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Oral manifestations of patients with lupus erythematosus

Michael T. Brennan, DDS, MHS*,
Manuel A. Valerin, DDS, Joel J. Napeñas, DDS,
Peter B. Lockhart, DDS

Department of Oral Medicine, Carolinas Medical Center, 1000 Blythe Boulevard, Charlotte, NC 28232, USA

Epidemiology

The prevalence of lupus erythematosus (LE) in the United States has been estimated at 500,000 to 1 million cases. Cutaneous LE is two to three times more common than systemic LE (SLE) [1]. Numerous factors seem to predispose patients to the cutaneous variants of LE; among them are genetic factors, environmental factors (sun exposure), and immune dysregulation [2].

In the United States the prevalence of SLE is 500/million, and the annual incidence is 70/million population [3]. Women are more commonly affected, with a ratio of 6 to 10:1 and a peak incidence between 15 and 40 years of age [4]. A genetic predisposition is one important factor in the development of SLE, because disease concordance in identical twins is 24%, compared with approximately 2% in dizygotic twins [5]. Other risk factors include hormonal and immune dysregulation; environmental factors such as infectious agents, stress, diet, and toxins; and physical agents such as sunlight [4,6].

Pathogenesis

The characteristic disease findings in LE include inflammation, blood vessel changes such as vasculopathy, and immune-complex deposition. Generalized autoantibody production in SLE is a hallmark immunologic

* Corresponding author.
E-mail address: mike.brennan@carolinas.org (M.T. Brennan).

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presentation, with antibodies directed to self-antigens of the nucleus, cytoplasm, cell surface, soluble IgG, and coagulation factors [4]. Production of autoantibodies seems to mediate tissue injury by an immune complex-mediated inflammatory response [7]. Of particular importance to SLE are serum autoantibodies that are directed to a range of cell nucleus components such as DNA, RNA, nuclear proteins, and protein–nucleic acid complexes. These antinuclear antibodies (ANA) are found in 95% of SLE patients [4].

The specific antibodies to nuclear antigens are of particular importance to SLE. Antibodies to double-strand (ds) DNA (anti-ds DNA) and to nuclear antigen Smith (anti-Sm) target small nuclear ribonucleoprotein are unique to SLE, found in the sera of 40% and 30% of patients, respectively. ANA, anti-ds DNA, and anti-Sm are part of the classification criteria for SLE (Box 1) [8]. Other nuclear antigen antibodies found in SLE include anti-Ro, anti-La, anti-ribosomal P proteins (anti-P), and antiphospholipid [9]. Although the clinical importance of specific nuclear antigen antibodies is not always clear, anti-ds DNA has been associated with glomerulonephritis. Other associations with clinical features of SLE include anti-P with psychosis and anti-Ro with congenital heart block and subacute cutaneous lupus [6].

A recent study by Arbuckle [10] demonstrated the relationship of ANA with disease progression. A retrospective analysis of serum from patients

Box 1. American College of Rheumatology criteria for systemic lupus erythematosus*

1. Malar rash
2. Discoid lesions
3. Photosensitivity
4. Presence of oral ulcers
5. Nonerosive arthritis of two joints or more
6. Serositis
7. Renal disorder
8. Neurologic disorder (seizures or psychosis)
9. Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
10. Immunologic disorder (anti-DNA, anti-Sm, or antiphospholipid antibodies)
11. Antinuclear antibody

* SLE diagnosis with 4 or more of 11 criteria present at any time.

Adapted from Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7; with permission.

who developed SLE demonstrated that 88% of SLE patients had at least one SLE autoantibody before receiving the diagnosis. The presence of ANA, anti-Ro, anti-La, and antiphospholipid antibody was found years (mean, 3.4 years) before the onset of SLE. On the other hand, anti-Sm and antinuclear ribonucleoprotein antibodies appeared within months (mean, 1.2 years) of the diagnosis of SLE. The presence of anti-ds DNA in relation to SLE diagnosis appeared between these time frames (mean, 2.2 years). The presence of ANA, anti-Ro, anti-La, or antiphospholipid antibody was associated with a 40-times increased risk of developing SLE, compared with age- and sex-matched controls [10].

Clinical features

The presenting symptoms of SLE are often nonspecific constitutional signs such as fever, fatigue, and weight loss [3]. Involvement of a variety of organs follows this initial presentation and can include mucocutaneous, renal, neurologic/psychiatric, cardiovascular, and hematologic manifestations (Table 1). The disease course is characterized by disease flares, which may require immunosuppression for symptom management but which frequently decrease over time, with periods of remission. Late mortality is more often related to cardiovascular disease [9]. The 10-year survival has been estimated at 80% to 90%, with early deaths often associated with infection secondary to immunosuppression [7].

Mucocutaneous disease

Mucocutaneous involvement affects 80% to 90% of SLE patients. Four of the 11 diagnostic criteria include mucocutaneous manifestations: malar rash, discoid lesions, photosensitivity, and the presence of oral ulcerations (see Box 1) [7,8]. Mucocutaneous manifestations of LE can be classified as chronic cutaneous lupus erythematosus (CCLE), subacute cutaneous lupus erythematosus (SCLE), and acute cutaneous lupus erythematosus (ACLE). The cutaneous and mucosal lesions of CCLE and SCLE can present alone or as part of the multisystem involvement of SLE. Patients with ACLE manifestations either have or will develop SLE.

Chronic cutaneous lupus erythematosus

CCLE can have multiple mucocutaneous manifestations including discoid LE (DLE), hypertrophic DLE, lupus panniculitis, lupus tumidus, and chilblains LE [11]. DLE is the most common form of CCLE and occurs in 15% to 30% of SLE patients; DLE also can exist without systemic disease. DLE lesions may occur at any age but occur most commonly during the fourth decade. Women are more commonly affected with DLE than men, by a 4.5:1 ratio [12].

Table 1
Prevalence of disease manifestations and impact on dental care

Disease manifestation	Prevalence (%)	Impact on dental care
Mucocutaneous	80–90	Presence of acute oral lesions may cause discomfort. Consider SLE or DLE in differential diagnosis of oral lesions.
Renal disease	50–67	For patients requiring hemodialysis: Because of heparinization, provide dental treatment day after dialysis. Antibiotic prophylaxis may be requested by nephrologist to cover dialysis shunts, but concern for cardiac valvular damage is a better rationale for prophylaxis.
Neuropsychiatric conditions	67	For patients with seizures, review history and type of seizures. Protect patient from harm if a seizure occurs during therapy. For patients with psychoses, ensure adequate medical management of condition.
Valvular damage	18–74	Use American Heart Association–recommended antibiotic prophylaxis for confirmed cardiac valvular disease.
Severe coronary atherosclerosis	45	Evaluate blood pressure and coronary artery disease (CAD) symptoms (ie, stable versus unstable angina). For advanced CAD, consider anxiolytics or defer treatment until patient is medically stable.
Infection	14–100	May have poor healing following invasive dental procedures. Evaluate closely postoperatively.
Anemia of chronic disease	80	Severe anemia may alter oxygen supply to organ systems. Evaluate laboratory values (ie, complete blood cell count); may need to consider blood products with severe anemia (<8 g/dL).
Leukopenia	50	Absolute neutrophil count (ANC) < 500 will predispose to infection. Evaluate laboratory values (ie, complete blood cell count and differential); consider antibiotics after therapy with ANC < 500.
Thrombocytopenia	25	Values $<50 \times 10^9$/L may result in prolonged bleeding following invasive procedures. Evaluate laboratory values (ie, complete blood cell count); consider platelet transfusion before invasive procedures with severe thrombocytopenia.
Antiphospholipid syndrome	14–20	Patients receiving warfarin may have increased bleeding following invasive procedures. Evaluate international normalized ratio (INR) before treatment. If INR < 3.5, no alteration in warfarin is usually necessary for invasive procedures. Use appropriate local measures for bleeding control. If INR > 3.5, discuss with physician appropriate measures to lower INR.
Secondary Sjögren's syndrome	7.5–30	Increased incidence of caries and fungal infections. Consider use of parasympathomimetics (eg, pilocarpine or cevimeline), fluoride gels, and antifungal agents with clinical evidence of a fungal infection.

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DLE lesions are characterized by erythematous plaques, frequently covered with a scale that tends to heal with scarring (Fig. 1) [12]. The most common locations for DLE lesions are the face, scalp, ears, and neck, with the head and neck area affected in 80% of cases (Fig. 2) [1,9]. Extracutaneous manifestations are present in 14% to 27% of patients with DLE lesions [1]. In a cohort of DLE patients, Burge [13] demonstrated mucosal lesions in 24% of DLE patients, ranging from mucosal lesions appearing as chronic plaques or lichen planus–like oral lesions, cheilitis, and plaquelike palatal lesions. In patients with DLE oral lesions, 56% also had DLE lesions of the skin. At the initial presentation of DLE patients with oral lesions, 15% also had an SLE diagnosis, and 8% developed SLE over a 6-year follow-up period. Oral lesions can resolve spontaneously but often persist for months to years [12]. Discomfort from oral lesions has been reported in approximately 75% of DLE patients with oral manifestations [14].

Subacute cutaneous lupus erythematosus

SCLE is another subset of cutaneous lupus erythematosus, usually presenting in the third to fourth decade of life. SCLE lesions appear in 7% to 27% of SLE patients and are characterized by erythematous, scaly papules or plaques that are more superficial than DLE lesions [9]. SCLE lesions are more photosensitive, commonly occurring on sun-exposed areas (eg, neck, shoulders, arms, chest, back). They primarily affect white women, and anti-Ro antibodies are a common presenting laboratory finding [9]. The neck is most commonly affected (in 83% of SCLE patients), followed by the face (in 66% of SCLE patients) [15].

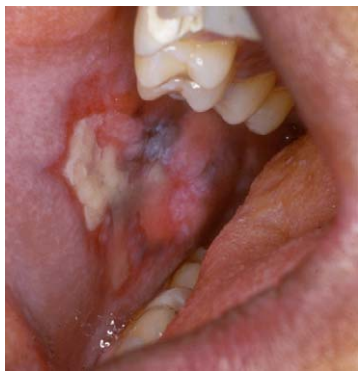

Fig. 1. Oral discoid lesion (18 months' duration) of the buccal mucosa in a patient with systemic lupus erythematosus. Patient had a contralateral buccal mucosa lesion of similar appearance with ulceration, plaque, and erythematous presentation.

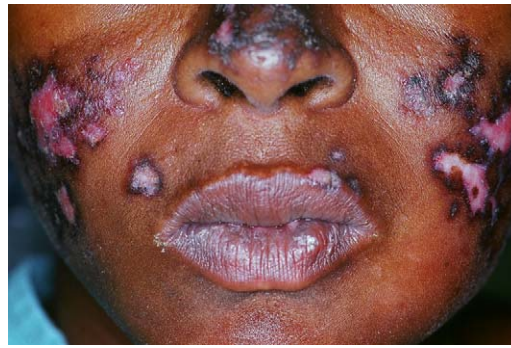

Fig. 2. Discoid lesions of the face characterized by pigment changes, scaling, and atrophy in a patient with chronic cutaneous lupus erythematosus.

Acute cutaneous lupus erythematosus

ACLE classically manifests as an erythematous/edematous rash that involves the malar eminences (butterfly rash), bridging the nose (Fig. 3) [2]. Patients with ACLE lesions often meet the diagnostic criteria and ultimately develop SLE [16]. The butterfly malar rash is seen in 30% to 60% of SLE patients. ACLE lesions are often triggered by sun exposure, and 33% to 67% of SLE patients have cutaneous or other systemic manifestations related to photosensitivity [7].

Systemic lupus erythematosus mucosal lesions

Mucosal ulcerations in patients with SLE most commonly involve the mouth, nose, and anogenital region. These lesions may include DLE-type

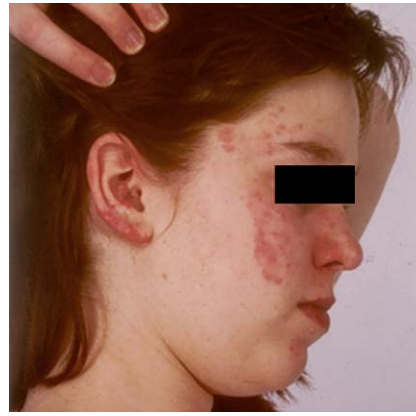

Fig. 3. Erythematous malar rash of a patient with systemic lupus erythematosus. Erythematous lesion is also present on patient's ear.

lesions or nonspecific LE ulcerations. Lesions in the oral cavity have been estimated to occur in 2% to 80% of SLE patients, with a median prevalence between 20% and 30% (Table 2). In a cohort of 182 SLE patients, Urman [17] found that 40% of patients had nasopharyngeal or oral mucosal lesions ranging from erythema to ulcerations, with 89% of these lesions appearing on the palate (Figs. 4 and 5). The majority of the lesions (82%) were asymptomatic. There was a clinically significant association with mucosal ulceration and SLE disease activity [17]. In another cohort of SLE patients, oral lesions were found in 45% of patients, with the most common clinical appearance being erythema (35%); discoid lesions were demonstrated in 16% and ulceration in 6% of SLE patients. Unlike the SLE cohort examined by Urman, no association with oral lesions and SLE disease activity was found [18]. Therefore, it is unclear if the presence of oral lesions is predictive of disease activity in SLE.

Histologically, LE lesions have characteristics similar to lichen planus. Because lesions can vary from erosions to a plaquelike appearance, a wide range of histologic changes can be present, such as acanthosis, parakeratosis, orthokeratosis, liquefactive degeneration of the basal epithelial layer, and subepithelial hyalinization and chronic inflammatory infiltrate [18,19]. Additional direct immunofluorescence studies can provide additional diagnostic information. Subepithelial immunoglobulin (such as IgG and IgM) and complement deposition at the basement membrane zone (lupus band test) can be found in most LE lesions. A positive lupus band test has also been demonstrated in clinically normal tissue of LE patients, especially in patients with SLE [18].

Table 2
Oral manifestations of lupus erythematosus

Oral sign/symptom	Cohort size	Prevalence (%)	Reference
Mucosal lesions	100	2	[53]
	53	21	[13]
	182	26	[17]
	275	29	[36]
	51	45	[18]
	20	80	[56]
Oral candidiasis	100	4	[53]
	4	75	[14]
Dysphagia	100	11	[53]
	16	75	[52]
Xerostomia	100	1	[53]
	51	40	[59]
	20	80	[56]
	16	100	[52]

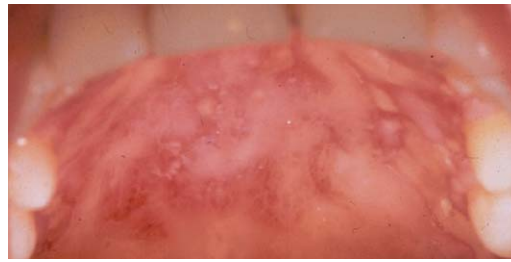

Fig. 4. Acute ulcerations and erythema on the palate of a patient with systemic lupus erythematosus.

Treatment of mucocutaneous disease

Guidelines from the American Academy of Dermatology for the management of cutaneous LE recommend (1) avoidance of sunlight with protective clothing or the use of at least UVB-15 protective sun blocks; (2) topical or intralesional corticosteroids; and (3) systemic therapies including first-line medications of aminoquinoline antimalarial agents, dapsone, and prednisone [20]. Approximately 50% to 80% of patients with cutaneous lupus respond to antimalarial agents [7]. In a survey of 61 lupus centers worldwide, the most frequent treatments for mucocutaneous manifestations included hydroxychloroquine (85%), azathioprine (59%), dapsone (41%), thalidomide (35%), and pulse steroids (27%) [21].

There are no large or controlled studies in the literature on the management of DLE- or SLE-associated oral lesions. For oral lesions, potent topical corticosteroids and antimycotic agents are often administered initially (Table 3) [12,22]. Intralesional corticosteroids also may be considered. If there is no response with topical therapy, the use of

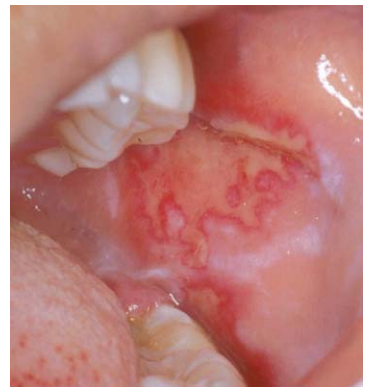

Fig. 5. Acute ulcerations and erythema on the buccal mucosa of a patient with systemic lupus erythematosus.

Table 3
Topical therapy for oral lesions of lupus erythematosus

Topical steroid therapy[a]	Directions for use[b]
0.05% fluocinonide gel	Place on affected area(s) 2×/day for 2 weeks
0.05% clobetasol gel	Place on affected area(s) 2×/day for 2 weeks
Dexamethasone elixir (0.5 mg/5 mL)	Swish and spit 10 mL 4×/day for 2 weeks
Triamcinolone acetonide 5mg/mL	Intralesional injection
Topical antifungal therapy	
10 mg clotrimazole troches	Dissolve in mouth 5×/day for 10 days
Nystatin suspension (100,000 units/mL)	Swish and spit 5 mL 4×/day for 10 days
Chlorhexidine rinse (0.12%)	Swish and spit 10 mL 2×/day until lesions resolve

[a] Fungal infections are a side effect of topical steroids.
[b] If lesions do not respond appropriately to topical steroids in 2 weeks, consider systemic therapy such as antimalarials, steroids, thalidomide, clofazimine, and methotrexate.

antimalarial agents and more potent systemic therapies including steroids, thalidomide, clofazimine, and methotrexate have been used [12,23–25].

Renal disease

Renal disease occurs in 50% to 67% of SLE patients, most commonly within 5 years of the diagnosis [9]. SLE onset in childhood more frequently involves kidney disease (in 80% to 90% of patients), whereas patients with late-onset SLE less commonly experience renal involvement [3]. Lupus nephritis is a predictor of poor overall outcome [9].

The pathogenesis of renal disease involves tissue damage that most likely results from an inflammatory reaction to immune complexes [26], probably enhanced by anti-DNA autoantibodies. The presence of hypocomplementemia and elevated anti-ds DNA seems to be associated with the severity of renal disease [27]. Treatment primarily involves steroids; the use of cytotoxic drugs such as cyclophosphamide may provide additional therapeutic efficacy [27].

Neuropsychiatric manifestations

Up to 67% of SLE patients have neuropsychiatric manifestations including organic brain syndrome such as memory impairment, delirium, or coma (20%), seizures (15%), peripheral neuropathies (10%), psychosis (10%), and cardiovascular accidents (5%) [27]. The pathogenesis seems to be related to vascular injury from immune complexes, with subsequent cerebral cortical infarcts [28]. Infection, atherosclerosis, and drug side effects may also play a role. Severe manifestations may require corticosteroids for appropriate management [9,27].

Cardiovascular disease

Valvular heart disease is common in SLE (occurring in 18%–74% of patients), in particular Libman-Sacks vegetations [29–32]. Although the mechanism for these vegetations is unclear, a combination of immune complexes, complement activation and other inflammatory reactions, fibrosis, scarring, and calcification are likely involved [4,33]. Although valvular disease does not seem to be related to the duration, activity, or severity of SLE, the presence of valvular disease is associated with increased morbidity and mortality [32].

Retrospective cohort analyses suggest an incidence of infective endocarditis of 0.4% to 1.8% in SLE patients [34–36]. Miller [36] analyzed data for 275 SLE patients to determine the prevalence of patients at risk of developing infective endocarditis and found that 3.3% to 4.4% of the SLE cohort had valvular problems identified by transesophageal echocardiography requiring antibiotic prophylaxis according to the American Heart Association recommendations [37]. It is unclear if this percentage is an underestimate, however, because only 8% of SLE patients in this study cohort had undergone transesophageal echocardiography [36].

Atherosclerosis is another important cardiovascular manifestation seen in SLE patients. Although the exact pathogenesis is unclear, numerous risk factors of atherosclerosis probably play a role in SLE. These risk factors include diabetes, hyperlipidemia, glucocorticoids, kidney disease, hypertension, and the presence of immune complexes [9,27]. Severe coronary atherosclerosis was demonstrated in 45% of SLE patients at autopsy [38]. In the SLE population the risk of mortality from coronary artery disease is nine times higher than population-based rates [39].

Infection

In developed countries, infection accounts for 25% to 50% of morbidity from SLE, and infection is an important reason for hospitalizations [40–43]. The pathophysiology of increased infection in SLE probably involves impaired inflammatory and immune responses, including low levels of complement and a variety of neutrophil abnormalities [44]. The most common bacterial infections in SLE involve gram-negative bacilli (eg, *Escherichia coli*, Klebsiella spp., Pseudomonas spp.) and gram-positive cocci (eg, Staphylococcus and *Streptococcus pneumoniae*) [41], which probably do not originate from the oral cavity. Herpes zoster is the most common viral infection, occurring at a rate of 16 episodes/1000 patient-years [39].

The presence of salivary dysfunction, treatment with corticosteroids and other immunosuppressant therapy, and the presence of lupus lesions predispose SLE patients to oral fungal infections (eg, *Pneumocystis carinii*, Candida spp) [14,41,44,45]. In a study by Schiødt [14], more than half of DLE patients with oral lesions had evidence of a yeast infection associated

with the oral discoid lesion. Concurrent treatment of the oral lesions with topical steroids was unrelated to the presence of a positive yeast smear. The lack of saliva decreases natural antimicrobial activity; steroids impair inflammatory and immune responses [44,46]; and mucosal surface changes, especially discoid lesions, provide an environment ideal for the overgrowth of yeasts [14].

As the most common viral infection in SLE, herpes zoster may initially present intraorally or at other head and neck locations as blister-type lesions followed by scab formation. These lesions are typically limited to one side of the body.

Hematologic disorders

Hematologic abnormalities are frequent findings in SLE. Approximately 80% of SLE patients have anemia of chronic disease, and 50% have a leukopenia [9]. Autoimmune thrombocytopenia occurs in up to 25% of SLE patients, and 5% have severely deficient levels ($<20 \times 10^9$/L) [27]. Low blood cell counts seem to result from peripheral destruction unrelated to bone marrow disease [9]. Submucosal hemorrhages (eg, petechiae) can appear intraorally with low platelet counts.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) increases the risk of venous and arterial thrombosis in SLE patients. The prevalence of APS is 14% to 20% in SLE patients [47,48], whereas SLE is diagnosed in 36% of APS patients [49]. The diagnosis is made by the presence of anticardiolipin antibodies or lupus anticoagulants, along with clinical evidence of recurrent venous or arterial clotting or fetal loss [7,50]. Deep venous thrombosis is the most common clinical manifestation of the venous circulation, whereas stroke or transient ischemic attacks are the most common presentation involving the arterial circulation [51]. Medical management of patients with APS often requires aspirin or warfarin therapy. If warfarin is required, the target therapeutic international normalized ratio (INR) to prevent thrombosis is three [50,51]. Submucosal ecchymosis may be seen in patients with an increased INR in areas of trauma.

Other head and neck manifestations

In addition to mucosal lesions in DLE and SLE, other head and neck manifestations have been reported, including glossodynia, dysgeusia, dysphagia, and xerostomia (see Table 2) [52]. Jacobs [53] reported on oral manifestations in 100 SLE patients, 2% of whom had oral ulcerations, 4% candidiasis, and 1% xerostomia. Eleven percent of this cohort reported dysphagia.

Patients with SLE can develop secondary Sjögren's syndrome (7.5% to 30%), an autoimmune exocrinopathy [54–58]. Assessment of sicca (dryness) complaints in SLE has shown a high prevalence (40% to 100%), although the impact of medication-induced xerostomia should also be considered [52,55,56,59].

In addition to xerostomia, other oral manifestations associated with secondary Sjögren's syndrome include increased incidence of caries and fungal infections, tooth erosion, salivary gland swelling, fissured or atrophic tongue, and salivary gland enlargement. Taste and olfactory dysfunction, dysphagia, nutritional compromise, and speaking difficulties are also found in patients with Sjögren's syndrome and are related to salivary dysfunction [45].

Summary

The mucocutaneous lesions of LE and the multisystem manifestations of SLE significantly impact the dental management of this complex patient population. DLE- and SLE-associated oral lesions often are challenging to resolve; appropriate therapy may range from topical steroids to the use of potent systemic immunosuppressive therapy. In addition to the oral lesions, which occur in approximately 20% to 30% of patients, the impact of renal, neuropsychiatric, cardiovascular, and hematologic disease often influences dental management. Additionally, concomitant manifestations of APS and secondary Sjögren's syndrome add to the complexity of managing this patient population. Nevertheless, with appropriate training and an understanding of the complex manifestations of LE, dental management can be provided by the patient's community dental practitioner.

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