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# SYSTEMIC LUPUS ERYTHEMATOSUS: UPDATE ON THE DIAGNOSIS, PREVALENCE, CLINICAL MANAGEMENT, INFLAMMATORY MARKERS, NEW HORIZONS IN THE PATHOGENESIS, MANIFESTATIONS AND PROGRESS IN TREATMENT

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## SUMMARY

***Introduction:*** *Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystem involvement, generating chronic inflammation and damage of more than one organ. It is usually clinically and serologically diagnosed with the presence of autoantibodies. "Lupus" is a Latin term meaning "wolf", due to the fact that the typical facial eruptions of the pathology are very similar to the bite marks of a wolf.*

***Objective:*** *to detail the current information related to systemic lupus erythematosus, description, etiology, epidemiology, pathophysiology, histology, classification, clinical manifestations, treatment and differential diagnosis.*

***Methodology:*** *a total of 45 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 35 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: lupus, SLE, autoimmune, multisystemic.*

***Results:*** *Familial segregation and high concordance rates in identical twins strongly suggest a genetic contribution to SLE, however there is no obvious pattern of inheritance. Females have 10 times the risk of developing SLE compared to males. Lupus in males is less common but has a propensity to be more severe. About 80 to 90% of individuals with SLE show musculoskeletal involvement in the*

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*course of the disease, ranging from mild arthralgias to deforming arthritis. Avascular necrosis with or without the use of steroids may occur in 10% of individuals with SLE and is most often bilateral and affects the hip joints.*

***Conclusions:*** *systemic lupus erythematosus presents a wide range of clinical and histopathologic manifestations. Adequate education of affected individuals with systemic lupus erythematosus about the possible clinical manifestations can lead to early recognition and intervention, which may prevent potential significant organ damage. The role of markers and autoantibodies in the differential diagnosis of the pathology is essential. Treatment of SLE is aimed at preventing organ damage and achieving remission. The choice of treatment will depend on the altered organ system(s) and the extent of the involvement. Education of the affected individual, physical measures, lifestyle and emotional support play an important role in the comprehensive treatment of SLE.*

**KEY WORDS:** *lupus, SLE, autoimmune, manifestations, treatment.*

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystem involvement, generating chronic inflammation and damage of more than one organ. It is usually clinically and serologically diagnosed with the presence of autoantibodies. "Lupus" is a Latin term meaning "wolf", due to the fact that the typical facial eruptions of the pathology are very similar to the bite marks of a wolf. The pathology presents multiple phenotypes, with different clinical manifestations, ranging from minor mucocutaneous presentations to multi-organ and major central nervous system involvement. Different immunopathological pathways play a role in the pathogenesis of SLE. Many pathogenic autoantibodies are known, however, the exact pathogenesis is still not well understood. The diagnosis of systemic lupus erythematosus can be challenging and although there are several categorization schemes and criteria, its usefulness clinically is a matter of debate. The treatment of SLE is performed according to its affection in the organ systems. At the moment there are multiple agents that have proven to be effective in the treatment of SLE, but it still presents a significant risk of morbidity and mortality in affected individuals(1-3).

## METHODOLOGY

A total of 45 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 35 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: lupus, SLE, autoimmune, multisystemic.

The choice of bibliography exposes elements related to systemic lupus erythematosus, description, etiology, epidemiology, pathophysiology, histology, classification, clinical manifestations, treatment and differential diagnosis.

## DEVELOPMENT

### Description and Etiology

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease of wide clinical heterogeneity and significant potential for morbidity and mortality. At the moment of unknown etiology, however, it presents multiple immunological, endocrine, genetic and environmental factors important in its etiopathogenesis(4).

Familial segregation and high concordance rates in identical twins strongly suggest a genetic contribution in SLE, however there is no obvious pattern of inheritance. Concordance rates between identical twins of about 50% have been reported, as well as more than 100 gene loci with polymorphisms related to polygenic SLE (and more than 30 genes have been shown to give rise to monogenic forms of SLE or SLE-like phenotype. These genes are related to the activation of the immune system in response to foreign antigens, the activation of the innate and adaptive immune systems, as well as the generation of autoantigens. Among other infrequent genetic mutations, however, considered at very high risk for the development of SLE are deficiencies of early complement components with a greater than 90% risk C1q, C1r, C1s, with a 50% risk C4, with a 20% risk C2 and TREX1. Some of the other associated genes are TNFAIP3, STAT-4, STAT-1, TLR-7, HLA-DRB1, HLA-DR2, HLA-DR3, HLA-DRX, IRAK1/MECP2, IRF5-TNPO3, ITGAM, among others. Usually the most frequent genetic predisposition is in the major histocompatibility locus (MHC), which includes genes for antigen presenting molecules.

There are studies which report that women have 10 times more risk of developing SLE compared to men, and the risk of SLE increases 14 times in Klinefelter syndrome 47, XXY, presenting a possible association with genes of the X chromosome. However, the specific genes have not yet been validated(1,5).

Being female, in addition to hormonal influence are notable risk factors for lupus erythematosus, because estrogen triggers CD8+ and CD4+ T cells, macrophages, B cells, thymocytes, the release of some specific cytokines such as IL-1, HLA expression and endothelial cell adhesion molecules such as ICAM and VCAM. Also, estrogens and prolactin stimulate autoimmunity, increase the manufacture of B-cell activating factor and modulate the activation of lymphocytes and plasmacytoid dendritic cells (pDC). Use of estrogen-containing contraceptives as well as postmenopausal hormone replacement therapy sometimes lead to flares in individuals with Lupus erythematosus. There are multiple environmental triggers of SLE, as well as many drugs that generate a lupus-like phenomenon by demethylating DNA and altering self-antigens. Ultraviolet rays and sun exposure also generate increased cell apoptosis and are triggers for SLE. In addition, multiple viral infections have been implicated and molecular mimicry is thought to be the underlying mechanism.

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Other probable risk factors include alfalfa sprouts, silica exposure, vitamin D deficiency, canavanine-containing foods, and other viral infections(1,6,7).

**Epidemiology**

Multiple prevalence and incidence rates of SLE have been reported and vary according to population differences. Studies show prevalences of 72.1 to 74.4 per 100,000 persons and incidence rates of 5.6 per 100,000 persons/year in mostly Caucasian and African-American populations. African Americans have higher rates, and the disease is more prevalent in Asian and Hispanic populations compared to Caucasians. The pathology usually presents at a younger age and is more prominent in African Americans. SLE occurs more commonly in African Americans and Asians compared to whites. Although lupus nephritis is more common in Asians than in Whites, the 10-year outcome and survival rate is seen to be more favorable in Asians(8-10).

Approximate SLE rates are between 24% and 56% in monozygotic twins, whereas in dizygotic twins the rate is about 2% to 4%(11).

SLE predominantly affects women of childbearing age, with a female to male ratio of 9 to 1 according to some literature and 10 to 1 in others. However, the risk decreases after menopause, but remains twice as high compared to men. Several clinical trials and some meta-analyses have shown that lupus in males is less frequent but has a propensity to be more severe. Also, male individuals are more likely to present with cytopenias, neurological involvement, thrombosis, renal disease, serositis, skin manifestations, cardiovascular disease, hypertension and vasculitis than females. Age plays an important role in SLE and although the pathology is more common in women of childbearing age, it has also been reported in the pediatric and elderly population. Systemic lupus erythematosus is more severe in children compared to adults, usually manifesting with malar rash, hematologic abnormalities, nephritis, pericarditis and hepatosplenomegaly. However, they have a more insidious onset in older people, showing more pulmonary involvement, serositis and less malar rash, Raynaud's syndrome, nephritis and neuropsychiatric complications(1).

**Pathophysiology**

The pathogenesis of systemic lupus erythematosus is complex and its understanding is advancing periodically. A breakdown of tolerance in genetically susceptible individuals to exposure to environmental factors leads to activation of autoimmunity. Cellular damage originating from infectious and other environmental factors exposes the immune system to autoantigens leading to activation of T and B cells, which become self-sustained by a chronic self-directed immune response. Complement activation, cytokine release and autoantibody manufacture result in organ damage.

Both the innate and adaptive immune systems play a specific role in the pathogenesis of SLE. Activation of the innate immune system is Toll-like receptor (TLR) dependent or independent. These cell membrane-bound TLRs (TLR 2, 4, 6) are activated upon exposure to extracellular DNA and RNA from decaying cells, leading to subsequent activation of the interferon regulatory family IRF-3, NF-κB and MAP.Which are kinases, acting as transcription factors for the manufacture of proinflammatory mediators such as IFN-b. In contrast, endosomal TLRs (TLR 7, 9) are activated by single-stranded RNA and demethylated DNA, leading to the generation of interferon alpha and RNA-binding autoantibodies, such as antibodies against Ro La, Sm and RNP. The TLR-independent pathway is activated by intracytoplasmic RNA sensors (RIG-1, MDA-5) and DNA sensors (IFI16, DAI) leading to activation of IRF3 and NF-κB. Both self DNA/RNA and foreign DNA/RNA, such as from viruses, can generate this activation. NETosis, a term used to describe the sequence of cellular events that led to the active release of TEN has recently gained attention in the pathogenesis of SLE. Following activation by multiple factors such as activated platelets, cytokines and vascular endothelial cells, neutrophils systematically release their nuclear aggregates extracellularly, which can subsequently stimulate the manufacture of interferon alpha by dendritic cells, mediate thrombosis and vascular damage, as well as being autoantigens for T lymphocytes.

T lymphocytes and B lymphocytes also play a notable role in the pathogenesis of SLE. Antigens derived from apoptotic and damaged cells are presented to T cells via antigen presenting cells. T cells in SLE show distorted gene expression leading to the generation of multiple cytokines. These T cells make less IL-2, leading to altered regulatory T cell production. Increased IL-6, IL-10, IL-12 and IL-23 upregulate mononuclear cell production, while increased IL-17 and IL-21 lead to more T-cell production. Increased Interferon-γ leads to defective T-cell manufacture. T cells lead to activation of autoreactive B cells by elaboration of CD40L and cytokines, resulting in autoantibodies. Toll-like receptors, interacting with DNA and RNA, produce activation of these B cells, as well as intranuclear complexes presenting nucleic acid and proteins are the most notable antigens leading to B cell activation.All these autoantibodies are pathogenic and cause organ damage by deposition of immune complexes, complement and neutrophil activation, modifying cell function, as well as generating apoptosis and cytokine production. In addition to that, autoreactive B cells in SLE, stimulated by autoantigens, are not eliminated simply because of a deficiency of the process involved in the functional neutralization of autoreactive B cells. In addition, B cells can be used as antigen-presenting cells by successfully activating T cells by presenting internalized soluble antigens to T cells, forming a circuit in which B and T cells activate each other, resulting in further autoimmunity(12-16).

**Histopathology**

Tissue pathology in SLE can present with a variety of aberrant immunologic mechanisms, including immune complexing, autoantibody generation, and immunologically mediated tissue injury. The LE body or hematoxylin body is a characteristic hallmark of SLE pathology, usually seen in the lungs, heart,

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lymph nodes, kidneys, spleen, serous and synovial membranes. The pathology of skin lesions in SLE allows to observe the generation of immune complexes that perform tissue damage, vascular and perivascular inflammation and chronic infiltration of mononuclear cells. Edema and erythrocyte extravasation can be seen in all SLE lesions. Immunofluorescence reveals deposition of immunoglobulins IgG, IgA and IgM and complement components along the dermal-epidermal junction. Vasculitis is common in SLE and vascular lesions may demonstrate various pathologies. In SLE, central nervous system pathology shows intracranial small vessel involvement with thrombotic lesions with or without perivascular inflammation and endothelial proliferation. Infrequently, necrotizing vasculitis is shown, in addition to having evidenced thromboembolism due to Libman-Sacks endocarditis.

Valvular involvement leads to Libman-Sacks endocarditis, which is a sterile warty endocarditis, affecting the mitral valve usually with vegetations. The pathology shows necrotic cell debris, protein deposits, platelet thrombi and mononuclear cells. Pericarditis with fibrinous exudate is frequent showing fibrinoid necrosis and perivascular infiltration of mononuclear cells. Lymphadenopathy shows plasma cell infiltration of interfollicular areas, necrosis of paracortical T-cell areas and follicular hyperplasia with giant cells. Splenomegaly presents an onion skin lesion with multiple concentric rings of perivascular collagen.

Individuals with lupus pneumonitis present interstitial pneumonitis, alveolar wall lesion, alveolitis, edema and hemorrhage. Lupus nephritis can attack glomeruli, tubules, interstitium and vessels with immune complex deposition.

There are 6 classes of lupus nephritis, each with unique pathologic features, which has given a different treatment point for each class, so it is crucial to know the World Health Organization classification criteria for lupus nephritis prior to treatment.
Class I: minimal mesangial lupus nephritis.
Class II: mesangial proliferative lupus nephritis.
Class III: focal lupus nephritis.
Class IV: diffuse segmental or diffuse global lupus nephritis.
Class V: membranous lupus nephritis.
Class VI: advanced sclerosing lupus nephritis(1,17,18).

**Clinical Manifestations**
SLE is a multisystem disease with multiple phenotypes. The clinical features may differ from an extremely mild disease with mucocutaneous involvement only to a major, life-threatening disease with multisystem involvement. All organ systems can be altered in SLE. Sometimes an autoantibody profile can help predict disease progression. Some investigations found serologic abnormalities prior to clinical onset of the disease, which was called preclinical lupus or more specifically called when the affected individual presents serologic abnormalities compatible with SLE and some clinical features without SLE criteria.

Constitutional symptoms: constitutional symptoms are present in about 90% of individuals with SLE. General malaise, fever, fatigue, weight loss and anorexia are common. A little more than 40% of those affected with the disease may present with a lupus flare as a cause of fever, however it is important to rule out infections first.

**Mucocutaneous Manifestations:** more than 80% of individuals affected with SLE have mucocutaneous involvement, these are usually specific to lupus:

- Subacute cutaneous lupus erythematosus (SCLE): includes annular and papulosquamous, the rash of which is a photosensitive, generalized, non-scarring and non-indurated eruption. Sometimes it can be papulosquamous similar to psoriasis or an annular/polycystic lesion with central clearing and peripheral desquamation. SCLE lesions may remain for many months, however they usually recover without scarring. The rash is seen in individuals with a positive anti-Ro antibody (SSA) up to 90% of the time. It can also be caused by some drugs such as hydrochlorothiazide and is common in individuals with Sjogren's syndrome and rheumatoid arthritis.
- Acute cutaneous lupus erythematosus (ACLE): includes localized, malar and generalized lupus, the characteristic lesion is the malar rash or butterfly rash, a raised, pruritic erythematous rash affecting the cheeks and bridge of the nose. The rash may be macular or papular and respects the nasolabial folds. It usually has an acute onset, however, it may occur over many weeks and give induration and desquamation. The malar rash may fluctuate with lupus disease activity. In addition other eruptions at this location that can be differentiated are seborrheic dermatitis, rosacea, erysipelas and perioral dermatitis. Acute generalized cutaneous lupus erythematosus leads to a generalized maculopapular or macular rash with a photosensitive pattern.
- Chronic cutaneous lupus erythematosus erythematosus (CCLE): which includes classical discoid lupus erythematosus (CDLE), being the most common form of chronic cutaneous lupus erythematosus (CCLE). It may present with or without SLE and may be localized or generalized. The changes are erythematous disc-like papules or plaques with adherent scaling and central clearing. SLE heals with scarring and is associated with permanent alopecia when found on the scalp. Mucosal lesions are seen in the oral cavity as painful round erythematous lesions with radiating white hyperkeratotic striae.
- Hypertrophic-verrucous: histologically similar to squamous cell carcinoma.
- Mucoid discoid lupus.
- Discoid lichenoid lupus.
- Deep lupus lupus panniculitis: it can occur above the waist and is less likely to be related to SLE. The

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alterations generate depressed surfaces and when related to overlying SCI lesions, it is called deep lupus.
- Lupus tumidus: smooth, erythematous and edematous plaques, without epidermal involvement.
- Lupus chilblains: painful erythematous plaques on the fingers and toes.

Oral and nasal ulcers are frequent in SLE and are usually painless, appearing as erythema of gradual onset, macula, petechiae, erosions or ulcers. They are usually seen more on the buccal mucosa, hard palate and vermilion border. Photosensitivity is seen in more than 90%, characterized by an abnormal skin reaction to ultraviolet A/B and visible light exposure, systemic symptoms worsen with sun exposure.

In addition, other non-specific cutaneous manifestations may be seen such as: acanthosis nigricans, cutaneous calcinosis, vasculopathy (livedo reticularis, superficial thrombophlebitis, Raynaud's phenomenon, erythromelalgia, periungual telangiectasia), cutaneous vasculitis (leukocytoclastic or urticaria), rheumatoid nodules, lichen planus, urticaria, erythema multiforme, sclerodactyly, blistering lesions and ulcers on the lower extremities.

**Musculoskeletal Manifestations:** about 80 to 90% of individuals with SLE show musculoskeletal involvement in the evolution of the pathology, ranging from mild arthralgias to deforming arthritis. Lupus arthritis usually presents as a symmetrical, non-erosive inflammatory polyarthritis that mostly affects the small joints of the wrists, hands and knees; however, any joint can be affected. Jaccoud's arthropathy is due to laxity of the joint capsule and ligaments, generating non-erosive deformities of the hands, as well as ulnar deviation and subluxation of the metacarpophalangeal joints that come to resemble rheumatoid arthritis. Avascular necrosis with or without steroid use may occur in 10% of individuals with SLE and is most often bilateral and affects the hip joints. About 10% of individuals with SLE present with inflammatory myopathy with similar histopathologic manifestations. Individuals with SLE are at high risk for fibromyalgia. There are multiple studies showing a wide range of musculoskeletal involvement in the feet of patients with SLE, presenting in addition to arthralgias, deforming arthropathy, deformities of the lesser toes, hallux limitus/rigidus and hallux valgus, the latter being the valgus deviation of the first orthotic with a varus deviation of the first metatarsal(19,20).

**Cardiovascular Manifestations:** SLE can involve any layer of the heart, including the pericardium, myocardium, endocardium, and even the coronary arteries. Pericarditis associated with exudative pericardial effusions is the most common cardiac feature. Cardiac tamponade is rare, as well as myocarditis and is linked to anti-Ro antibodies (SSA). Hydroxychloroquine-associated cardiomyopathy must be ruled out. Valvular abnormalities, including Libman-Sacks endocarditis affecting the mitral valve, are common and may be associated with antiphospholipid antibody syndrome. Individuals with SLE are at high risk for coronary artery disease due to coronary vasculitis or generalized atherosclerosis.

**Hematologic And Reticuloendothelial Manifestations:** anemia is seen in more than 50% of individuals with SLE and is most often an anemia of chronic disease. Other origins of anemia in this pathology are usually Coomb's positive autoimmune hemolytic anemia, red cell aplasia, iron deficiency anemia and microangiopathic hemolytic anemia, and can be correlated with antiphospholipid antibody syndrome. Leukopenia secondary to neutropenia or lymphopenia is common. Thrombocytopenia may be linked to antiphospholipid antibody syndrome and autoantibodies against platelets, glycoprotein IIb/IIIa or thrombopoietin receptor. Pancytopenia is also common and is associated with myelofibrosis. Splenomegaly is frequent, however, there are reports of splenic atrophy and asplenism.

**Neuropsychiatric Manifestations: T**he central nervous system (CNS) and peripheral nervous system (PNS) may be involved in SLE, as well as psychiatric manifestations. The most common CNS manifestation is headaches, but there may be focal or generalized seizures, aseptic meningitis, demyelinating syndrome, movement disorders such as chorea, cognitive dysfunction and ischemic strokes. Strokes are 1.5 to 3 times more frequent in patients with systemic lupus erythematosus, with a 3 times higher risk of ischemic stroke and 3 times higher risk of hemorrhagic stroke. Peripheral nervous system manifestations include cranial and peripheral neuropathies, mononeuritis multiplex, autonomic neuropathies and syndromes mimicking Guillain-Barré syndrome and myasthenia gravis. Psychiatric manifestations are complex to diagnose and manage and may present as depression, anxiety and sometimes even frank psychosis(21).

**Renal Manifestations:** lupus nephritis is a frequent complication. The involvement can range from mild subnephrotic proteinuria to diffuse progressive glomerulonephritis leading to chronic renal damage. Lupus nephritis usually shows early in the course of the pathology. Hematuria, proteinuria, new onset hypertension, lower extremity edema and increased creatinine suggest lupus nephritis. Biopsy is essential to stage lupus nephritis, as well as to rule out other probable pathologies. The results of the biopsy determine the management of lupus nephritis. The prognosis is different according to each class, with an excellent prognosis for classes I and II and a poor prognosis for classes III and IV. Class V presents a favorable prognosis, except for the complications of the nephritis syndrome. Some other renal manifestations are thrombotic microangiopathy, vasculitis, interstitial nephritis, lupus vasculopathy and arteriolosclerosis. The most important mission of the treatment of lupus nephritis is the normalization of renal function or at least the prevention of progressive deterioration of renal function.

**Pulmonary Manifestations:** pleuritis is the most frequent pulmonary manifestation and is not always related to pleural effusion. Acute lupus pneumonitis with bilateral pulmonary

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infiltrates, pulmonary arterial hypertension, exudative pleural effusion, shrinking lung syndrome, interstitial lung disease such as nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP), diffuse alveolar hemorrhage associated with capillaritis and pulmonary embolism may also occur.

**Gastrointestinal Manifestations:** anywhere in the gastrointestinal tract can be compromised by SLE. Dysphagia is usually the most common manifestation and is related to heartburn, retrosternal pain, odynophagia or regurgitation. The origin is due to gastroesophageal reflux motility disorder, gastroesophageal reflux disease or pill esophagitis. Affected individuals may present with peptic ulcer, which debuts as epigastric pain, in addition to early satiety. A differential diagnosis should be made with other pathologies that may present the same symptomatology. In addition to esophageal dysmotility, mesenteric vasculitis, lupus enteritis, peritonitis and ascites, protein-losing enteropathy, pancreatitis and lupoid hepatitis can be observed. Individuals with SLE and antiphospholipid antibody syndrome may show thrombosis of mesenteric vessels, hepatic veno-occlusive disease and Budd-Chiari syndrome(21).

In pregnancy: women with SLE with positive antiphospholipid antibodies are at high risk of preeclampsia, maternal thrombosis, miscarriages and fetal loss. Anti-Ro (SSA) and anti-La (SSB) antibodies can cross the placenta and generate fetal heart block and neonatal lupus manifested with cytopenias, transaminitis and photosensitive rash.

**Other Manifestations:** ocular involvement is common such as keratoconjunctivitis sicca, uveitis, scleritis, retinal vasculitis, optic neuritis, peripheral ulcerative keratitis and episcleritis, in addition to drug-induced ocular damage. Ear involvement may give sudden sensorineural hearing loss. Adrenal infarction secondary to thrombosis of the adrenal vessels may also be present in individuals with antiphospholipid antibody syndrome and systemic lupus erythematosus(1,22-26).

**Classification Criteria**

The American College of Rheumatology (ACR) created the SLE classification criteria in 1971 and they were revised years later. The 1997 ACR criteria required 4 of 11 criteria for SLE categorization, including malar erythema, discoid rash, photosensitivity, oral/nasal ulcers, arthritis, serositis, renal disease, hematologic disease, neurologic disease, immunologic criteria, and antinuclear antibody positivity. The Systemic Lupus International Collaborative Clinics (SLICC) criteria made modifications, needing at least one of the four criteria to be clinical and at least one of the four criteria to be immunologic, as well as individuals with biopsy-proven nephritis and positive ANA or double-stranded anti-DNA could be placed directly as SLE even in the absence of other criteria. In 2019, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) presented new criteria for the classification of SLE(27,28).

**Evaluation**

SLE is diagnosed based on a set of signs, symptoms and appropriate laboratory tests, imaging and histopathology play an important role. Antinuclear antibodies (ANA) are the essential feature of the disease and will be the initial test to be performed, immunofluorescence is considered the gold standard test for ANA. A positive ANA is observed in more than 97% of SLE cases, having a specificity of only 20%, therefore, a positive ANA does not confirm the diagnosis of SLE, however a negative ANA makes it significantly less likely(1,29).

Other disorders associated with a positive ANA include drug-induced lupus, mixed connective tissue disease, Sjogren's syndrome, cutaneous lupus, rheumatoid arthritis, juvenile idiopathic arthritis, systemic sclerosis, polymyositis/dermatomyositis, Raynaud's disease, fibromyalgia, autoimmune hepatitis, multiple sclerosis, Hashimoto's thyroiditis, idiopathic thrombocytopenic purpura, as well as some infections and malignancies.

Antibodies against deoxyribonucleic acid (DNA) can be classified into those that react with denatured single-stranded (ss) DNA and those that identify native, double-stranded (ds) DNA. Especially, anti-ssDNA antibodies are considered non-specific and can be observed as a laboratory alteration or in the healthy population. Anti-double-stranded deoxyribonucleic acid (bsDNA) antibodies have more than 95% specificity for SLE, however they are only present in 60% to 70% of individuals with SLE. Anti-dDNA antibodies can be seen in drug-induced lupus. In SLE, anti-dsDNA antibodies can be linked to disease activity and the development of lupus nephritis.

Anti-Ro (SSA) and anti-La (SSB) antibodies target ribonucleoprotein particles, these are seen in up to 90% of cases of Sjogren's syndrome, they are also seen in SLE with anti-Ro in up to 50% and anti-La in up to 20% frequency.

Anti-Smith antibodies are seen in less than 30% of SLE patients, but have a specificity of 99% for SLE. These are often associated with anti-U1-RNP antibodies, which are present in up to 30% of SLE patients.

Anti-histone antibodies are not specific for drug-induced lupus and can be seen in 50% to 70% of SLE patients.

Anti-ribosomal-P antibodies are very specific for SLE, however their prevalence in SLE is less than 5% and can be linked to neuropsychiatric manifestations of SLE.

Anti-centromere and anti-topoisomerase-I (SCL70) antibodies are seen in systemic sclerosis and infrequently in SLE. Individuals with SLE may also have antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-beta-2-glycoprotein I antibodies).

C3 and C4 complements should be evaluated, low complement levels indicate complement consumption and are related to disease activity. Inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate may be elevated. Complete

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blood counts, liver and kidney function tests, urinalysis and urine protein quantification should be performed. X-rays of the joints may show periarticular osteopenia, deformities or subluxation. In addition, a renal biopsy should be performed if lupus nephritis is suspected(30,31).

**Treatment**

The treatment of SLE is aimed at preventing organ damage and achieving remission. The choice of treatment will depend on the organ system(s) involved and the extent of the involvement. Treatment may vary from minimal treatment with NSAIDs and antimalarials to intensive treatment with cytotoxic drugs and corticosteroids. Education of the affected individual, physical measures, lifestyle and emotional support play an important role in the comprehensive treatment of SLE. Photoprotection is of utmost importance, as well as smoking cessation because it can worsen the symptoms of SLE. Dietary recommendations are to avoid alfalfa sprouts and echinacea and to include a vitamin D-rich diet.

**Cutaneous Manifestations:** if mild, can be managed with topical corticosteroids or topical calcineurin inhibitors such as tacrolimus. Hydroxychloroquine is the drug of choice for most cutaneous manifestations and is effective. Quinacrine can be used in contraindication to hydroxychloroquine, as well as methotrexate in case of no response. When the pathology is important or resistant, systemic corticosteroids, mycophenolate mofetil and belimumab can be used. Other alternatives include IVIG, dapsone, azathioprine, thalidomide, cyclophosphamide and rituximab.

**Musculoskeletal Manifestations:** hydroxychloroquine is the treatment of choice for lupus arthritis; if it does not work, methotrexate or leflunomide may be chosen, and when there is refractoriness, belimumab and rituximab may be considered.
Hematologic manifestations: mild cytopenias do not require treatment, moderate to severe cytopenias require corticosteroids as well as azathioprine or cyclosporine-A as steroid sparing agents. Severe refractory cytopenias may require steroids in pulsed intravenous doses, as well as cyclophosphamide, plasmapheresis, mycophenolate mofetil, rituximab, recombinant G-CSF or splenectomy.

**Cardiopulmonary Manifestations:** serositis usually responds to NSAIDs or oral corticosteroids in moderate to high doses. Acute lupus pneumonitis requires high doses of corticosteroids in intravenous pulses. Plasmapheresis and/or cyclophosphamide is sometimes needed. Interstitial lung disease is managed with corticosteroids as well as immunosuppressive agents such as azathioprine or mycophenolate mofetil. Pulmonary arterial hypertension needs vasodilator therapy and thrombotic complications need anticoagulation. High-dose corticosteroids control myocarditis and coronary arteritis. In addition, optimization of lipid levels, blood pressure control, no smoking, exercise, aspirin are recommended(21).

**CNS Manifestations:** continued use of warfarin is recommended in cases of CNS thromboembolic events related to antiphospholipid antibody syndrome. Corticosteroids in high doses with immunosuppressive agents such as azathioprine, cyclophosphamide or rituximab are used in aseptic meningitis, optic neuritis, demyelinating disease, among others.

**Renal Manifestations:** lupus nephritis (LN) will be confirmed with a biopsy. Class I and II LN will be treated with renin-angiotensin-aldosterone system blockade. Immunosuppression with high-dose corticosteroids with azathioprine is indicated when proteinuria is greater than 1 gram/day. Membranous or class V LN will also be treated with renin-angiotensin-aldosterone system blockade.If there is proteinuria of more than 1 gram/day, high doses of corticosteroids and azathioprine in mild disease or intravenous tacrolimus/cyclosporine-A/mycophenolate mofetil/cyclophosphamide in moderate to severe disease are given and then maintenance therapy with azathioprine, mycophenolate mofetil, cyclosporin A or tacrolimus should be performed. Corticosteroids will be tapered in maintenance therapy. Proliferative NL (class III/IV) needs more aggressive management, with intravenous methylprednisolone pulses followed by high-dose oral steroids combined with mycophenolate mofetil, intravenous cyclophosphamide or azathioprine. Renal replacement therapy or transplantation may be required in some individuals.

**Characteristics In Pregnancy:** in mild presentations azathioprine and corticosteroids in low doses can be used. Some immunosuppressive agents such as methotrexate, mycophenolate mofetil, cyclophosphamide and leflunomide are teratogenic and contraindicated in pregnancy. Hydroxychloroquine is considered safe during pregnancy. In addition, rituximab and belimumab should be avoided at this stage. Women with positive Anti-Ro or Anti-La antibodies with a history of neonatal lupus in a previous pregnancy, adequate fetal cardiac monitoring with weekly or alternating weekly fetal echocardiography in the second trimester is indicated.

**Extra Considerations:** hydroxychloroquine should be used in all affected individuals with systemic lupus erythematosus given its benefits beyond simple management of active manifestations. They will require regular ophthalmologic examinations to monitor for maculopathy. Corticosteroids are routinely used in SLE, long-term adverse effects such as osteoporosis, glaucoma, cataracts and avascular necrosis will be considered and monitored. Many of the immunosuppressive agents used in SLE show potential adverse effects, ranging from cytopenias, hepatotoxicity to an increased risk of urinary bladder cancer with cyclophosphamide. These individuals should be monitored adequately and closely for adverse effects of these agents(1,32,33).

**Differential Diagnosis**

Systemic lupus erythematosus presents multiple diseases with which a differential diagnosis can be made as follows:

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**Other Autoimmune Diseases**

Rheumatoid arthritis (RA) may show multiple extra-articular manifestations as well as classic polyarticular inflammatory arthritis. They may show positive ANA, Anti-Ro and Anti-La, however, other SLE-specific autoantibodies and hypocomplementemia are uncommon. SLE may be related to a positive rheumatoid factor, but Anti-CCP is negative in SLE. Drug-induced lupus can be difficult to differentiate from SLE. This is characterized by resolution of symptoms after drug withdrawal; autoantibodies may remain positive for some years. Lupus may be a differential diagnosis of melasma(34).

Adult-onset Still's disease usually presents with arthralgias, lymphadenopathy, splenomegaly and fever. There is no malar rash, no organic manifestations, and no SLE-specific autoantibodies. Sarcoidosis manifests with dyspnea, fatigue, night sweats, fever, cough, rash and uveitis. It also presents with a non-caseating granuloma on chest X-ray and bilateral adenopathy, which are uncommon in SLE. Behcet's disease manifests with aphthous ulcers, uveitis and arthralgia, however, it does not present other systemic and serologic features of SLE(1,35).

**Infections**

Multiple viral infections can mimic SLE. Parvovirus B19 infection usually causes skin rash, inflammatory arthritis, fever and cytopenias. There is evidence of ANA and rheumatoid factor. CMV and EBV viral infections usually show transaminitis, fatigue, cytopenias and fever. Both hepatitis B and C are associated with inflammatory arthralgia-arthritis, positive ANA and rheumatoid factor. HIV may show with oral ulcers, fever, fatigue and cytopenias. Infective endocarditis manifested with arterial embolisms, arthralgias, fever, myalgias and cardiac murmur, can be dismissed as one of the cardiac manifestations of SLE, however to define it, absence of specific autoantibodies associated with SLE and positive blood cultures must be present.

**Malignant Neoplasms**

Lymphomas, mainly non-Hodgkin's lymphoma, may manifest with weight loss, fever, fatigue, cytopenia, arthralgia, lymphadenopathy and positive ANA. The more specific autoantibodies related to SLE are not present. In older individuals they show lupus-like symptoms, so it is recommended to rule out malignancy.

## CONCLUSIONS

Systemic lupus erythematosus presents with a wide range of clinical and histopathologic manifestations. Proper education of affected individuals with systemic lupus erythematosus about the possible clinical manifestations may lead to early recognition and intervention, which may eventually prevent possible notable organ damage. The role of markers and autoantibodies in the differential diagnosis of the pathology is essential. Treatment of SLE is aimed at preventing organ damage and achieving remission. The choice of treatment will depend on the altered organ system(s) and the extent of the involvement. Education of the affected individual, physical measures, lifestyle and emotional support play an important role in the comprehensive treatment of SLE.

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