNS	20	21
Renal	31	35
Vasculitis	9	10
Minor organ involvement	59	52
Steroid use	44	42
Mean dose, mg/day, ± SD	16.7 ± 11.4	12.0 ± 6.3
Immunosuppressive use	21	30
Antimalarial use	30	41

AMS: adjusted mean SLEDAI.

Outcome post-CASQ period. Of the 58 patients who had followup after their last CASQ defining visit, 9 remained CASQ for 39 ± 23.0 months. Forty-nine patients changed their designation after 10.8 ± 12.9 months. Twenty-one patients became serologically active, 5 patients became serologically active but clinically quiescent (SACQ), and 23 became both clinically and serologically inactive.

Clinical features in the post-CASQ period (Table 1). The mean SLEDAI-2K post-CASQ was 10.4 ± 5.9. Forty-two patients were on steroids with a median dose of 12.0 ± 6.3 mg/day, 29 were on IS, and 38 AM medications.

DISCUSSION

The use of serologic markers as predictors of disease exacerbations in SLE has been a controversial issue in recent literature[6,20]. Despite several studies that have shown serial measurements of anti-ds DNA[21] and serum complement levels[22] can be used to predict flares and treat active disease, some authors have questioned the strength and nature of the relationship of these variables[6,9,23]. As a result, the utility of monitoring SLE patients with batteries of expensive serological tests at frequent intervals has also been questioned[24].

Some have invoked the concept of the existence of distinct subsets of SLE patients in terms of serologic and disease activity characteristics as a possible confounding factor that has contributed to these discrepancies[25]. We have previously shown that 12% of the clinic population was discordant for a significant period, with active serology in the face of clinical quiescence. In this study, we show that an additional 12% of the population is discordant the other way for a significant period, with clinical activity in the face of serologic quiescence. Thus, up to approximately one quarter of SLE patients may exhibit serologic and clinical discordance. This is not an insignificant proportion of patients, and it has the potential to account for some of the wide variation observed between and within the results of both positive and negative studies relating serologic abnormalities to disease activity and flare.

During CASQ periods, our patients had clinical features of both major and minor organ involvement and required steroid, IS, and AM medication. In the post-CASQ period, the majority of our patients remained clinically active, some

having been serologically quiescent developing these laboratory features, and about 20% of the patients becoming SACQ.

We were unable to identify factors that could be used to separate concordant from discordant patients before the eventual course of each individual patient was observed. This suggests that serological monitoring of SLE patients would be useful only if followed longitudinally and frequently, first to identify the concordance status of the patient, and then to incorporate this information into subsequent clinical decisions. This also suggests that in future longitudinal studies of this issue, discordant patients should be identified and separated out from analyses of concordance.

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