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The Importance of an Early Diagnosis in Systemic Lupus Erythematosus

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ABSTRACT: **Background:** Systemic lupus erythematosus (SLE) is an autoimmune disease with a high degree of variability at onset, making it difficult to reach a correct and prompt diagnosis.

Objectives: To present the difficulties faced by the clinician in making a SLE diagnosis, based on the characteristics at study entry of an Italian cohort of SLE patients with recent onset as compared to two similar cohorts.

Methods: Beginning on 1 January 2012 all patients with a diagnosis of SLE (1997 ACR criteria) and disease duration of less than 12 months were consecutively enrolled in a multicenter prospective study. Information on clinical and serological characteristics was collected at study entry and every 6 months thereafter.

Results: Our cohort consisted of 122 patients, of whom 103 were females. Among the manifestations included in the 1997 American College of Rheumatology (ACR) criteria, cutaneous, articular and hematologic symptoms were the most prevalent symptoms at study entry.

Conclusions: Data from the literature confirm that the diagnosis of SLE is challenging, and that SLE is a severe disease even at onset when a prompt diagnosis is necessary for initiating the appropriate therapy.

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KEY WORDS: systemic lupus erythematosus (SLE), recent-onset SLE, early SLE, autoantibodies, anti-DNA antibodies, anticardiolipin antibodies

Systemic lupus erythematosus (SLE) is a disease characterized by a broad spectrum of clinical manifestations and a multitude of laboratory abnormalities. The complexity of the disease could also explain why it is difficult to identify SLE patients at an early stage of the disease. In fact, there are no pathognomonic clinical or serological features that would help clinicians in diagnosing SLE. Criteria for the classification of SLE were elaborated by the American College of Rheumatology (ACR) in 1971, and revised in 1982 and again in 1997 [1]. The new Systemic Lupus International Collaborating Clinics (SLICC) classification criteria have a higher sensitivity when compared to the revised ACR criteria [2]. The SLICC criteria are meant to be clinically more relevant, allowing the inclusion of more patients with clinically defined lupus than with the current ACR criteria. However, even the SLICC classification criteria are not diagnostic criteria and cannot be applied to every individual case.

So, the diagnosis of SLE remains very difficult, especially in the early stage of the disease when it is crucial to start the correct treatment. It is well known that delay in treatment is associated with a worse prognosis [3-5]; the progressive decrease in the time elapsed between disease onset and diagnosis is one of the major contributors to increased survival [6] and improved quality of life [7] in SLE patients over time.

In 2012 we began a multicenter prospective study of patients with recent-onset SLE (< 12 months) from nine Italian centers, with the purpose of collecting information on the clinical and laboratory characteristics of SLE patients at the start of the disease and during the first years of follow-up.

In this communication we discuss the difficulties faced by the clinician in making a diagnosis of SLE at disease onset, based on the characteristics at study entry of an Italian cohort of SLE patients with recent disease onset as compared to two similar cohorts.

PATIENTS AND METHODS

In 2012 we initiated a multicenter prospective study with the purpose of creating an inception cohort of SLE patients with recent-onset disease. Nine Italian centers with longstanding experience in lupus management were involved. All patients with a diagnosis of SLE according to the 1997 ACR classification criteria [1] and disease duration (from diagnosis until study entry) of less than 12 months are consecutively enrolled in this ongoing study.

Information on demographic characteristics, medical history, clinical symptoms, physical examinations, laboratory results, disease activity, disease damage, patient's quality of life, were collected at study entry and every 6 months thereafter. The data are documented on a specific form and subsequently transferred into an electronic database. Global SLE disease activity is measured by the ECLAM, a validated measure of disease activity in SLE [8,9]. Cumulative damage is scored according to the SLICC Damage Index, a validated measure to

assess damage in SLE [10]. Patient's quality of life is estimated by means of a visual analogue scale (VAS).

Our study obtained approval from our institutional review board and adheres to the principles of the Declaration of Helsinki.

AUTOANTIBODY ASSESSMENTS

Autoantibodies are measured locally at each participating center. The following autoantibodies were considered in this study: antinuclear antibody (ANA), anti-dsDNA, anti-SSA (Ro), anti-SSB (La), anti-Sm, anti-RNP, anticardiolipin (aCL), anti-beta2 glycoprotein I (anti-β2GPI), and lupus anticoagulant (LA). ANA are measured by immunofluorescence using Hep2 cells as substrate. Anti-dsDNA are measured either by immunofluorescence using *Crithidia luciliae* or the Farr technique. Anti-SSA, anti-SSB, anti-Sm and anti-RNP are measured by immunoblot technique. aCL and anti-β2GPI are measured by enzyme-linked immunosorbent assay (ELISA). Lupus anticoagulant is measured by coagulometric assay. Importantly, at each center the same technique is used throughout the study.

STATISTICAL ANALYSIS

Statistical analysis was performed by means of the Openstat program using the information stored in the database program. Results of the analysis of continuous variables are indicated as mean ± standard deviation or median and range, as appropriate. Conventional chi-square and Fisher exact tests were used for analyzing qualitative differences between independent samples. McNemar test was used for analyzing qualitative differences between patients at enrolment and after a 1 year follow-up period. Student's *t*-test was used for analyzing mean differences. A P value < 0.05 indicates statistical significance.

RESULTS

As reported in a recently published paper [11], during a 2 year period we enrolled 122 patients with recent-onset SLE. Of them, 103 were females and 19 were males (84.4% and 15.6% respectively); 115 were Caucasians (94.3%) and 7 (5.7%) were of other ethnicities. The mean age (SD) of the patients at study entry was 37.3 years (14.3), mean age at disease onset (first symptom of SLE) was 34.8 years (14.3), and mean age at diagnosis 36.9 (14.3). Mean disease duration (from diagnosis until study entry) was 2.9 months (3.9). Demographic features of this cohort are depicted in Table 1.

The frequency of the manifestations (from onset until enrolment) included in the classification criteria is reported in Table 2, in comparison with two other important cohorts, the Early SLICC Cohort and the Euro Lupus Project. In our cohort, the cumulative frequency of the mucocutaneous classification criteria was 77.8%, confirming them as among the most common clinical manifestations in the ACR classification criteria at SLE onset. ANA were present in all but three patients at disease onset. Two of these three ANA-negative patients had anti-Ro antibodies and one had antiphospholipid antibodies only (aCL anti-β2GPI at medium-high titer). All three patients reported to be ANA negative at disease onset were found to be ANA positive at the enrolment visit.

Drug therapy at study entry is reported in Table 3, as compared to the Euro Lupus Project. Evident is the widespread use of glucocorticoids in lupus patients (85.1% in our cohort) at study entry compared to other immunosuppressive drugs. Hydroxychloroquine is also given to a high proportion of patients (63.6%).

At the enrolment visit, median (range) disease activity (ECLAM) was 4 (0–10), median damage (SLICC) was 0 (0–3), and median patient's quality of life (VAS) was 53 (0–100).

Table 1. Demographics of the 122 patients with recent-onset SLE

Women	103 (84.4%)
Ethnicity	
White	115 (94.3%)
Black	4 (3.3%)
Asian	3 (2.4%)
Age at onset (first symptom/s of SLE), mean (SD) years	34.8 (14.3)
Age at diagnosis (fulfillment of ACR criteria), mean (SD) years	36.9 (14.3)
Age at enrolment, mean (SD) years	37.3 (14.3)
Disease duration (from diagnosis until enrollment), mean (SD) months	2.9 (3.9)

SLE = systemic lupus erythematosus, ACR = American College of Rheumatology

Table 2. Frequency (%) of the manifestations included in the ACR classification criteria in the cohort of 122 patients with recent-onset SLE (Early Lupus Project) in comparison with the Early SLICC Cohort and Euro Lupus Project

	Early Lupus Project	Early SLICC cohort	Euro Lupus Project
ANA	97.5	99	98.5
Immunologic disorders*	85.2	77.7	78.5
Arthritis	61.8	75.5	48.1
Hematologic manifestations	55.7	62.1	18.2
Malar rash	31.1	34	31.1
Photosensitivity	29.5	39.6	22.9
Serositis	27	27.7	16
Nephropathy	27	27.2	17.9
Mucosal ulcers	11.5	36.9	12.5
Neurologic disorders	8.2	26	19.4
Discoid rash	5.7	11.2	7.8

*Anti-dsDNA, anti-Sm, antiphospholipid antibodies
ANA = antinuclear antibodies

Table 3. Drug therapy (%) in the cohort of 122 patients with recent-onset SLE (Early Lupus Project) in comparison with the Euro Lupus Project

	Early Lupus Project	Euro Lupus Project
Prednisone	85.1	72.5
Hydroxychloroquine	63.6	47.8
Azathioprine	10.7	16.3
Cyclophosphamide	9.1	20.4
Methotrexate	10.7	6
Mycophenolate	7.4	–
Rituximab	0.8	–
Belimumab	0.8	–
Epratuzumab	0.8	–
Abatacept	0	–
Other DMARDs	5	–

DMARDs = disease-modifying anti-rheumatic drugs

Eighty-three patients had at least one hospitalization in the period from diagnosis until study entry. The mean (SD) hospitalization number was 1.54 (1.58) and the median (interquartile range) 1 (1–2); the mean number of days of hospitalization was 14.4 (14.5) and median 12 (0.5–20.5).

DISCUSSION

Systemic lupus erythematosus is an autoimmune disease mostly affecting women during their thirties and forties. Its nature of being a "multisystemic disease" is associated with a high degree of variability at onset, ranging from more specific symptoms such as the typical malar rash, nephropathy and anti-double-stranded DNA antibodies (anti-dsDNA), to non-specific findings such as fever, anemia, arthritis and antinuclear antibodies (ANA). Thus, especially at onset, the diagnosis of SLE can be challenging, in some cases even for experienced physicians, and this can result in a dangerous diagnostic delay. A prompt diagnosis is usually followed by implementation of the appropriate therapy, which has a significant impact on the patient's prognosis. In addition, the natural history of SLE is characterized by episodes of relapse or flares intercalated with remissions, and the outcome is highly variable, ranging from sustained remission to death. In recent decades, both morbidity and mortality have been modified due to a number of possible reasons, including better knowledge of the pathogenetic mechanisms and prognostic factors of SLE, reduction of the time elapsing from disease onset to diagnosis, and the use of immunosuppressive regimens [12-14].

For these reasons, in view of the importance of assessing the clinical and serologic profile of SLE patients at the start of their disease, we focused our attention on an inception cohort of lupus patients with a short disease duration (less than 12 months) from nine Italian centers.

In our cohort, only 31.1% of patients presented with the typical malar rash at the onset. On the contrary, the majority of patients presented with non-specific symptoms such as arthritis and constitutional symptoms, e.g., fever (about 50%). This could make the early diagnosis of SLE more difficult. On the other hand, the relatively high proportion of musculoskeletal manifestations at SLE onset suggests that a prompt referral of such patients to the rheumatologist could significantly reduce delay of the correct diagnosis.

Recently, Nossent et al. [15] described the early disease course in a European multinational inception cohort of 200 SLE patients. Similar to us, they showed that arthritis was a predominant symptom at SLE onset, but in their patients leukopenia (54%) and malar rash (53%) were also more prevalent (as compared to 27.9% and 31.1%, respectively, in our study), suggesting that SLE phenotypes are susceptible to genetic and geographic influences.

Mean age at onset of symptoms was 35 years in our patients; when four or more of the ACR criteria of SLE were met, the mean age was 37 years. Therefore, the mean time between the first manifestations and the final classification of SLE was 2 years. The lag time between the onset and the diagnosis of SLE reported in major cohort studies was approximately 50 months before 1980 [16] and 25–26 months after 1980 [17]. The progressive decrease in time between disease onset and diagnosis is one of the major contributors to the improvement of survival and quality of life in SLE patients over time. However, additional efforts should be made to further improve the diagnostic procedures, which would help us make the diagnosis of SLE as early as possible.

Anti-dsDNA antibodies, the hallmark antibody for SLE diagnosis, were present at baseline in the large majority of patients (78%), representing the most frequent SLE-specific classification criterion. A similar high prevalence of anti-dsDNA antibodies was also seen in the Euro Lupus Project (78%) [13], far exceeding the 21% prevalence in the Caucasian patients in the LUMINA cohort [18]. Whether this reflects a difference in testing strategies or type of anti-DNA assays or a true difference in disease characteristics remains to be determined. The second most important serologic feature was hypocomplementemia in about 50% of patients. Low complement levels are much more prevalent in SLE than in other connective tissue and inflammatory joint diseases and, when combined with the presence of anti-dsDNA, will probably be highly specific for SLE as well, strongly suggesting the diagnosis.

When comparing the prevalence of the major clinical features and of the major immunologic features at the onset of the disease in our cohort to that reported in two large previous studies, the Early SLICC cohort [19] and the Euro Lupus project [20], it appears that hematologic manifestations, serositis

and nephritis are represented much less in the Euro-Lupus Project than in our cohort and the Early SLICC cohort, whereas mucosal ulcers are more frequent in the Early SLICC cohort. It is hard to explain these discrepancies, probably due to different enrolment criteria or to the different ethnic composition of the cohorts. Furthermore, whereas our study and the SLICC cohort included patients with recent disease onset, the Euro-Lupus study included consecutive lupus patients with no regard to disease onset and was performed during the last decade of the 1990s, 20 years earlier than the present study. It is possible that the higher frequency of nephropathy and hematologic disorders in our cohort reflects a better awareness of the disease and related problems today than in the past.

In conclusion, we have presented the preliminary results of a multicenter prospective study of a cohort of Italian patients affected by SLE at disease onset. We described the demographic and clinical characteristics obtained at patient enrolment, and compared these data with other reports of similar patients. Our work underlines the importance of an early diagnosis in SLE, both for the prognosis of lupus patients [21] and for obtaining new insights into the pathogenesis at an early disease stage [22].

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"Begin – to begin is half the work, let half still remain; again begin this, and thou wilt have finished"

Marcus Aurelius (1st century AD), Roman Emperor and one of the most important Stoic philosophers

"Sometimes laughter hurts, but humor and mockery are our only weapons"

Cabu (pen name of Jean Cabut) (1938-2015), French cartoonist and co-founder of Charlie Hebdo. He died in the January 2015 shooting attack on the Charlie Hebdo newspaper office