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DIAGNOSIS AND MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract:

Introduction: *Systemic lupus erythematosus (SLE) is considered a chronic autoimmune disease that mainly affects females. It is recognized by a wide spectrum of clinical conditions, but, its course and organ involvement are unpredictable. Though over the last years an enhancement in survival for SLE patients has been found, pathogenic mechanisms causing this disease are under investigation. Comorbidities, due to both disease and treatment, as well as multiple aspects of SLE, are under intensive investigation. There are many reviews and studies on SLE focusing on pathogenesis, clinical and laboratory features, as well as current and new therapeutic strategies published over the last year.****Aim of work:*** *In this review, we will discuss Diagnosis and management of Systemic lupus erythematosus*

Methodology: *We did a systematic search for Diagnosis and management of Systemic lupus erythematosus using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *Systemic lupus erythematosus (SLE) is considered a chronic autoimmune disease that mainly affects females. It is recognized by a wide spectrum of clinical conditions, but, its course and organ involvement are unpredictable. Though over the last years an enhancement in survival for SLE patients has been found, pathogenic mechanisms causing this disease are under investigation. But a major knowledge in the SLE pathogenesis and consequently the implication of therapeutic strategies are still needed to better prevent and cure SLE.*

Key words: *Presentation, diagnosis, management, systemic lupus erythematosus*

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INTRODUCTION:

Systemic lupus erythematosus (SLE) is considered a chronic autoimmune disease that mainly affects females. It is recognized by a wide spectrum of clinical conditions, but, its course and organ involvement are unpredictable. Though over the last years an enhancement in survival for SLE patients has been found, pathogenic mechanisms causing this disease are under investigation. Comorbidities, due to both disease and treatment, as well as multiple aspects of SLE, are under intensive investigation. There are many reviews and studies on SLE focusing on pathogenesis, clinical and laboratory features, as well as current and new therapeutic strategies published over the last year.

In this review, we will discuss the most recent evidence regarding Diagnosis and management of Systemic lupus erythematosus

METHODOLOGY:

We did a systematic search for Diagnosis and management of Systemic lupus erythematosus using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.
The terms used in the search were: Presentation, diagnosis, management, systemic lupus erythematosus

Pathogenesis

Systemic lupus erythematosus (SLE) is considered a chronic autoimmune disease recognized by an abnormal autoimmune response to self-antigens that could virtually affect any organs and tissues. The effects of environmental factors in genetically predisposed individuals, result in the breaking of self-tolerance and to the activation of innate immune cells and autoreactive lymphocytes. New understandings of SLE pathogenesis have been provided by animal models of the disease.

Regarding the human counterpart, the recognition of genetic factors linked with to SLE susceptibility or to the development of specific autoantibodies or clinical feature is a topic under intense investigation briefly conclude the data published over the last year. As far as human leukocyte antigen (HLA) and linked genes are concerned, DRB3, DRB4 and DRB5 do not change the risk of developing SLE [1] while single nucleotide polymorphisms (SNPs) of CFB, MICB and MSH5 increase SLE susceptibility [2].

Biomarkers

Urinary biomarkers

The early correct diagnosis and assessment of disease activity and monitoring of disease flares in patients with LN continue to be a huge difficulty and great challenges because of the lack of reliable biomarkers with high sensitivity and specificity. Recently, several promising, non-invasive candidate biomarkers have been evaluated, but their utility in routine clinical practice has yet to be decided. Urinary biomarkers are attractive candidates since relatively easy to measure and reflecting the local pathophysiological changes. Urinary B cell activating factor (uBAFF) and proliferation-inducing ligand (uAPRIL) (that help activation, maintenance and plasma cell survival) and urinary osteoprotegerin (uOPG) levels are raised markedly in patients with proliferative lupus nephritis with respect to healthy controls and patients with active lupus without nephritis.

Autoantibodies

Many new studies have assessed the relationship of subgroups of autoantibodies with specific clinical features of SLE, with the goal of a better understanding of its pathogenesis and their

prognostic value. In a retrospective study on LN patients with a median follow-up period of 16.8 ± 9.4 months, Wang *et al.* concluded that the prevalence of p-ANCA is not uncommon, that more multisystem damage occurred in ANCA positive than in ANCA negative LN patients. But ANCA positive LN patients showed high scores on the pathological chronic index, outlining ANCA as an independent risk factor for poor renal outcomes in LN patients[3]. Two prospective studies have assessed the role of autoantibodies reactive to classic complement activation proteins and regulators of early complement activation. In the first, the combination of positive anti-C1q antibodies and low level of C3 had the highest reasonable predictive values for LN flare [4]. Contrariwise, in the second, comparing anti-C1q with anti- C3b IgG antibodies, these last seem to be more specific for LN [5].

Regarding the hardship in differential diagnosis, the detection of new biomarkers for NPSLE could be very helpful in clinical practice. Starting from previous reports on increasing serum levels of anti-microtubule-related protein 2 (MAP-2) antibodies in NPSLE patients, a new study established that these autoantibodies are highly specific for NPSLE, being also elevated in the cerebrospinal fluid[6].

Other serological markers

Bonciani *et al.* showed that homocysteine serum levels are much higher in patients with SLE than healthy controls and seem to correlate with active skin manifestations both in patients with SLE and cutaneous lupus erythematosus (CLE) [7]. A close association between the serum level of prolactin and SLE disease activity, and the titres of the ds-DNA antibody, IgM and IgG has been suggested. The frequency of programmed death ligand 1 (PD-L1)-expressing neutrophils was significantly elevated in SLE patients, especially in subjects with high SLEDAI score, and decrease during treatment: it has been believed that the increased level of PD-L1-expressing neutrophils may act as a negative feedback mechanism in response to excessive autoimmune response during disease activity in SLE patient [8].

Clinical manifestations

The disease has a broad spectrum of well-defined clinical manifestations. It has been mentioned that age of onset affects clinical and laboratory profile. Men gender is linked with a higher level of disease activity at the time of diagnosis independently of age or race/ethnicity and time to criteria accrual, however the clinical manifestation in the disease course does not seem to be strikingly different in both genders[9]. A cohort study showed that SLE patients display a higher death rate in comparison to the general population, and such rate is higher in man than in females.

Neuropsychiatric involvement

Understated NPSLE syndromes such as emotional disorders involving depression and anxiety are often considered as “non-NPSLE” when the patients have no history of “neuropsychiatric disorders” and normal conventional brain MRI scans. Bai *et al.* concluded that depression and anxiety were very common in “non-NPSLE,” and they were significant risk factors of each other. Depression was linked with disease activity, anxiety with negative anti-P0 antibody, while both were associated with proteinuria and higher cumulative dosage of HCQ [10]. These symptoms revealed higher prevalence in SLE females compared to SLE males and control females, with a negative effect on the quality of life in both genders. In the women patients a correlation between depressive/ anxiety symptoms and unemployment, and the use of higher doses of corticosteroids was observe [11]. Age, disease activity, anxiety and depression were markedly determinants of sleep quality, impairing the health-related (HR) QoL. Especially, anxiety was linked to some of the sleep quality components, including sleep latency, sleep disturbance and overall sleep quality, while depression was related to sleep efficiency, need for sleep medications and daytime dysfunction [12].

Patients with insomnia symptoms had increased perceived stress, less effective coping strategies, and higher rates of psychiatric symptoms, particularly depression, in comparison to SLE patients with no insomnia symptoms. Moreover, these patients revealed more often a renal involvement reflecting a greater degree of disease severity in SLE patients [13]. SLE patients with headaches, especially those with migraine, were found to have less cerebral grey matter (GM) and larger white matter (WM) volumes compared to SLE patients without headaches. But, headaches were not linked with the presence of neuronal anti-NR2 and anti-P antibodies [14].

Renal involvement

LN is well established to be one of the most dangerous complications of SLE and it is the main predictor of poor prognosis. The presence of autoantibodies directed against several cytoplasmic (ANCA) has a very critical role in the pathogenesis of LN. Multisystem damage and higher frequency of

antinucleosome antibodies, antihistone antibodies, antimitochondrial M2 antibodies, and anticardiolipin antibodies happened in ANCA-positive LN patients compared to ANCA-negative.

Furthermore, ANCA-positive LN patients showed high scores on the pathological chronic renal index and had poor renal outcomes [15]. In an international multi- ethnic/racial observational cohort of newly diagnosed SLE patients, LN occurred in 38.3% of subjects, frequently as the initial presentation with a poor prognosis in terms of end-stage renal disease (ESRD). SLE ESRD patients with anti-phospholipid antibodies (aPL)/lupus anticoagulant (LA) had higher all-cause mortality risk than SLE ESRD patients without these antibodies, while the effects of aPL/LA on mortality were comparable among non-SLE ESRD patients.

Gastrointestinal involvement

Intestinal pseudo obstruction (IPO), earlier was thought to be a rare complication of SLE, may occur as initial presentation of SLE, thus leading to difficult diagnosis and delayed care. It frequently occurs together with pyeloureterectasis or megacholedochus due to vasculitis of the visceral smooth muscles, which implies poor prognosis. Moreover, the incidence of IPO is related to the activity of SLE disease [16].

Pulmonary involvement

Pérez-Peñate *et al.* conducted a prospective study using an algorithm based on pulmonary arterial hypertension (PAH) predictors such as dyspnea, DLCO, and N-terminal pro–brain natriuretic peptide (NT-proBNP). The study concluded these last predictor factors of pulmonary hypertension (PH) and PAH and SLE-PAH low prevalence [17]. Pericardial effusion and positive anti-RNP antibody have been recognized as risk factors for PAH in SLE, however long SLE disease duration, the presence of interstitial lung disease, without acute skin rash, positive anti-SSA antibody, low SLEDAI and ESR, and high uric acid levels were also associated.

Nail and nailfold involvement

There is a great types of nail abnormalities in SLE patients and also a great variety of nailfold videocapillaroscopy (NVC) abnormalities, similarly early scleroderma pattern. Higuera *et al.* found NVC abnormalities in 43,8% of the nail distrophy (ND) patients and in 13.8% of the patients without ND.

Haematological manifestations

The severity of thrombocytopenia can be a helpful independent prognostic factor to measure the survival as also the response to treatment.

Treatment

Phase III and post-marketing trials (real-life registers)

In 2016, data were published on the use of new medications in SLE and a new knowledge on traditional drugs has been achieved; for the latter, international initiatives and registries gave a major contribution, particularly in recently diagnosed patients [18].

As far as biological medication are into consideration, some interesting data were published on belimumab establishing their effectiveness on several clinical outcomes. In a *post-hoc* analysis on 966 patients on GC at study entry in 2 randomized clinical trials of belimumab in SLE, a markedly smaller elevation in cumulative corticosteroid dose over 1 year and a marked decreases in oral GC dose, in the belimumab group compared with the placebo group were found, thus proposing a GC-sparing effect of the drug[19].

In 2016, new data from real life were released for Rituximab from the international Registry for Biologics in SLE; It is estimated that the off-label use of Rituximab resulted limited to one percent of SLE patients and refractory renal, musculoskeletal and blood disorders manifestations were the main indications.

In 2016, new drug development failures were also reported. In the phase III trial on 1164 SLE patients with moderate- to severe disease activity (ILLUMINATE- 1), subcutaneous injections of tabalumab (a monoclonal antibody that neutralises membrane and soluble B-cell activating factor) failed to show clinical superiority over placebo despite the conclusion of biological activity in inducing changes in anti-dsDNA, complement, B cells and immunoglobulins levels. In the other phase III trial (ILLUMINATE-2) the primary end-point was achieved by the dosage of 120 mg every 2 weeks but key secondary end-points were not met.

CONCLUSIONS:

Systemic lupus erythematosus (SLE) is considered a chronic autoimmune disease that mainly affects females. It is recognized by a wide spectrum of clinical conditions, but, its course and organ involvement are unpredictable. Though over the last years an enhancement in survival for SLE patients has been found, pathogenic mechanisms causing this

disease are under investigation. But a major knowledge in the SLE pathogenesis and consequently the implication of therapeutic strategies are still needed to better prevent and cure SLE.

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