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EXPERT'S CORNER: A PERSONAL APPROACH

How I diagnose and treat lupus

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Introduction

Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease of unknown origin with a waxing and waning course and a significant morbi-mortality. The objective of this paper is to provide an SLE overview, as well as recommendations regarding diagnosis and therapeutic concepts. In the first stage of the disease, the combination of genetic, gender and environmental factors culminate in the formation of autoantibodies years before the onset of symptoms is observed. In the second phase, there are clinical manifestations and associations with comorbidities. Management of patients with SLE should be predictive, preventive, personalized, and participatory in order to achieve remission and prevent relapses. We can divide SLE into three categories according to the severity of the disease: mild, moderate, and severe. Corticosteroids are the mainstay of therapy, but the use of another agent is mandatory in order to reduce side effects. Some of the biological agents used in immunosuppressive therapy in SLE treatment include methotrexate, antimalarials, azathioprine, mycophenolate mofetil, cyclophosphamide, belimumab and rituximab.

Background

Diagnosing Systemic Lupus Erythematosus (SLE) has been a challenge over the years. The first reports of the disease only considered skin manifestations. Later, William Osler recognized the systemic involvement of the disease.[1] SLE is a multisystemic autoimmune disease of unknown origin.[2] SLE has an incidence of 1–10 per 100,000 person-years and a prevalence of 20–70 per 100,000 inhabitants.[3] SLE prevalence in Hispanics is 138.7–244.5 per 100,000 people.[4] For every 9–10 women with SLE, 1 male will be affected.[2] SLE has a waxing and waning course with significant morbidity that can be fatal – if not treated early – in some patients. A diagnosis of SLE should be considered when a patient has characteristic features of SLE associated with autoantibody formation[5]; thus, the presence of anti-nuclear antibodies (ANA) is considered necessary for an SLE diagnosis. Patients without ANA will have less than a 3% probability of developing the disease.

The objectives of this paper are to provide an overview based on the literature and on the personal experience of 30 years of treating patients with SLE, provide general and specific recommendations regarding the diagnosis of this challenging disease, and share therapeutic concepts that

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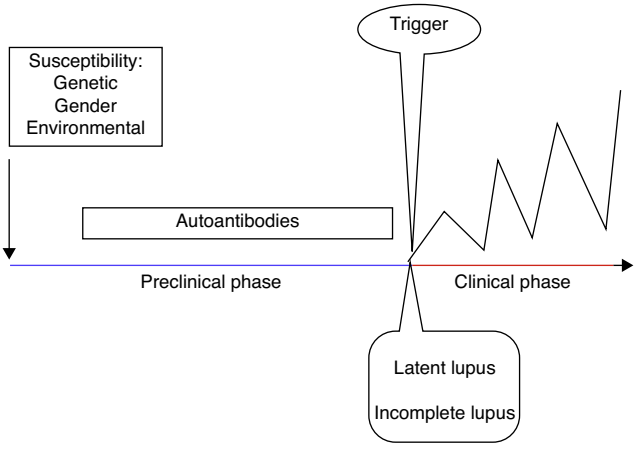

Figure 1 Proposed current stages for developing clinical manifestations of Systemic Lupus Erythematosus.

are fundamental for the comprehensive management of the disease.

SLE stages

SLE stages include a preclinical and a clinical phase, as well as its related comorbidities.

Clinical manifestations only develop in predisposed individuals and are secondary to a loss of tolerance with a subsequent immune dysregulation[6] (Fig. 1). The development of autoimmunity is determined by genetic, gender, and environmental factors. Advances in genetic techniques have identified more than 30 genetic associations with SLE including variants of HLA and Fcγ receptor genes, IRF5, STAT4, PTPN22, TNFAIP3, BLK, BANK1, TNFSF4 and ITGAM.[7] Moreover, the genetic contribution to the development of SLE has been observed in twins, with a concordance between monozygotic twins of 24–56% vs 2–5% in dizygotic twins.[8] Female preponderance in the pathogenesis of SLE has been demonstrated in transgenic mice. Smith-Bouvier et al. observed that mice with the XX chromosome were more susceptible to developing lupus when compared to XY mice.[9] Environmental factors can contribute to the development of SLE by the inhibition of DNA methylation.[10] These factors include drugs (e.g. procainamide), diet, smoking, UV light exposure and infections (Epstein–Barr virus).[11] Finally, there is a pathogenic autoantibody production in SLE patients, reflecting loss of tolerance.[6]

Different authors have described the development of autoantibodies before the clinical onset of the disease in the past. Arbuckle et al. described the presence of at least one SLE autoantibody before the diagnosis (up to 9.4 years earlier; mean, 3.3 years) in asymptomatic patients. Antinuclear, antiphospholipid, anti-Ro and anti-La antibodies preceded the other autoantibodies in this cohort of patients.[12] Subsequently, McClain et al. described the clinical significance of the presence of antiphospholipid antibodies prior to an SLE diagnosis, as well as the presence of these autoantibodies in patients with a more severe clinical outcome.[13]

In order to classify patients in the early stages of the disease, different authors have proposed definitions according to the symptoms and the presence of classification criteria. First, the term undifferentiated connective tissue disease (UCTD) is used in individuals with a disease manifestation suggestive but not diagnostic of a specific connective tissue disease. UCTD accounts for 10–20% of referred patients, 10–15% will fulfill the classification criteria for SLE 5 years later.[14] Factors that predict evolution to SLE are young age, alopecia, serositis, discoid lupus, a positive anti-human globulin (Coombs) test and anti-Sm or anti-DNA antibodies.[15]

Ganczarczyk et al. described the term ''latent lupus'' to define patients with features consistent with SLE which may or may not be a part of the American College of Rheumatology (ACR) classification criteria, but still are $\leq$4.[16]

Incomplete lupus refers to patients with less than four ACR classification criteria for SLE. Swaak et al. in a multicentric study, observed that only three of 122 incomplete lupus patients developed SLE during 3 years of follow-up, and suggested that incomplete SLE forms a subgroup with a good prognosis.[17] Later, Greer et al. confirmed this observation. They followed 38 incomplete lupus patients over 19 months and only two developed SLE.[18] An additional term is preclinical lupus, which defines individuals with increased genetic risk for the development of SLE but no clinical symptoms.[19]

After the preclinical stage, the clinical stage occurs with the onset of symptoms. The GLADEL (Grupo Latinoamericano de Estudio de Lupus) cohort, a multinational inception prospective cohort in Latin American centers, described the symptoms in 1214 patients with SLE. They found that arthralgia and/or arthritis, fever, photosensitivity, alopecia and malar rash were the most common symptoms at onset.[20]

Table 1 General recommendations for SLE* patients.

Balanced diet and exercise
Avoid substances and drugs that might induce lupus
No smoking
Vaccination schedule
Assessment of cardiovascular risk factors
Screening of cancer
Evaluation of reproductive health
Assessment of cognitive function

* Systemic lupus erythematosus.

SLE treatment

SLE management represents the ''P4'', a new paradigm of modern medicine. P4 Medicine stands for Predictive, Preventive, Personalized and Participatory Medicine.

SLE is a syndrome with high variability in the disease course as well as in the severity of the manifestations; therefore each SLE patient should be treated on an individualized basis in order to implement a proper treatment.[21] The goal of the treatment is to achieve remission, prevent flares and use of drugs with the minimum dose required to prevent long-term side effects. The treatment includes lifestyle modification, patient education, physical activity and medical or (in some cases) surgical intervention.

There are general recommendations that are given to SLE patients (Table 1). All patients should have a balanced diet and exercise regularly. Patients are advised to