Systemic Lupus Erythematosus: A Review for Dentists

Jonathan B. Albilia, DMD; David K. Lam, DDS; Cameron M.L. Clokie, DDS, PhD, FRCD(C); George K.B. Sándor, MD, DDS, PhD, FRCD(C), FRCSC, FACS

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic disease with far-reaching systemic implications. The hallmark feature in SLE is chronic inflammation. It can affect the skin, joints, kidneys, lungs, nervous system, serous membranes such as the pleura and pericardium, mucous membranes and other organs of the body. It is imperative that the dental practitioner be familiar with the broad range of systemic and oral implications, including the clinical and biochemical features of SLE. This review article offers an overview of the multiple organ systems affected by this complex heterogeneous disease process that are most relevant to both the general practitioner and the dental specialist. In particular, ways to recognize and manage the oral and dental manifestations of this systemic illness are presented.

Patients with systemic lupus erythematosus (SLE) experience a myriad of symptoms. The most common pattern is a mixture of constitutional complaints of skin, musculoskeletal, hematologic and serologic involvement.

The clinical course of SLE is variable and may be characterized by episodes of recurrent acute or chronic inflammation, and intervening periods of remission. Women, especially those in their 30s and 40s, are affected more frequently than men (average ratio 10:1). The worldwide prevalence of SLE ranges between 12 and 50 per 100,000, depending on location and ethnicity. Knowledge of this condition facilitates understanding of most other autoimmune rheumatic diseases. Many of the early features of SLE may overlap with those of other autoimmune conditions, but SLE has an impact on most organ systems.

In rheumatic diseases, chronic inflammation affects the heart, lungs, bones, joints, kidneys, skin and, frequently, other organs. Some examples include rheumatoid arthritis, rheumatic fever, SLE, Sjögren’s syndrome, scleroderma, CREST syndrome, polymyositis, fibromyalgia, ankylosing spondylitis, psoriatic arthritis, polyarthritis rheumatica, vasculitis, temporal arteritis, Henoch-Schönlein purpura, Wegener’s granulomatosis and mid-line granuloma. Immunologic abnormalities are another important feature of rheumatic conditions.

Pathogenesis

In the presence of appropriate antigens, SLE develops as a result of the formation of soluble immune complexes that are mainly composed of IgG and IgM. The pattern is that of a type III hypersensitivity reaction triggered by an endogenous antigen that may...
be generalized or organ-specific (Table 1). Because of the affinity of the antibody and the size of the immune complexes, the kidneys, lungs and joints are frequently targeted in persons with SLE.

Tissue damage is caused by platelets and neutrophils. The lesions contain primarily neutrophils and deposits of immune complexes and complement, namely C3a, C4a and C5a. Macrophages infiltrating in later stages are involved in the healing process (Fig. 1).

Genetic factors and specific gene loci are important in the pathogenesis of SLE. In predisposed persons, environmental triggers, including exposure to sunlight (photosensitivity), drugs (pharmacogenetics) and infections (particularly with Epstein-Barr virus), are thought to precipitate the development of SLE.

Clinical Presentation

The diagnosis of SLE requires several compatible clinical features and supportive laboratory studies. Table 2 outlines the 1997 American College of Rheumatology diagnostic criteria for SLE, which has been modified since Tan and others revised it in 1982.

Constitutional symptoms of SLE, such as complaints of fatigue, malaise, arthralgia, myalgia and mucocutaneous lesions, are common.

Musculoskeletal signs and symptoms predominate in SLE. Arthralgia, asymmetric and migratory, is usually present and is often the earliest manifestation. The joints of the hands are most often affected. The arthritis is moderately painful and nondestructive. Deformities observed are usually due to tendon inflammation (Jaccoud-type arthropathy), rather than degeneration.

Generalized sun-induced skin rashes, and discoid lesions secondary to epithelial atrophy and subsequent scarring, are quite common. Of these, the classic malar or butterfly rash, that spares the nasolabial crease, is a highly common occurrence. Hair loss caused by hair follicles plugged with keratin is also reported.

Oral lesions such as desquamative gingivitis, marginal gingivitis or erosive mucosal lesions have been reported in up to 40% of patients. Patients with advanced cases of SLE may have features of Sjögren’s syndrome, such as dry eyes, mouth and skin.

Renal disease or lupus nephritis is a grave complication of SLE that affects 30% of patients. Renal tests (Table 2) may unmask lupus nephritis and its severity. Chronic renal failure because of SLE will influence the choice or dosage of medications prescribed by dentists.

--- Sándor ---

**Table 1** Hypersensitivity reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Antibodies involved</th>
<th>Mechanism</th>
<th>Clinical examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE</td>
<td>IgE bind to basophils and mast cells, releasing histamine, trypsin, arachidonic acid. Manifestations are local and systemic.</td>
<td>Conjunctivitis, Asthma, Anaphylaxis</td>
</tr>
<tr>
<td>II</td>
<td>IgG, IgM</td>
<td>Antibodies bind to cell surfaces, triggering immune response by complement activation.</td>
<td>Transfusion reaction, Hashimoto’s thyroiditis</td>
</tr>
<tr>
<td>III</td>
<td>Soluble IgG and IgM aggregates</td>
<td>Antibody complexes are deposited in various tissues such as skin, kidneys or joints, triggering immune response by complement activation.</td>
<td>Serum sickness, Arthus reaction, Systemic lupus erythematosus</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-mediated immunity (delayed hypersensitivity)</td>
<td>Cytotoxic T cells (CD8) and helper cells (CD4) recognize antigen in a major histocompatibility complex, resulting in further macrophage-mediated proliferation of helper cells.</td>
<td>Contact dermatitis, Temporal arteritis, Transplant rejection</td>
</tr>
</tbody>
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**Figure 1:** Schematic representation of type III hypersensitivity reaction. Only preformed antigen-antibody complexes can bind to the IgG constant fragment receptor (Fc gamma RIII) located on immune cells (PMN-polymorphonuclear leucocyte) and activate them, causing degranulation and tissue destruction. (Reproduced with permission from Nick Holmes, Cambridge University, United Kingdom, http://www-immuno.path.cam.ac.uk.)
Changes in the central nervous system from cerebral lupus are quite variable. Headache, depression, seizures and psychosis have been documented, as well as peripheral neuropathies. Migraines seem to be more prevalent in patients with SLE than in the general population. The dentist’s role in such cases is paramount to rule out odontogenic, temporomandibular joint and associated myofascial sources of pain (Box 1).

Generalized chest pain aggravated by deep inspiration (pleuritic pain), cough and rapid shallow breathing may be apparent during episodes of active lung disease. Pleural effusions and parenchymal damage often lead to pneumonitis. Subsequently, a hospitalized patient with SLE would be at great risk of acquiring pneumonia. Chest pain warrants a detailed workup to rule out pulmonary embolism and myocardial infarction, especially in those who test positive for antiphospholipid antibodies.

Two well-known cardiac features of SLE are pericarditis and endocarditis. Pericarditis, which sounds like a rub, is audible with a stethoscope. Endocarditis has an autoimmune basis. Resulting rheumatic valvular damage takes the form of sterile vegetations that are susceptible to bacterial colonization. Antibiotic prophylaxis before bacteremia-associated dental and oral surgical interventions is required to prevent infectious endocarditis in SLE patients with valvular damage.

Advanced SLE-induced vasculitis can lead to multi-organ dysfunction (Fig. 2). However, cold- or stress-

<table>
<thead>
<tr>
<th>SLE criterion</th>
<th>Definition or examples</th>
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<tbody>
<tr>
<td>Malar rash (butterfly rash)</td>
<td>Fixed erythema over the malar eminences</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches, may scar</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Often painless sores</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive: Jaccoud’s arthropathy</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis — pleuritic pain, pleural rub, pleural effusion</td>
</tr>
<tr>
<td></td>
<td>Pericarditis — ECG changes, pericardial effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Proteinuria (with 3+ or more protein noted in urin-</td>
</tr>
<tr>
<td></td>
<td>alysis specimen or 0.5 g of protein/day)</td>
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<td></td>
<td>Cellular casts in urine</td>
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<tr>
<td>Neurological disorder</td>
<td>Seizures Psychosis</td>
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<tr>
<td>Hematological disorder</td>
<td>Hemolytic anemia Leukopenia Lymphopenia Thrombocytopenia</td>
</tr>
<tr>
<td>Immunological disorder</td>
<td>Anti-DNA antibodies Anti-Sm antibodies Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Antibodies to nuclear constituents</td>
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ECG = electrocardiogram

(Table 3). Patients with end-stage renal disease may become candidates for renal transplantation.

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Advanced SLE-induced vasculitis can lead to multi-organ dysfunction (Fig. 2). However, cold- or stress-

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<tr>
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<tr>
<td>Penicillins</td>
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<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Tetracycline</td>
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<td>Antifungals</td>
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Suggested adjustments:
Consider increasing dose intervals and decreasing dosage
Consider contacting physician if renal function is unknown

Suggested alternatives:
Acetaminophen
Narcotics
Clindamycin

Box 1 Possible oral and dental manifestations in patients with systemic lupus erythematosus

- Mucocutaneous lesions (desquamative gingivitis, marginal gingivitis or erosive mucosal lesions)
- Indwelling odontogenic and other head and neck infections with no obvious symptoms, because of a reduced immune response
- Temporomandibular joint disorders (arthralgia, arthritis)
- Sjögren’s syndrome (keratoconjunctivitis sicca, xerostomia and generalized hypohidrosis)
- Suboptimal oral hygiene because of painful oral lesions
- Caries in patients with Sjögren’s-like syndrome

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<th>Drugs commonly prescribed by dentists with predominantly kidney-dependent elimination</th>
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induced triphasic colour changes of the hands and feet, referred to as Raynaud’s phenomenon, are a far more common occurrence.\

Other less severe forms of lupus exist. Chronic cutaneous (discoid) lupus erythematosus is a mild form of lupus in which integumentary changes prevail, with or without mucosal changes. Subacute cutaneous lupus erythematosus is an intermediate form of lupus in which skin lesions are mild, without discoid appearance, do not scar, and are usually accompanied with some degree of musculoskeletal involvement. Renal, cardiac and cerebral disease is usually not present in these mild and intermediate forms of lupus.\

Serologic Tests

If a diagnosis of SLE is suspected, then the most useful preliminary testing includes a complete blood count with differential white blood cell counts. This count will reveal chronic anemia that is normocytic-normochromic with thrombocytopenia and lymphocytopenia.}\n
Other disease-specific tests for autoantibodies and the information yielded are outlined in Table 4.

**Table 4** Autoantibodies found in patients with SLE\(^3,4\)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Significance</th>
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<tr>
<td>Antinuclear antibody</td>
<td>Indicative of rheumatic diseases Not specific for systemic lupus erythematosus</td>
</tr>
<tr>
<td>Antibody to double-stranded DNA</td>
<td>Suggestive of systemic lupus erythematosus Predictive for renal involvement</td>
</tr>
<tr>
<td>Anti-Smith antibody</td>
<td>Predictive for renal involvement</td>
</tr>
<tr>
<td>Anti-Ro antibody</td>
<td>Suggestive of secondary Sjögren’s syndrome</td>
</tr>
<tr>
<td>Antiphospholipid antibody</td>
<td>Increased risk of thromboembolism</td>
</tr>
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**Histopathology of Oral Lesions**

Microscopic features of lupus mucosal lesions are quite similar to those of lichen planus and erythema multiforme. A common microscopic feature of these lesions is the band-like subepithelial inflammation. However, in patients with SLE and erythema multiforme, the inflammatory infiltrate extends deeper into the underlying connective tissue and shows a perivascular pattern. Deep submucosal vesicles may also be apparent. Lupus lesions will exhibit periodic acid-Schiff staining in the basement membrane zone. Direct immunofluorescent testing will show immunoglobulin and complement deposition along the basement membrane zone in a granular pattern that is characteristic of type III hypersensitivity reactions.

**Differential Diagnosis**

Several diseases mimic the initial course of SLE and make its differentiation from other conditions difficult. The onset of symptoms of many rheumatic disorders often overlap.

Lupus-related mucocutaneous lesions can mimic those of erythema multiforme, lichen planus and other vesiculobullous lesions. Histologic and immunohistochemical confirmation of intact tissue adjacent to a given lesion remain the criterion standards for definitive diagnosis.\(^3\)

Medications implicated in the cause of drug-induced lupus are hydralazine, procainamide, phenytoin and isoniazid.\(^4\) Withdrawal of these medications, after appropriate medical workup, should reverse an apparent lupus-like syndrome. In addition, patients with drug-induced lupus do not show seropositivity for antinuclear antibody.

**Treatment**

The goals of SLE management are based on prevention, reversal of inflammation, maintaining states of remission and alleviation of symptoms.\(^5,6\) Avoidance of flare-ups of lupus and skin lesions consists of protection from ultraviolet sunlight.
Systemic Lupus Erythematosus

• Compromised immunity
• Atherosclerosis
• Hypertension
• Hypercholesterolemia
• Hyperglycemia
• Cushingoid appearance
• Acne
• Cataracts
• Avascular necrosis of the hip
• Severe osteoporosis
• Pharmacologically induced adrenal insufficiency

Box 2 Side-effects of long-term corticosteroid intake

Various medicinal therapies exist for the management of persons with SLE. Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors and antimalarials are generally effective for musculoskeletal complaints and mild serositis. Patients exhibiting skin manifestations often benefit from antimalarials, such as hydroxychloroquine.

Systemic corticosteroids, such as prednisone, are reserved for patients with morbid symptoms associated with significant organ involvement, particularly renal, central nervous system and systemic vascular diseases. The dosage of corticosteroid is progressively tapered as signs and symptoms resolve. However, some patients may require a maintenance dose to remain in remission. The side effects of chronic corticosteroid intake are listed in Box 2. A discussion of these side effects is beyond the scope of this article.

Other immunosuppressive agents such as cyclophosphamide, methotrexate and azathioprine are reserved for severe organ disease such as advanced lupus nephritis.

**Perioperative Management by the Dentist**

Dentists must enforce preventive dental care and monitor patients with SLE closely for head and neck infections because they are predisposed to severe infections. These infections are often silent and difficult to detect because of a paucity of pain and swelling (Figs. 3a–3c). Thorough clinical examination is required to avoid overlooking infections. Infections can progress rapidly in patients with SLE because of disease or therapy-related immunosuppression.

To further complicate matters, patients with SLE can have a superimposed antiphospholipid antibody syndrome that predisposes them to thromboembolic events, such as arterial and venous thrombosis, pulmonary embolism, stroke and myocardial infarction. It is therefore important to document whether these patients are managed with anticoagulation therapy, aspirin or warfarin before dental surgery. Recent laboratory tests may be indicated preoperatively to determine platelet count, prothrombin time and the international normalized ratio (INR) for blood clotting time. Local measures for maintaining hemostasis may also be required.

Patients suffering from chronic renal failure are often on dialysis. Dental surgery should be planned one day after dialysis treatment to ensure elimination of administered medications and their by-products.

Patients on long-term corticosteroids may require supplemental dosing on the day of a potentially stressful dentoalveolar surgery.

A multidisciplinary approach to medical consultation and appropriate referrals ensures comprehensive medical and dental management of patients with SLE.
Box 3  Oral and dental considerations in patients with systemic lupus erythematosus

- Subacute bacterial endocarditis prophylaxis for patients with valvular damage because of Libman-Sacks endocarditis
- Alteration of drug dosages for patients with systemic lupus erythematosus who have severe renal involvement
- Attention to the possibility of drug interactions because this patient group may be taking many different medications
- Management of mucocutaneous lesions
- Aggressive workup and definitive treatment of infections involving the head and neck

Prognosis

Although a potentially debilitating disease, survival rates for SLE have doubled since the 1950s. Death due to SLE was more than 5 times higher in women than in men, and more than 3 times higher in black than white women. The major cause of death in the first few years of the onset of SLE is active disease that involves multiorgan systems or infection from drug-induced or lupus-related immunosuppression. Delayed deaths are caused by SLE, or associated with end-stage renal disease or complications of treatment, including infection, coronary disease and malignancy.

Poor prognostic factors are being young at onset, being male, having a poor socioeconomic status and having positive titres of antiphospholipid antibodies.

Conclusion

SLE can run a varied clinical course, ranging from a relatively benign illness to a rapidly progressive disease with fulminant organ failure and death. Most patients have an episodic relapsing and remitting course that may be managed with high-dose steroids during severe flare-ups. SLE is probably the most difficult of all autoimmune rheumatic disorders to control, putting prevention of infections at the forefront of disease management. For patients with SLE, emphasis is therefore placed on the dental team’s continuous reinforcement of good oral hygiene, provision of close monitoring for and aggressive treatment of dental and oral infections, and assistance with the diagnosis of mucocutaneous lesions of the head and neck (Box 3).

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