Systemic Lupus Erythematosus: Clinical Aspects

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4.1 Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder that results from a combination of genetic, environmental, and hormonal factors. The disease is characterized by a heterogeneous clinical presentation, a different course in different individuals, and a variability in the disease progression/fluctuations within the same patient.

Patients with SLE are mostly young women, adolescents, and some ethnic groups are more prone to a severe course of disease. The unpredictable and fluctuating flares of disease, the need for long-term treatment, and the side effects and damage caused by the disease itself severely reduce quality of life (QoL).

The clinical picture of SLE is extremely variable and may be related to disease activity, organ damage, drug toxicity, and quality of life. Assessment of patients with SLE in clinical practice relies upon the experience of the treating doctor and thus is subject to great variability between centers and between doctors. Several indices have been developed and validated to measure these parameters. Although there are some concerns about feasibility, the use of validated indices facilitates the collection of relevant data that otherwise may be overlooked. It is currently accepted

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that assessment of patients with SLE cannot be accomplished with a single index. Formal evaluation of three aspects of the disease, disease activity, disease damage, and patient-related quality of life is required.

No data are available in the literature to suggest an optimal frequency of clinical and laboratory assessment in patients with SLE. The European League Against Rheumatism (EULAR) made some recommendations for monitoring patients with SLE in clinical practice and in observational studies [1, 2]. The committee arbitrarily agreed on the need to assess patients with inactive disease, in the absence of organ damage and comorbidities, every 6–12 months. Patients with active disease should be assessed as often as necessary to evaluate the response to medication of clinical features as well as laboratory parameters.

Despite the heterogeneity of clinical presentation, a classification attempt can be done in order to establish some therapeutic approaches. Clinical features of SLE can be considered mild, moderate, or severe depending on the impact they can have in the patients' life.

This chapter aims to provide a critical overview on SLE clinical manifestations according to their severity. Specific features such as new insights into classification criteria and recent advances on cardiovascular risk, antiphospholipid syndrome, and QoL are also discussed.

4.2 Revised Classification Criteria

Recently, a major development has been the publication of the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [3]. This classification aimed to rationalize the clinical criteria and provided a modest expansion in recognized laboratory abnormalities (Table 4.1). One of the major differences when compared to the American College of Rheumatology Classification criteria is that biopsy-proven nephritis compatible with SLE in the presence of antinuclear or anti-double-stranded DNA antibodies in the absence of other lupus features is regarded as sufficient for a patient to be diagnosed as having SLE. The symptoms and laboratory abnormalities are cumulative and need not to be present concurrently.

4.3 Clinical Classification

4.3.1 Mild SLE

We can consider SLE mild when patients suffered with conditions that do not threaten their life and do not have a big impact in their health and quality of life. Mild skin involvement, arthralgia, fatigue, fibromyalgia, and mood disorders could be some of these symptoms. These manifestations are usually controlled with hydroxychloroquine. Skin and join involvements are discussed separately in this volume.

Table 4.1 Clinical and immunological criteria used in the Systemic Lupus International Collaborating Clinics (SLICC) classification system

Clinical criteria
1. Acute cutaneous lupus, including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of systemic lupus erythematosus, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus (psoriasiform or annular polycyclic lesions or both)
2. Chronic cutaneous lupus, including classic discoid rash (localized and generalized), hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, and discoid lupus/lichen planus overlap
3. Oral ulcers or nasal ulcers
4. Non-scarring alopecia
5. Synovitis involving two or more joints and at least 30 min of morning stiffness
6. Serositis
7. Renal (urine protein-to-creatinine ratio [or 24-h urine protein]) representing 500 mg protein per 24-h or red blood cell casts
8. Neurological: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral and cranial neuropathy, acute confusional state
9. Hemolytic anemia
10. Leukopenia (<4000 cells per μL at least once) or lymphopenia (<1000 cells per μL at least once)
11. Thrombocytopenia (<100,000 cells per μL) at least once
Immunological criteria
1. Antinuclear antibody concentration greater than laboratory reference range
2. Anti-double-stranded DNA antibody concentration greater than laboratory reference range (or twofold the reference range if tested by ELISA)
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following: positive test result for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium-titer or high-titer anticardiolipin antibody concentration (IgA, IgG, or IgM), or positive test result for anti-2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement C3, low C4, low CH50
6. Direct Coombs' test in the absence of hemolytic anemia

Fatigue is a common and often crippling symptom experienced by about 85–92 % of patients with SLE, with 50 % rating it as the most disabling symptom [4]. Indeed, it deeply impacts on QoL in SLE patients [5]. The pathophysiological mechanisms of SLE-related fatigue are probably multifactorial. Psychological domains such as mood disorders, poor sleep quality, anxiety, and chronic pain syndrome play a predominant role, and they have shown consistent associations with fatigue in SLE [6, 7]. Fatigue is usually poorly responsive to standard treatment for SLE and remains an unmet need. However, gentle exercise programs have been reported to have a positive impact on fatigue among SLE patients [8].

Fibromyalgia is a chronic pain disorder characterized by diffuse generalized pain, often associated with fatigue, anxiety, and sleep disturbances. The prevalence of fibromyalgia is much higher in autoimmune conditions to include SLE patients,

when compared with the general population [9]. Fibromyalgia in SLE impacts QoL and correlates with psychosomatic and affective symptoms but not with disease activity or damage [9–11]. The widespread pain of concomitant fibromyalgia can represent a diagnostic challenge for the physician, leading to potential overtreatment if symptoms are mistaken for SLE disease activity.

Mood disturbances (mainly depression) are very common in patients with SLE [12, 13]. Depression may backside fatigue and cognitive dysfunction, contributing to a lower QoL in patients with SLE [14–16]. Although psychological effects of dealing with a chronic disease may contribute to the high prevalence of depression, disease-specific mechanisms probably can also play a significant role. Associations with specific antibodies and alterations in cerebral blood flow have been reported in depressed SLE patients [17, 18]. However, the data are not conclusive and depression in patients with SLE should be treated with conventional measures similar to the general population.

4.4 Moderate SLE

Previous symptoms if persists or are limiting patients' life in some way plus the presence of serositis, moderate lung involvement, and hematological involvement might be classified as moderate SLE. In details, moderate lung involvement includes pleuritis, abnormalities in diffusion as tested by diffusing capacity for carbon monoxide (DLCO), and mild fibrosis, while pulmonary hemorrhage and pulmonary hypertension severely impact on prognosis in patients with SLE. Similarly, from the cardiological perspective, patients with noncomplicated pericarditis and mild valve involvement may be classified as having moderate SLE; however, heart involvement can be life threatening when complicated pericarditis or myocarditis occurs.

4.4.1 Hematological Involvement

Hematological involvement is common in SLE and no specific treatment is necessary in mild asymptomatic cases, but close monitoring of cytopenia is warranted in most patients. Any significant changes in previous stable cell lineage parameters should be considered to be an indication of SLE flare and will need close investigation and monitoring. A detailed medical history for possible drug-induced myelosuppression should be part of the evaluation in order to identify all medications potentially interfering with bone marrow function.

There are various immune cytopenias associated with SLE. The most common is anemia. There are different etiologies for the anemia in SLE, to include chronic disease, renal insufficiency, hemorrhage, and drug-induced or autoimmune hemolysis. Red cell aplasia, aplastic anemia, and microangiopathic hemolytic anemia should be also mentioned.

Anemia of chronic disorder is the most common type of anemia in SLE, but autoimmune hemolytic anemia (AIHA) with high reticulocyte count is an SLE

diagnostic criteria. Treatment of the anemia would be according to the cause. Glucocorticoids are the main treatment of AIHA, and about 96 % of patients have initial response to glucocorticoids, but rituximab, cyclosporine, IVIg, and cyclophosphamide have successfully been used in selective cases.

4.4.2 Leukopenia

Leukopenia is a well-known hematologic complication associated with SLE, and in majority of cases, no treatment is required. For classification purpose in SLE, leukopenia is defined as <4000/mm^3 on two or more occasions (according to the ACR and SLICC criteria). The pathogenic mechanisms of SLE itself, and several other factors to include immunosuppressive drugs, may contribute toward low white cell count in SLE patients. Leukopenia constitutes a paucity of granulocytes as well as lymphocytes, yet a greater absolute deficiency of granulocytes than lymphocytes is usually found [19].

Lymphopenia is common and T-cell lymphopenia is the most common type of lymphopenias, and absolute lymphopenia correlates with SLE activity and high DNA antibody titers. Lymphopenia per se can predispose to autoimmunity and can also be a consequence of disease activity in the setting of active SLE. Concomitant lymphopenia and thrombocytopenia are highly indicative of disease activity rather than as a cause for autoimmunity [19]. Lymphopenia is defined as $<1.5 \times 109$ lymphocytes/L on two or more occasions according to current classification criteria. Low lymphocyte counts commonly occur in SLE with a prevalence ranging from 20 % to more than 90 % [19]. Lymphopenia is observed frequently in patients with active or severe disease [20, 21], and lymphocyte levels may fluctuate during the clinical course, irrespective of treatment [21].

Presence of lymphopenia may be clinically silent or associated with infections and/or active SLE. Data on the increased risk of infection are controversial and are complicated by the use of immunosuppressive therapies. Ethnicity may also play a role in explaining the heterogeneous results. However, glucocorticoids and immunosuppressive drugs may contribute to the lymphopenia in severe disease. In about 10 % of patients with SLE, lymphopenia can be quite striking with values $<0.5 \times 109$/L. Lymphopenia usually occurs independently of neutropenia.

Neutropenia is usually defined as an absolute neutrophil count <1000 cells/mm^3. Although leukopenia occurs in about half of patients with SLE, WBC count <1000/mm is observed in about 15 % of the patients [22, 23]. The definition of a low WBC and/or low neutrophil count is complicated by the presence of benign ethnic neutropenia in many (25–50 %) persons of sub-Saharan African heritage [24]. In individuals with this condition, an abnormally low neutrophil count is not easily definable. Neutropenia is less common but may be associated with significant systemic infection when compared to lymphopenia. However, moderate/severe neutropenia (neutrophil count <1000/μL) is not a common hematologic finding in patients with SLE. Several mechanisms are responsible in inducing neutropenia, to include drug toxicity and disease activity.

4.4.3 Thrombocytopenia

Thrombocytopenia is a common and well-described manifestation of SLE directly related with morbidity and mortality. According to ACR classification criteria and the new SLICC criteria for SLE, the definition of thrombocytopenia is a platelet count <100,000/mm^3 (or 100×109/L) without any other identifiable cause. It is worth noting that distinguishing from thrombocytopenia as a result of pharmacological therapy may be especially difficult in patients with SLE. A careful examination of the peripheral blood smear looking for platelet aggregation and adherence to leukocytes may be helpful in recognizing pseudothrombocytopenia. Thrombocytopenia in patients with SLE can be thought of generally in two categories [25, 26]. One group of patients has thrombocytopenia as part of an SLE flare. In this setting, thrombocytopenia can be severe with the danger of life-threatening hemorrhage. The platelet count in these patients usually responds acutely to treatment with glucocorticoids. The other group of patients with SLE with low platelet count has a more chronic form that may present even when the disease is quiescent. In these patients, the glucocorticoid therapy may be less effective. However, they are also more likely to have only a modest decrease in the platelet count that may not require specific therapy.

There are growing evidences that thrombocytopenia in SLE is related to the presence of at least two types of autoantibodies, anti GPIIb/IIIa and anti-thrombopoietin receptor antibodies. Of importance of these two different autoantibodies is thrombocytopenia of patients with anti-thrombopoietin receptor antibody, which is less responsive to IVIg. It has been suggested that on the basis of presence of one of these autoantibodies or both, there are two different subsets of SLE patients with thrombocytopenia [26]. Corticosteroids are the first modality of treatment in SLE-associated thrombocytopenia, and about 20 % of patients have long-term remission. Intravenous pulse corticosteroid therapy is an alternative in unresponsive cases. Immunosuppressive drugs usually should be considered when initial treatment with steroids is not effective or if a dose higher that 10 m/daily of prednisone is required as maintenance therapy [27]. There are some emerging studies that show that rituximab and mycophenolate may be helpful in lupus-related thrombocytopenia.

4.5 Severe SLE

We can consider SLE severe when patients suffered with one or more major organ involvement potentially leading to life-threatening condition and/or having a big impact in their health and quality of life. Organ damage (due to both previous disease activity and/or drug toxicity) plays also a crucial role in this setting. Lupus nephritis (LN), neuropsychiatric SLE (NPSLE), cardiovascular involvement (myocarditis or events happening in the context of the antiphopsholipid syndrome (APS)), and infections are some of the conditions affecting patients with severe SLE. LN and NPSLE are discussed separately in this volume.

4.5.1 Lung Involvement

The involvement of the respiratory system is frequent, being pleuropulmonary manifestations present in almost half of the patients during the disease course. Pleurisy, coughing, and/or dyspnea are the most frequent symptoms. However, they are rarely the presenting symptoms of SLE. In some cases, however, abnormal pulmonary function tests (PFTs), including DLCO and/or abnormal chest radiographs, may present in asymptomatic patients. Pleuritis with or without pleural effusion and interstitial lung disease are usually mild to moderate symptoms in patients with SLE; conversely, lupus pneumonitis and alveolitis, pulmonary hemorrhage, pulmonary arterial hypertension, and pulmonary thromboembolic disease may severely impact on prognosis of patients with SLE as they can be life threatening. Complications due to secondary causes include pleuropulmonary manifestations of cardiac and renal failure, atelectasis due to diaphragmatic dysfunction, opportunistic pneumonia, and drug toxicity. The prevalence, clinical presentation, prognosis, and response to treatment vary, depending on the pattern of involvement. Pulmonary abnormalities usually do not correlate with makers of SLE activity (complement levels, or autoantibody levels such as anti-double-stranded DNA (dsDNA) and anti-Sm). Patients with SLE and lung involvement must always be evaluated for infection, particularly that due to bacteria or viruses. Given that many are immunocompromised, tuberculosis, fungal infections, and other opportunistic infections should also be considered.

4.5.2 Cardiac Involvement

Cardiac involvement is frequent in SLE, being as high as 50 % in some studies [28]. Any part of the heart can be affected, including the pericardium, myocardium, coronary arteries, valves, and the conduction system. In addition to pericarditis and myocarditis, a high incidence of CAD has become increasingly recognized as a cause of mortality.

In the past, cardiac manifestations were severe, often leading to death, and they were frequently found in postmortem examinations. Nowadays, thanks to early diagnosis, cardiac manifestations are often milder and asymptomatic, and they can be recognized by echocardiography and other noninvasive tests [29].

Pericarditis is a well-described cardiovascular manifestation of SLE, although often not evident clinically, and it is included in the ACR classification criteria for SLE. Pericarditis can be acute or chronic, and it appears more frequently at SLE onset or during SLE flares, although it can occur at any time of the disease [29]. Pericardial involvement usually occurs as an isolated attack or as recurrent episodes [30]. Clinical (symptomatic) pericarditis is estimated to occur in 25 % of SLE patients at some point in the course of their disease. Asymptomatic pericardial effusion is clearly more common than clinical pericarditis [31]. Coexistent pleurisy, effusion, or both are common [32]. Complications of pericarditis, such as cardiac tamponade, constrictive pericarditis, and purulent pericarditis, are rare.

Myocarditis is a potentially severe feature of myocardial involvement in SLE and myocardial involvement ranges from 3 % to 15 %, although it appears to be much more common in autopsy studies, suggesting the largely subclinical nature of lupus-associated myocarditis [33].

Signs and symptoms (including dyspnea, tachycardia, arrhythmias) do not differ from those of myocarditis due to other causes. A progression to ventricular dysfunction, dilated cardiomyopathy, and heart failure can occur. Cardiac enzymes may be normal and there are no typical findings on ECG.

Myocarditis is a potentially life-threatening condition and has to be treated immediately with high-dose steroids; in the most severe forms, it is necessary to use intravenous pulse corticosteroid followed by high oral doses. The addition of immunosuppressant such as azathioprine, cyclophosphamide, or intravenous immunoglobulines (IVIG) may be helpful in [34].

Heart valve abnormalities including vegetations and/or thickening are the most frequent cardiac manifestations of SLE, especially when associated to APS. These alterations were known as Libman–Sacks endocarditis, a verrucous endocarditis of valve leaflets, papillary muscles, and mural endocardium, originally described in SLE patients [28]. Valvular disease is usually mild and asymptomatic. Usually, less than 5 % of the patients with SLE, mainly those with antiphospholipid antibodies, develop valve disease severe enough to consider surgical treatment.

The valvular abnormalities resulting from Libman–Sacks lesions may predispose patients to bacterial endocarditis, so prophylactic antibiotics should be used for dental or surgical procedures with an increased risk of transient bacteremia.

4.5.3 Antiphospholipid Syndrome

APS can be an isolated disease or can be associated with SLE. It is characterized by recurrent venous or arterial thrombosis and/or pregnancy morbidity and persistent presence of antiphospholipid antibodies (aPL). Although 30–40 % of patients with lupus have aPL, the APS complicates only 10–15 % of cases of SLE. More than 40 aPL have been described so far, but only three are used currently for the confirmation of diagnosis [35]. Triple positivity for lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein 1 antibodies (at least one must be positive for the diagnosis of APS on two or more occasions 12 weeks apart) [36] has a strong association with the clinical symptoms of this syndrome.

APS has a broad range of clinical features, reflecting the site of thrombosis. The therapeutic approach to APS is mainly centered on modification of the general risk factors for thrombosis and use of antiplatelet and anticoagulant agents, notably heparin or warfarin [37]. However, the use of the new oral anticoagulants (namely, rivaroxaban, an inhibitor of factor Xa) is currently under investigation [38].

Statins are a very attractive addition to the drug regimen used for treatment of APS due to their anti-inflammatory/thrombotic effects [39].

4.6 Infection and Disease Activity

Infection is a common problem in SLE and is one of the main causes of mortality. Immunological dysfunction may play a critical role in the susceptibility to infections in patients with SLE [40]. Furthermore, immunosuppressive agents (mainly glucocorticoids) used in the treatment of moderate and severe lupus increase the risk of infections including opportunistic agents. Infections may mimic lupus flare, leading to confusion over the diagnosis and adequate treatment. It can be extremely difficult to distinguish between infection and disease exacerbation in some cases. Moreover, some infections may produce a systemic infection mimicking SLE, either superimposed or trigger a flare [41, 42].

Several studies evaluated characteristics of major infections in SLE patients requiring hospitalization [43–45]. According to these studies, acquired pneumonia, urinary tract infection, and vaginal infection are the most common infections in patients with SLE. Infections are usually attributed to the same pathogens as in the general population. Of note, some patients may develop tuberculosis. However, despite the pathogens often being the same as the general population, the clinical manifestations of the infections can be atypical, due to an abnormal immunological response or to ongoing treatment. Careful evaluation and timely collection of the specimens for bacterial culture are crucial to avoid misdiagnosis.

Viral, fungal, and protozoan infections can also occur. Rarely, multiple organisms can be detected [44].

In an outpatient setting, infections are usually non-life threatening and it has been reported that they are associated with disease activity only, independently of sociodemographic and therapeutic factors [42]. Infection in SLE can occasionally require hospitalization, especially when concomitant with a flare (mainly involving the kidney or central nervous system) or when therapy with steroids or immunosuppressive drugs is ongoing [46].

Infections are diagnosed by clinical features and positive cultures and/or response to antibiotic therapy. When cultures of bacterial isolates are negative or not available, diagnosis of infection relies on clinical findings, which can mimic a lupus flare. Physicians have to make treatment decisions based on clinical judgment as no laboratory parameters are totally reliable to distinguish between active disease and infection. In some patients, both situations can coexist making the diagnosis and therapeutic approach a real challenge.

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