INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with a highly heterogeneous pattern of clinical and serological manifestations. Its course differs in different individuals and is unpredictable within the same patient over time, which makes it interesting and challenging to manage.

The pathogenesis of SLE is the result of interactions between genes, hormones and the environment, but its precise etiology is mostly unknown. Recently, >80 risk genes for the disease have been described. Certain genetic features are also associated with increased disease activity.

Systemic lupus erythematosus (SLE) has various clinical presentations from soft, slowly progressive symptomatology to rapidly progressive and sometimes fatal disease. Pathogenesis of SLE consists in the formation of soluble immune complexes often involving autoantibodies to nuclear proteins, with anti-dsDNA autoantibodies observed in over 70% of SLE patients compared to only 0.5% of healthy control subjects.

The American College of Rheumatology (ACR) has proposed revised classification criteria for SLE requiring 4 of 11 criteria, to be met to classify the patient as having lupus.

More recently, the SLICC group proposed another set of classification criteria. Using the SLICC classification, at least four criteria, including at least one clinical criterion and one immunological criterion, should be present to be classified as having SLE. The latter also includes oral and nasal ulceration as well as mucosal lupus, sometimes embracing a diagnosis of overlapping discoid lupus / lichen planus.

Some studies have identified oral lesions in 54% of SLE patients. Mucosal lesions deserve to be detailed. Secondary Sjögren's syndrome can develop in patients with SLE, and differentiating between SLE and secondary Sjögren's syndrome can be difficult. The development of squamous cell carcinoma in skin-mucosal lesions of lupus is rare.

In the last 30 years, major efforts have been made to define some key aspects of the condition, notably disease activity and damage, using standardized indices. These tools are essential for comparing
different cohorts, assessing disease progression and prognosis, and measuring response to treatment. This approach is particularly important now that new biological drugs are beginning to show encouraging signs of efficacy in lupus. This review focuses mostly on the recent advances in understanding and managing SLE [1].

**CASE PRESENTATION**

A 39-year-old woman is referred to the Department of Oral Medicine and Surgery of the University Clinic of Monastir, by her Neurologist for the exploration of a left facial neuralgia in the form of painful crises with a background of persistent pain.

Interrogation reveals that the patient has been followed since the age of 30, in Internal Medicine, for hypothyroidism and SLE diagnosed following skin rashes aggravated by exposure to the sun and joint pain mainly affecting the limbs. She presents an old laboratory examination with positive ANA.

The patient regularly takes prednisone 10 mg, plaquenil 200 mg, levothyrox and adalate and is partially relieved.

At the extraoral examination, we noticed sclero-atrophic lesions of the lips and squamo-erosive perinarinal lesions (Fig. 1. A and B). Elsewhere, superficial erythematous skin lesions on the trunk are associated with Raynaud's syndrome noted in the fingers (Fig. 2).

The examination of the mouth opening is strictly normal without limitation of movements, no noise or joint pain during mobilization either.

**Fig-1:** A and B. sclero-atrophic lesions of the lips and squamo-erosive peri-narinal lesions.

**Fig-2:** Raynaud's sign, bluish appearance of the fingers that is numb

The intraoral examination shows mouth dryness with acceptable oral hygiene. The 46 is in the state of roots and the 47, 36, 37 and 27 are restored with amalgam and asymptomatic. The left cheek mucosa shows a superficial erythematous area with a burning sensation reminiscent of a lichenoid reaction to amalgam (Fig.3. A and B).
Fig. 3: A and B. Dental condition and erythematous area of the right cheek mucosa.

Gingival examination reveals scattered erythematous areas on the maxillary and mandibular gingiva which persist despite brushing and scaling. This aspect is suggestive of desquamative gingivitis (Fig. 4. A and B).

Fig. 4: A and B. aspect suggestive of desquamative gingivitis.

On the palatal mucosa, there is an erythematous zone finely furrowed by white streaks, giving the appearance "in honeycomb" (Fig. 5) characteristic of a SLE palatal lesion.

Fig. 5: "Honeycomb" aspect of a palatal lesion

The evocated diagnosis is skin and mucosal manifestations of SLE and neuralgia related to the neurological complications of this disease.

Thus, we recommended the patient to continue the specific treatment with the addition of a local treatment in mouthwash based on Solupred 20 mg per day for its mucosal symptoms and carbamazepine (Taver 200 mg) at a rate of 3 half tablets per day, for her facial neuralgia.

We made a point of redoing a complete checkup (complete CBC, VS, CRP, ANA, anti-dsDNA, thyroid checkup, renal checkup, etc.) and we summoned the patient after 10 days. At check-up, she returned with a report in favor of systemic inflammatory syndrome, positive ANA and anti-dsDNA and the rest of the report was without particularities. In addition, the patient mentioned a complete disappearance of facial pain and a clear regression of oral symptoms.

An extraction of the dental roots, a motivation for hygiene and scaling, and the replacement of amalgams by composites have been established. Also, the patient is readdressed to her internist doctor for possible adaptation of her systemic treatment.

Remaining under the same treatments and monitored every month, the patient remained asymptomatic after six months of follow-up.
D I S C U S S I O N

Understanding

Patients with Systemic Lupus Erythematosus (SLE), a prototypic autoantibody disease, develop autoantibodies to nuclear molecules in many of their cells, cell components and tissues. Clinical manifestations appear to result from deposition of antigen antibody complex in the tissues. Cytokines are thought to play a key role in SLE; however, the extent to which they affect progression of lupus is not clear.

Another theory might be that SLE autoantibodies are a sequel of cross reactions to exogenous antigens e.g. RNA retroviruses. Extrinsic factors such as exposure to sunshine, infections and drugs may trigger SLE reactions in some patients. No matter the etiology, genetic predisposition is a probability, as expressed in associations with specific HLA/MHC antigenic profiles. Dysfunction of B-lymphocytes is one of the main defects in SLE. In addition, suppressor T-lymphocytes are also reduced in number, permitting a considerable increase in autoantibodies [2].

SLE commonly affects young women of child bearing age, like our case, with a female: male ratio of 10:1 (90% of cases are in women), more predominantly in young women due to higher levels of estrogen, while at premenstrual and post-menopausal women, ratio with males decreases to 3:1.

Cutaneous manifestations are seen in the form of erythematous patches on the face that coalesce to form a symmetrical pattern over the cheeks across the bridge of the nose in a butterfly pattern of distribution which is known as malar rash. Skin around the neck, arms, shoulders and fingers are also affected. They may also be associated with itching or burning sensation, and areas of hyper pigmentation. Macules or papules occur on the face, or a generalized rash occurring on the body, which may or may not be sun induced.

Diffuse alopecia can generally occur when the disease is active and is usually reversible during remission. Patchy alopecia, on the other hand, may lead to scarring and can become permanent [3, 4]. Cardiovascular and respiratory symptoms are also common and include chest pain on inspiration due to pleurisy or pericarditis. Renal complications (glomerulonephritis and microvascular thrombosis) and neuropsychiatric complications (seizures, psychosis, neuropathies, stroke, and depression) are common as well [5]. This is our case, where the patient complained about facial neuralgia. Ophthalmic and gastrointestinal manifestations are usually uncommon but can be serious, including kerato-conjunctivitis sicca, pancreatitis, hepatitis, and subacute bowel obstruction. Pain in the joint and arthritis are common manifestations [3]. Present case showed similar cutaneous involvement and joint pains in the form of arthralgia.

If a patient fulfills more than 4 of 11 criteria made by American College of Rheumatology, then the diagnosis of SLE can be made with about 95% specificity and 85% sensitivity. Diagnosis of SLE is based on clinical judgment. SLE can be suspected whenever 2 or more organ systems are involved.

Treatment

There is no known cure for Systemic Lupus Erythematosus; hence treatment is based on relieving symptoms, suppressing inflammation, and preventing future pathology. As our case shows, symptomatic treatment for the specific involved organ as per the severity of the disease: topical sunscreens, avoidance of UV light and estrogens, NSAID’s for arthritis, antimalarials for dermatologic manifestations, topical steroids for rash, use of systemic steroids for prevention of end organ damage, Calcium and Vitamin D supplements to fight osteoporosis and corticosteroids as immunosuppressant drugs for serious organ involvement (e.g. nephritis). There is also the Biological therapy [6] (e.g. Belimumab, Rituximab). To date, the most logical and widely used biological option in SLE has been B cell depletion achieved by direct B cell elimination or inhibition of B cell survival agents. However, all medications used to treat SLE require monitoring periodically for potential toxicities [7].

Preventive dental hygiene care in Lupus patients is very important. Chlorhexidine mouthwashes help contain periodontal disease by chemical plaque control. Mucous membrane ulcers can be managed with hydrogen peroxide gargle or steroid impregnated gel. Intralesion infections of corticosteroids are also effective modality. Bacterial, viral and fungal infection should be treated using conventional, proven therapy specific for the infection. No Dental procedures should be undertaken on patients with active Lupus, and if necessary, antibiotic premedication is always advisable due to high incidence of bacterial endocarditis.

Adverse effects of Lupus therapy in oral cavity [8]

Long term use of medications to control Lupus can induce significant intra-oral pathology such as mentioned below:

- Corticosteroids: lead to root canal calcification, delay of tooth eruptions and root dilacerations and cause necrotizing ulcerative gingivitis.
- NSAID’s: induce gingival bleeding, but due to the inherent property of NSAID’s to inhibit alveolar bone resorption, periodontal health in some patients with Lupus has been found to improve.
- Cyclosporine: causes gingival enlargement (hyperplasia).
- Immunosuppressive treatment: fights against intra-oral infections but promotes Candidiasis and Herpes Simplex Virus opportunistic infections.

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Oral mucosal lesions in lupus erythematosus

In 20-50% of patients’ oral lesion of SLE are seen. These manifestations of the oral cavity may be seen either prior to or following the development of skin lesions or even in the absence of skin manifestations. In a decreasing order, locations more frequently affected are buccal mucosa, hard palate and lower lips in the form of ulcers, erythema or hyperkeratosis. Oral lesions appear as erythematous areas, without induration and with white spots. The margins of these lesions are not sharply demarcated but quite often show the formation of narrow zone of keratinization. Hyperemia with edema is a common occurrence and there may be a tendency for bleeding [Table 1].

<table>
<thead>
<tr>
<th>Table-1: Clinical presentations of oral LE lesions [9]</th>
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<tbody>
<tr>
<td><strong>Chronic lesions: discoid lesions</strong></td>
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<td>Lesions are almost always asymmetrically distributed on buccal cavity.</td>
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<tr>
<td>– Atrophic or ulcerated round lesions with peripheral keratotic striae</td>
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<tr>
<td>– Linear ulcers with keratotic striae.</td>
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<tr>
<td>– “Honeycomb plaques” (longstanding scarring lesions) (which are noted in our case)</td>
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<tr>
<td>– Intensely keratotic lesions (verrucous LE)</td>
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<tr>
<td>– palatal discoid lesions</td>
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<tr>
<td>– Labial discoid lesions</td>
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<tr>
<td>– Squamous cell carcinoma may arise in longstanding scarring lesions</td>
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The main clinical differential diagnoses are lichen planus, leukoplakia, squamous cell carcinoma and even vesiculobullous diseases. That depends on the morphology of the analyzed lesion. The main differential diagnoses for keratotic discoid lesions are LP, lichenoid reactions to dental fillings, traumatic and smoker’s keratosis, and verrucous carcinoma. Ulcerated discoid lesions should be differentiated from aphtha, erosive LP, traumatic ulcers, deep mycoses, Langerhans cells histiocytosis and SCC (SCC can develop in old scarring LE lesions). Lip lesions may simulate contact cheilitis, factitious cheilitis, actinic cheilitis, LP, psoriasis, erythema multiform, pemphigus vulgaris and SCC. Erythematous or purpuric macules may resemble LP, erythema multiform, mucous patches of syphilis, petechiae of viral exanthema, and negative pressure purpura (“fellatio syndrome”). Finally, differential diagnoses for oral bullous LE include pemphigus vulgaris, mucous membrane pemphigoid, herpes simplex, varicella, and erythema multiform with its variants (Stevens-Johnson disease and toxic epidermal necrolysis).

Histological appearance of SLE is not pathognomonic but is suggestive of the disease. Histopathological features include, changes at the dermo-epidermal junction that include thickening of the basement membrane (best demonstrated by periodic Acid-Schiff staining) and vacuolar degeneration of the basal cells along with perivascular inflammatory cell infiltration of a variable degree in the reticular dermis. Hyperkeratosis is more evident and follicular plugging may be seen in more mature lesions [10]. [Table 2]

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<th>Table-2: Histopathological comparison between oral LE, oral LP and oral lichenoid drug reactions [9]</th>
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<td><strong>Epithelial alterations</strong></td>
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<td>Hyperkeratosis, granulosis, acanthosis and atrophy, spongiosis, hydropic degeneration (patchy or widespread), colloid bodies, hyperproliferation of basal layer, sometimes with presence of atypical keratinocytes.</td>
</tr>
<tr>
<td>Basement membrane (Epithelial and vascular wall)</td>
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Direct immunofluorescence testing is often used to detect the presence of IgG, IgM and IgA at the basement membrane. The antinuclear antibodies (ANA) test is highly specific with a positive result in >95% of SLE patients. The anti-dsDNA antibody test is positive in 60% of SLE patients and is considered the best marker for disease activity, with a specificity of almost 100%, except in elderly patients who have a lower prevalence of anti-dsDNA. Complement levels (C3 and C4) are negatively correlated with lupus activity and their levels deplete because of consumption.

Facial calcinosis cutis in a patient with systemic lupus

Calcinosi cutis refers to a group of disorders that are characterized by soft tissue calcification. Dystrophic calcinosis is the most common subtype and is associated with a variety of autoimmune disorders. It is rarely described in association with SLE, and there are only approximately 45 documented cases to date [11, 12]. Possible etiologies of dystrophic calcification in this case include preceding panniculitis, discoid lesions, mechanical trauma or repeated tissue trauma secondary to photosensitivity.

Oral Manifestations of Sjogren ‘s syndrome and Skin Manifestations of Lupus

Sjogren’s syndrome (SS) is an autoimmune disorder that affects multiple exocrine glands, particular those that produce moisture to coat exposed epithelia such as the oral and ocular surfaces. The prevalence of secondary SS in SLE is reportedly from 8 to 30% in different studies [13].

Patients with SLE have dry eye and mouth symptoms that last longer than healthy ones. Also, the importance of dry symptoms and signs of exocrinopathy in SLE has implications for treatment and follow-up. We can also emphasize the high risk of developing a secondary SS by patients with SLE with anti-SSA and / or anti-SSB antibodies, particularly for those with dry symptoms and fatigue.

Periodontitis and systemic lupus erythematosus

The existence of similar destructive mechanisms could explain an eventual association between periodontitis and SLE. These potential mechanisms in common may involve deregulation, especially in the innate immune system, with action of phagocyte cells and of proinflammatory cytokines and polymorphism of IgG receptor [14, 15].

Periodontal tissue is also affected by immunosuppressive medication given in SLE. The most frequent periodontal manifestations are acute ulcerative necrotic gingivitis, periodontitis and gingivitis [16].

The treatment consists in the improvement of the periodontal condition and the activity of the systemic disease.

Temporomandibular joint disorders and systemic lupus erythematosus [17]

Temporomandibular joint disorders can be arthritic or infectious arthritis. Osteonecrosis can be also favored by treatment with glucocorticoids. It results in pain and movement limitation. MRI and CT x-ray examination are necessary to confirm the diagnosis. Likewise, chronic pain in the ATM can result from depressive disorders and neuropsychiatric manifestations of lupus.

Here are some guidelines for combating ATM disorders related to SLE

The first step is to treat the systemic disease and educate the patient to change their maladaptive habits and behavior. Use of dental therapies such as stabilization or repositioning appliance and physiotherapy appear to enhance the effect of behavioral treatment. Treatment of degenerative and inflammatory etiologies includes analgesics, anti-inflammatory agents, muscle relaxants, corticosteroids, anti-anxiety agents, and low-dose of antidepressants [18]. Infectious etiology should be treated with antibiotics. Decompression and surgical treatment are indicated for osteonecrosis.
Facial Angioedema and Systemic Lupus Erythematosus

Angioedema, a non-pitting, non-pruritic, non-erythematous, and non-painful swelling, involves subcutaneous and submucosal tissues. It results from increased vascular permeability by activation of complement and kinin systems.

Besides prednisone therapy, the antifibrinolytic tranexamic acid, rituximab, and plasmapheresis have been therapeutically advocated and have met with some success [19]. Because recurrent angioedema episodes are possible, long-term prophylaxis is needed.

Perioperative Management by the Dentist [20]

Our case emphasizes that the dentist and especially the specialist in oral medicine and surgery must be able to diagnose SLE and request the necessary checkup.

Although investigation plan for a case of SLE will depend on the clinical picture, the minimum laboratory workup should include:

- Haemoglobin, WBC, Differential count, ESR
- Urine routine (preferably a fresh sample examined) and microscopy, and 24-hour protein and creatinine estimation if necessary
- Serum chemistry (urea, creatinine, liver function tests, lipid profile)
- Chest x-ray
- ANA, anti-dsDNA, C3, C4

The dentist 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. 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 antivitamin K 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.

To conclude, Chlorhexidine in mouthwash helps relieve periodontal disease. Mucosal ulcerations can be managed with topical steroids. Intraleosional corticosteroid injections are also an effective modality. Infections should be treated with appropriate antibiotics. No dental procedure should be performed in patients with active SLE, and if necessary, antibiotic prophylaxis is always advised due to the high incidence of bacterial endocarditis.

Like our case, a multidisciplinary approach to medical consultation and appropriate referrals ensures comprehensive medical and dental management of patients with SLE.

Indeed, 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.

Conclusion

Systemic lupus erythematosus is an autoimmune disorder that can affect several organ systems, including the skin, kidneys, and Central Nervous System. Of patients with SLE, 25% have associated oral lesions, which are usually superficial ulcers with surrounding erythema. It is essential that dental practitioners should know these pathologies and diagnose them at an early stage of the disease to help assist in providing more effective treatment to improve survival rates. The intraoral examination should be incorporated as a part of dermatologic examination as the oral manifestations can represent preliminary signs or can coexist with the disease.

Data availability

All data are made available in the publication.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.
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Dental Faculty of Monastir

**REFERENCES**
