LUPUS AND THE MOUTH

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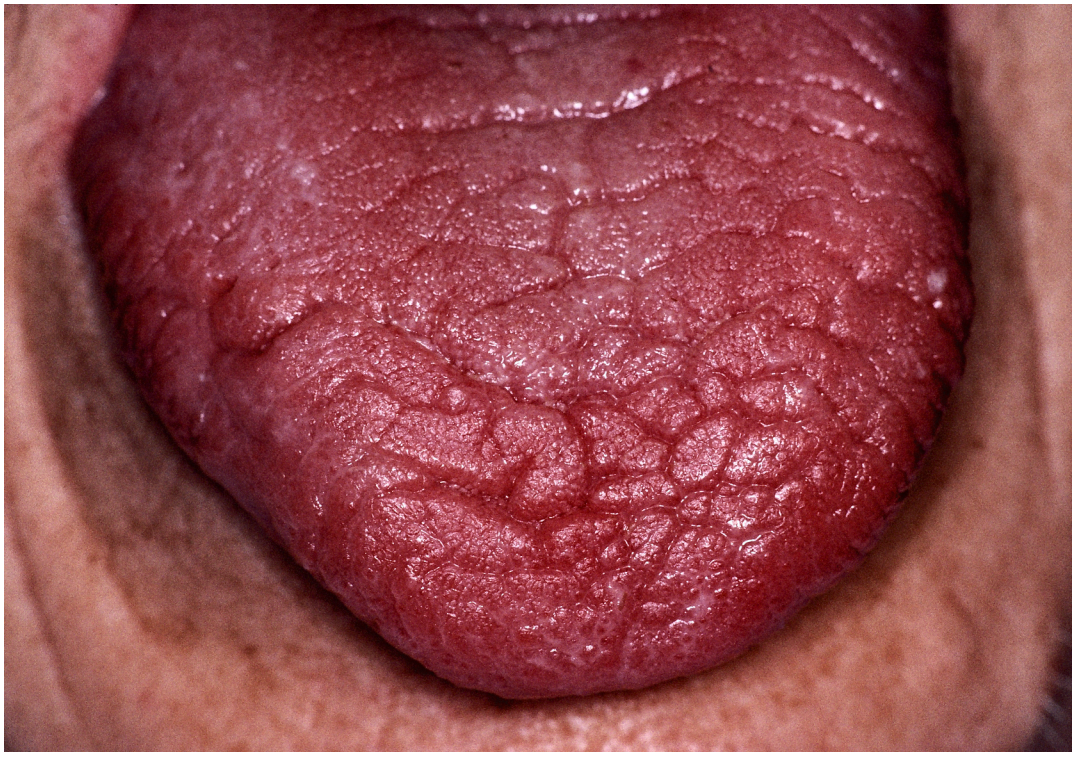
Introduction

The oral cavity is often referred as a "mirror of the body" and can be the first site with clinical signs of a sometimes distant systemic disease. The oral manifestations of various systemic conditions may precede or follow closely the involvement of other districts of the body and in some instances can be the dominant feature that warrants a particular emphasis upon investigation and/or treatment. Oral disease can sometimes be having the greatest negative impact upon a patient with systemic illness.
The presence of oral ulcers (including nasopharyngeal ulcers) is one of the 11 criteria defined by the American College of Rheumatology for the diagnosis of systemic lupus erythematosus (SLE)[1]. A thorough examination of the oral tissues can provide useful information to clinicians for an early diagnosis of systemic lupus erythematosus (SLE).
Oral lesions would normally improve if lupus is adequately controlled and their reoccurrence is often an indicator of a new disease flare-up.
A wide spectrum of oral signs and symptoms caused by SLE has been described[2] and might be related not only to the disease itself, but also to concomitant secondary conditions or be the effect of different medications.

XEROSTOMIA

Xerostomia is described as the complaint of oral dryness[3]. The presence of symptoms of dry mouth has been reported in more than 75% of patients with SLE[2]. It is often associated with multiple signs and symptoms (Table 2). Xerostomia can derive from inadequate salivary secretion secondary to abnormal function of the salivary glands or it can be described in patients reporting oral dryness despite normal salivary gland function[4].
A reduced salivary flow can be directly caused by SLE or be secondary to the concomitance of Sjögren's syndrome (SS) (Figure 1).

Figure 1. Notable dryness of the tongue in a patient complaining of xerostomia



The prevalence of SS in SLE is high and estimated to be on average 18% (range 8% to 19%)[5,6]. However it must be borne in mind that the most common reason of objective oral dryness in all individuals, with or without lupus disease will be drug therapy and in the case of SLE opioid analgesics and/or antidepressants (both tricyclic and serotonin reuptake inhibitors) are likely to be particular causes of this symptom. Further, lifestyle factors may occasionally contribute to dry mouth including Tobacco smoking, alcohol use (including use of mouthrinses), and (rarely) drinking caffeinated beverages[7].

Table 2 Signs and Symptoms of Xerostomia

Symptoms	Signs
✓ **Dysathria** ✓ **Dysphagia (especially with dryn foods)** ✓ **Dysgeusia (altered taste)** ✓ **Ageusia (loss of taste)** ✓ **Coughing episodes** ✓ **Burning-like sensationof the oral mucosa** ✓ **Discomfort while wearing dentures** ✓ **Dysphonia**	➢ Dryness of the oral mucosa ➢ Increased adherence of mucosal surfaces and/or lips ➢ Foamy saliva ➢ Absence or minimal saliva accumulation in the floor of the mouth ➢ Dental caries (especially cervical, root caries or around the margins of restorations) ➢ Oral Candidiasis (may manifest as pseudomembranous, median rhomboid glossitis, denture associated stomatitis, angular cheilitis ➢ Salivary gland swellings (e.g. due to inflammation, acute suppurative sialadenitis or lymphoma secondary to Sjogren's syndrome) ➢ Fissured or Lobulated tongue ➢ Erythematous mucosa ➢ Glassy oral mucosa ➢ Loss of papillae of the tongue dorsum ➢ Food deposits on the gingivae or rarely buccal vestibules oral mucosa ➢ Oral malodour (halitosis) secondary usually to food deposits and/or plaque-related gingival inflammation

The extent and severity of dry mouth can be evaluated via questionnaires such as the Summated Xerostomia Inventory— Dutch Version[8] (Table 3). However there remains no truly effective means of assessing the severity of oral dryness and its impact upon oral and general well being.

Table 3. The Summated Xerostomia Inventory

The Summated Xerostomia Inventory—Dutch Version
1 My mouth feels dry when eating a meal
2 My mouth feels dry
3 I have difficulty in eating dry foods
4 I have difficulties swallowing certain foods
5 My lips feel dry.

The patient scores each statement on a numerical scale from 1 to 5 (“ Never,” scoring 1; “ Occasionally,” 2; and “ Often,” 5). The responses are then summed to give a cumulative score, with higher scores representing more severe clinical manifestations.

Objective estimation of salivary flow can be determined using the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria of assessing the unstimulated whole saliva flow rate. This is considered to be abnormal when below 0.1ml per minute[9]

Diagnostic tests for oral dryness directly related to immunologically mediated disease in SLE

Oral dryness in relation to SLE is typically either due to medication or Sjogren’s syndrome. If it assumed that the patient is not receiving medication likely to cause salivary gland dysfunction it is advisable to follow the investigations expected for the objective diagnosis of primary SS.

Histopathology of labial gland biopsy material and the demonstration of anti-Ro antibodies are central to the diagnosis of SS although a number of radiological investigations may be of help but not fool proof and should not replace those advocated by the ACR/EULAR guidelines. Ultrasound scans (USS) of salivary glands of SS will usually demonstrate a picture or micro or macrocystic heterogenous areas in all major salivary glands that are of small size. Similar changes may be observed with Magnetic Resonance Imaging (MRI) and the ductal abnormalities (sialectasis) can also be demonstrated by sialography – although this technique is rapidly dimishing in application in view of the need for patient exposure to radiation and the excellent results that can be obtained with USS alone. Radionuclide scanning will demonstrate loss of salivary function – but so will simple sialometry.

Management

Considering that dry mouth is often a side effect of certain medications, discontinuing or switching them to alternative agents might ameliorate patients’ symptoms of xerostomia.

The first line treatments recommended for dry mouth are topical agents. Chewing gums, candies (both sugar-free to prevent caries), salivary stimulants and saliva substitutes are the more commonly used medications to

stimulate saliva secretion and reduce friction of the oral mucosa[9]. Salivary stimulants and substitutes, including toothpastes, mouthwashes, and gels, can improve salivary gland function. Saliva substitutes supposedly resemble natural saliva and increase salivary viscosity[10]. Saliva substitutes might contain carboxymethylcellulose, xanthan gum, mucins, hydroxymethylcellulose, polyethylene oxide, or linseed oil and are used to increase the volume and viscosity of the saliva. Furthermore, a sialogogue spray, composed of 1% malic acid, has been used to treat anti-depressants related xerostomia[11]. Mucin sprays, tablets, and lozenges may be used in reducing the symptoms of dry mouth. Intraoral electrostimulation has also been experimented[12].

With regards to systemic sialogogues, oral pilocarpine and cevimeline are the agents most commonly used for this purpose. .

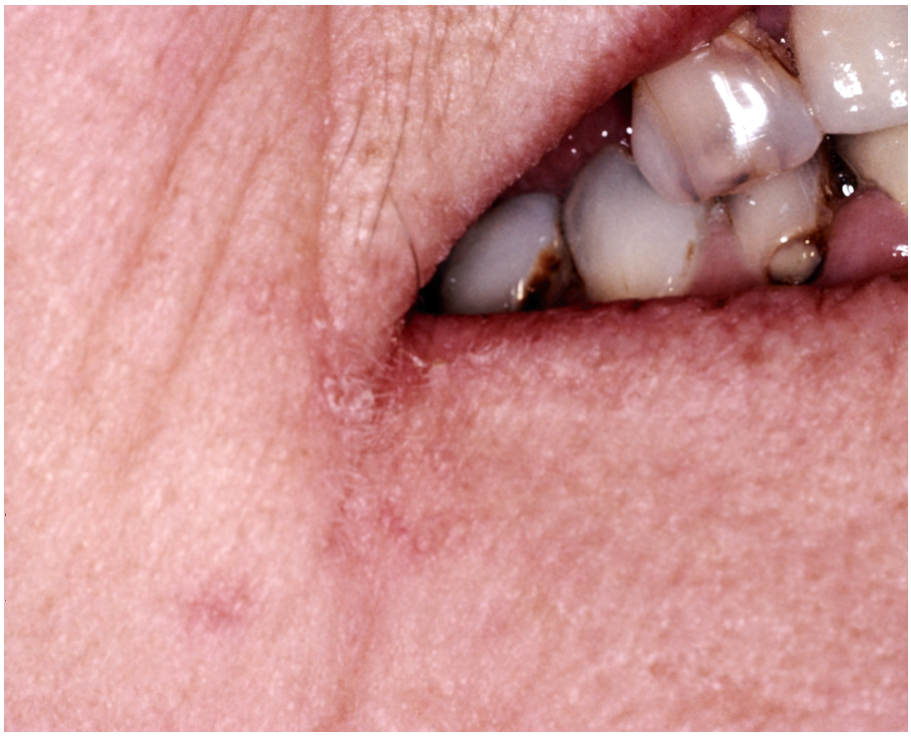
Pilocarpine is a nonselective muscarinic agonist and parasympathetic agent. The recommended starting dose is 5 mg daily up to a maximum of 30 mg daily[13]. Patients are typically instructed to take 5 mg three times daily for at least 3 months[14]. Side effects include visual disturbance, hiccups, bradycardia, hypotension, bronchoconstriction, nausea, vomiting, abdominal pain, diarrhoea, cutaneous vasodilation, and increased urinary frequency. Sweating is common and tends to arise within the first hour of each dose. . It is contraindicated in certain types of glaucoma and clearly should not be prescribed to patients with known asthma or other pulmonary disease likely to be compromised by the cholinergic effects.

Cevimeline is a muscarinic agonist that is selective for M1 and M3 receptors, of the lacrimal and salivary glands. It has fewer side effects than pilocarpine, because it does not affect M2 receptors. Standard dosing is 30 mg three times daily for at least 3 months. It is also longer acting than pilocarpine[15]. Its most common side effect is dyspepsia. Cevimeline is however contraindicated in patients with chronic pulmonary disease and uncontrolled asthma, as well as those taking β -adrenergic blockers. In addition, caution should be taken in patients with uncontrolled hypertension and active gastric ulcers. Civimeline, alas, is not available in Europe and the evidence that other systemic sialogogues including bethanechol, anethole trithione are of clinical benefit is very weak.

Novel preventive measures for xerostomia such as botulinum toxin or systemic growth factors, producing regenerative salivary gland tissue through transplantation or gene therapy have also been experimented but all require further studies[7]. Electrostimulation of the salivary glands is without doubt the most promising way forward for the management of salivary gland dysfunction of SLE (and hence SS) with appropriate studies under way.

ANGULAR CHEILITIS

Angular cheilitis is an inflammatory condition that occurs in 1 or both angles of the mouth (Figure 2).
Figure 2. Angular cheilitis – redness and soreness of the corner of the mouth



This condition typically presents with erythema, painful cracking, scaling, bleeding, and ulceration at the corners of the mouth[16]. Angular cheilitis reflects local accumulation of oral candida (and bacterial species) and/or cutaneous *Staphylococcus aureus* and the corners of the mouth. In the main it is caused by saliva becoming trapped at the corners of the mouth that is most commonly underlined by a loss of vertical face height by wearing down of the teeth or dentures (the patients have a crumbled lower face appearance). It can be also abnormal skin folds at the corners of the mouth (e.g. wrinkles of normal aging) iron, Vitamin B12 or folate deficiencies, lip enlargement (e.g. with recurrent persistent angioedema, labila enlargement in Crohn's disease or sarcoidosis) or , drooling (e.g. secondary to Parkinson's disease). In patients with SLE angular cheilitis may also reflect anaemia, neutropenia or oral dryness.

Management

The treatment of angular cheilitis is highly dependent on the cause. There is no evidence that local application of petroleum jelly is of benefit. More effective methods are the local application of miconazole gel or agents that are cominations of corticosteroid, anti-antibacterial and/or antifungal. There may be aneed to also manage any clinically obvious oral candida infection, for example denture-associated stomatitis by application of miconazole to the

fitting surface of the denture, regular cleaning of the denture and immersion in chlorhexidine gluconate solution. Systemic antifungal therapy is rarely warranted and long trem use should be avoided in view of the known risk of emergence of azole-resitant strains. High recurrence rates of angular cheilitis have been described in patients with SLE (up to 80%) therefore measures to prevent the onset of disease are recommended[17].

MUCOSAL LESIONS

SLE has been associated with a wide spectrum of oral mucosal lesions: cheilitis, erythematous patches, `honeycomb' plaques, discoid lesions, lichen planus (LP)-like lesions and discrete ulcers[18,19] (Figure 3)(Table 5). In established disease, reported prevalence rates range from 9% to 45% of cases[20].

Figure 3. Lupus type erosion and white patching of the left buccal mucosa

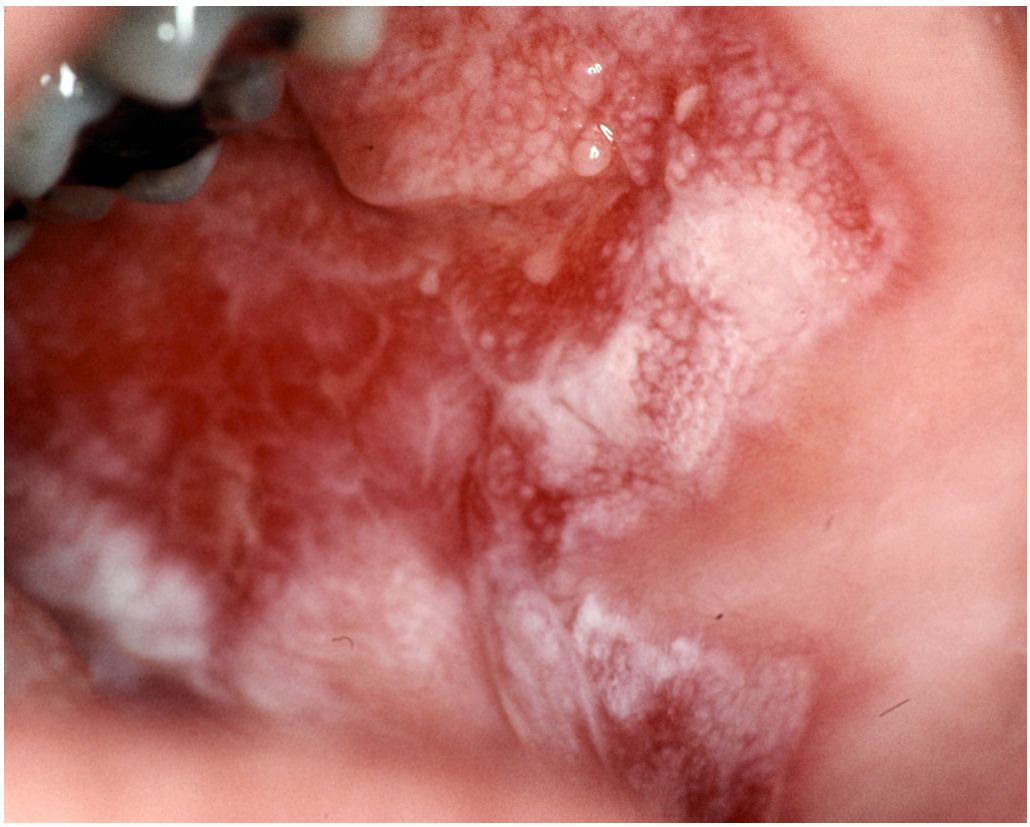


Table 4 *Clinical characteristics of oral lesions seen in lupus erythematosus (adapted from Orteu et al.[20])*

Type of lesion	Appearance	Commonest site
Cheilitis	Erythema and scaling	Lower lip, vermilion border
Erythematous patches	Poorly demarcated telangiectasia and oedema	Hard palate
`Honeycomb' plaques	Well-circumscribed, white lacy hyperkeratosis and erythema	Palatal mucosa
Discoid lesions	Red atrophic centre and peripheral radiating	Buccal/labial mucosa and gingiva

	white hyperkeratotic striae and telangiectasia	(often at sites of missing teeth)
Lichen planus-like lesions	Reticulate leucokeratosis	Buccal mucosa
Discrete ulcers	Red/grey base and hyperkeratotic borders	Palatal mucosa (but other sites are possible)

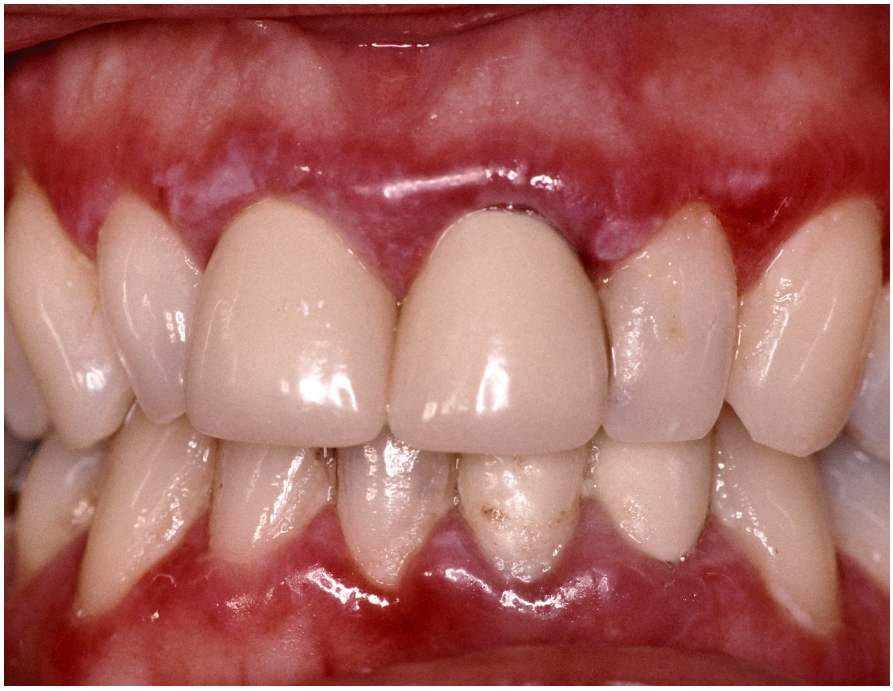
Oral mucosal lesions are frequently chronic and may be asymptomatic in 50 to 80% of patients[21].

Oral mucosal lesions are common manifestations of both chronic discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE). Approximately one fourth of patients with cutaneous DLE also have oral discoid lesions. Approximately 40% of patients with SLE can present oral mucosal ulceration[19,21,22]. In addition, oral reticular, red and white plaques have also been associated with SLE. Oral lesions constitute an appreciable clinical manifestation in SLE patients.

There are two main types of these ulcers: a) those with classical LE histological changes representing oral discoid lesions (FIGURE 3) and b) non-specific ulcers in keeping with aphthous ulceration. The lupus specific lesions begin with solitary erythema and haemorrhaging patches before developing into discoid ulcers with a reticulate border. Typically, the lesions are painless and located on the hard palate. However this type of lesion can arise on any oral mucosal surface and when there is ulceration within the lesions there is likely to be some pain, particularly with hot, citrous or spicy foods.

Of note some patients can have these lupus lesions on the gingivae giving rise to areas of painful redness and/or white patches – termed desquamative gingivitis (Figure 4).

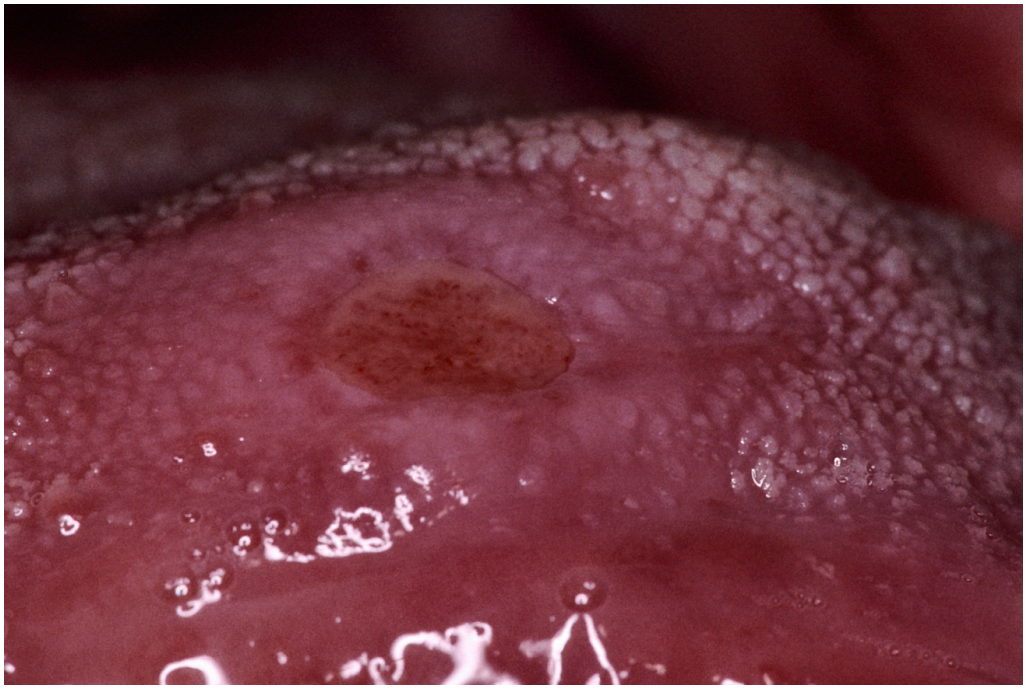
Figure 4. Desquamative gingivitis – the gums are notably painful



The clinical features of this type of lupus disease are similar to those of oral lichen planus (OLP) and indeed it is difficult to distinguish the 2 disorders when on the oral mucosae or gingivae. Lupus disease may give rise to assymetrical disease and affect the palate while OLP tends to have a symmetrical pattern within the mouth and usually does not affect the central palate. Confusingly hydroxychloroquine can cause OLP and hence patients may have oral features of both disorders – the term lupus lichenoid overlap has sometimes been used to describe this.

The non-specific aphthous ulcers are usually painful, with multiple lesions on the buccal mucosa, lips and nasal septum, whilst also having a tendency to bleed[23] (Figure 5).

Figure 5. Superficial aphthous-like ulceration in systemic lupus erythematosus



There are several causes of this type of ulceration: 1. anaemia (e.g. haemolytic, iron deficiency secondary to NSAID-induced gastric erosion or secondary to chronic disease and 2. Neutropenia secondary to immunosuppressive therapy or the presence of an autoimmune neutropenia.

Oral and nasopharyngeal ulcers are suggested to be most likely during active disease and subside with disease remission in JSLE and adult SLE patients.

Telangectasia of the oral mucosa is rare in SLE (being much more likely in scleroderma) while occasional patients with autoimmune thrombocytopenia of lupus may have petechiae or ecchymoses of the oral mucosa and/or gingivae. Theoretically a low platelet count will cause spontaneous gingival bleeding.

A rare but possible oral feature of SLE is amyloidosis. This may present as golden-coloured lobules on the lateral aspects of the tongue (true macroglossia is extremely rare) or non-specific sessile lumps on the oral mucosa or gingivae, having a normal overlying surface. Amyloidosis can also cause trigeminal neuropathy (hence paraesthesia or anaesthesia) and enlargement of a salivary gland.

Management

The treatment for oral mucosal lesions aims to control the symptoms. Methotrexate[24], dapsone[25] and gold have been used. Antimalarials (for example hydroxychloroquine and mepacrine) and azathioprine in patients with oral manifestations of SLE have shown some benefit. Biopsy should be taken in patients presenting with cutaneous or systemic manifestations suggestive of SLE.
Topical steroid mouthwash, in the form of either betamethasone (0.5mg,) or prednisolone (5mg), held in the mouth for five minutes three times daily might reduce the discomfort. The possibility that intra-oral changes represent a lichenoid reaction rather than lupus itself must always be considered since such mucosal lesions are seen relatively frequently with the use of the nonsteroidal anti-inflammatory drugs that patients with lupus may be taking. Therefore, if the onset of any oral symptoms coincides with the start of a new medication it may be necessary to consider an alternative option.

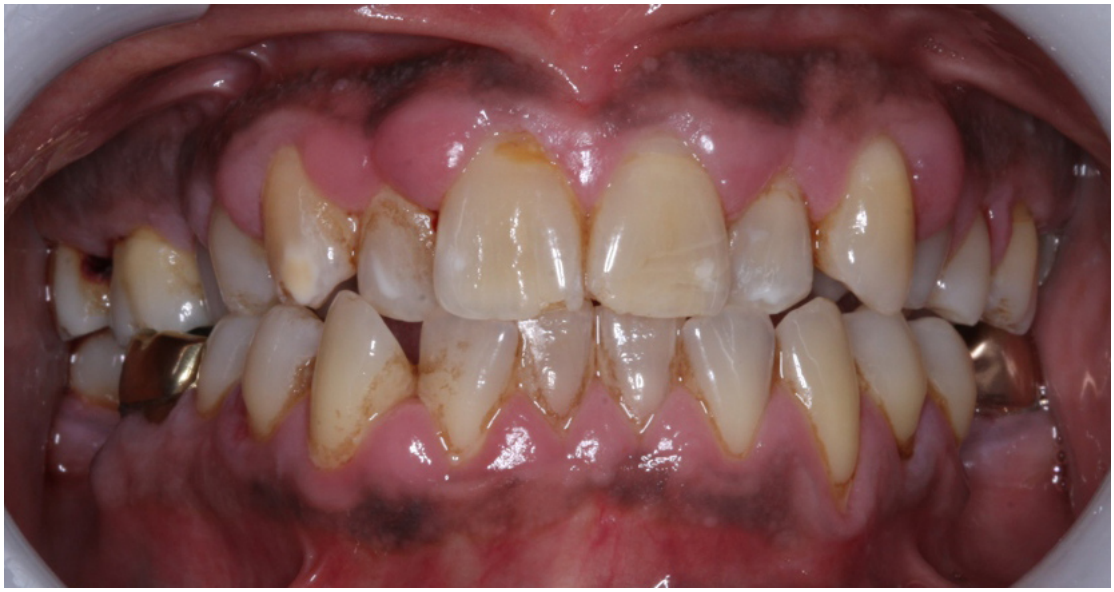
There remains concern that the oral lesions of lupus may increase the risk of oral squamous cell carcinoma, and certainly those patients who develop lichenoid change of the oral mucosa as a consequence of drug therapy should be considered to have about 1% risk of development of this oral malignancy.

Although not likely to be restricted to the oral mucosa, trigeminal neuralgia has been reported in occasional patients with SLE. This is often described as a lancinating (“sword-like”) pain of one branch of the trigeminal nerve, although patients usually describe it as “electric shock” type pain. The pain may arise spontaneously or secondary to touch or movement of the mouth and/or face. The management of this very rare feature of SLR typically involves the use of gabapentin, pregabalin, carbamazepine or other similar agents.

PERIODONTITIS

Periodontitis (PD) is a chronic inflammatory and infectious condition affecting the tissues supporting the teeth (gingival, periodontal ligament and alveolar bone)[26]. The natural development of the disease is characterized by a slow course, with active phases of gingival inflammation, connective tissue and bone loss. When left untreated the disease will eventually cause tooth mobility, drifting and aesthetic changes, reduced masticatory function and tooth loss (Figure 6).

Figure 6. Periodontitis



An early clinical study reporting on the periodontal status condition of 16 female patients with SLE reported a prevalence of periodontitis of approximately 94%.[2] However, a subsequent case-control study reported lower prevalence estimates and very similar to those patients without SLE [27]. Further, same authors suggested that the long-term administration of non-steroidal anti-inflammatory (NSAIDS) or immunosuppressive drugs in patients with SLE could have been linked to improved gingival condition.
Within the last 20 years few more observational studies have evaluated the periodontal health in patients with SLE and a recent systematic review and meta-analysis has summarized the available data reporting statistically significant increased odds of periodontitis in patients with SLE compared to controls[28].
Furthermore, in presence of a concomitant SS, the odds of developing periodontal inflammation is 2.2 times greater than in controls[29]. This could be related to a low salivary secretion promoting a rapid plaque accumulation and a reduced immune-protective action of the saliva.

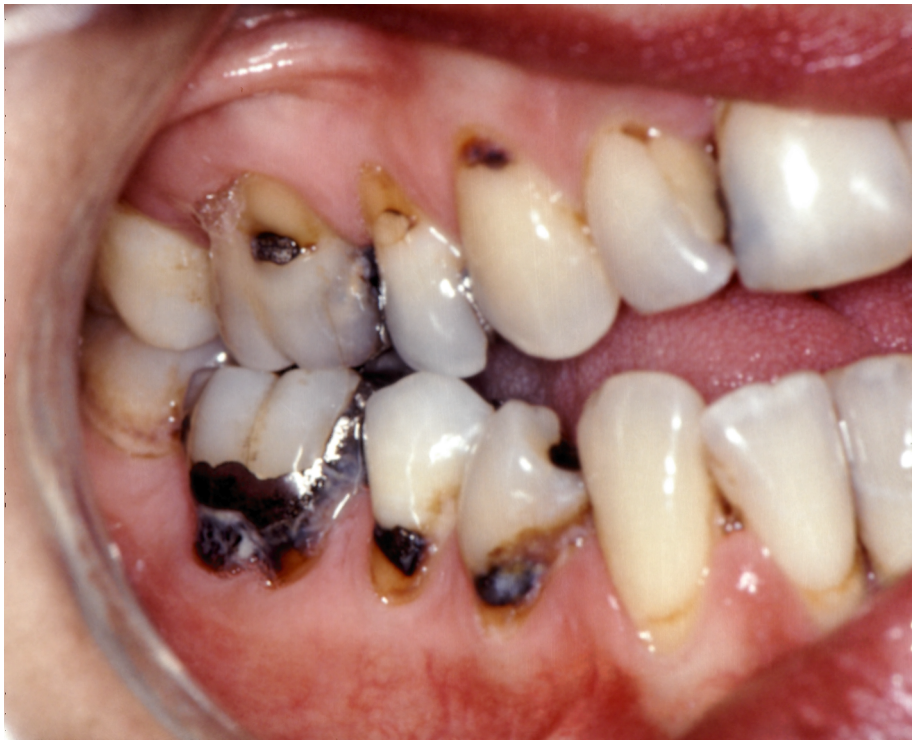
Management

The treatment of periodontitis relies on the removal of the causal factors, primarily bacteria and is performed by means of ultrasonic or hand instrumentation of the diseased dentition. Lifestyle risk factors such as oral hygiene habits and smoking require also to be addressed[30].
Periodontal therapy is delivered over three phases: initial, then a corrective and a final supportive phase. During the initial phase, any essential dental care, oral hygiene advice and teeth cleaning (scaling of the teeth including subgingival root debridement) are performed. Following at least 8 weeks from the start of the first dental cleaning session, a re-evaluation of the periodontal condition is performed together with an assessment of the patient's self-performed oral hygiene. A corrective phase of therapy includes additional surgical periodontal therapy (if patient oral hygiene is optimal) or a repetition of the scaling and root debridement (if oral hygiene is suboptimal). This second phase is usually completed within 1-2 months. After 3 months from the last periodontal surgical session a final re-assessment is completed to define the third phase of therapy. This is the supportive phase of periodontal therapy, an open-ended protocol of three monthly sessions of oral hygiene advice and professional non surgical dental cleaning as required.
Considering the elective nature of periodontal therapy, a specialist referral for the management of this condition is strongly advised.

DENTAL CARIES

In patients with hyposalivation/ SS, the reduced amount of saliva predisposes to the development of atypical or unusual dental decay, i.e., cervical, incisal, or in cusp tips (in the border of teeth), as well as radicular lesions (Figure 7).

Figure 7. Dental Caries



This is a constant demineralization, a rapidly progressing (rampant) and aggressive form of dental decay. The presence of SS affects the saliva pH and buffer capacity[31]. The presence of dental erosion is frequent, and it is very common to find edentulous patients.

Management

Dietary sugars can be reduced by avoiding sweet sticky foods at all times, not snacking on sweets between meals and restricting sweet foods to meal times. Sweets or foods that contain non-sucrose sweeteners cause less caries than sugar, but can cause gastrointestinal upset in some people. Diet need not be boring. There is no need to entirely avoid sugars - as provided individuals are sensible and maintain a high standard of oral hygiene (see below) their risk of caries will generally be low. Snacks that contain crisps, nuts (if they are not too hard and not going to cause TMJ pain) and many other savoury agents contain low levels of sugar and also may stimulate saliva that will neutralise the action of acids.

Clean teeth well

The teeth should be cleaned at least twice a day using a suitable toothbrush and a fluoride-containing toothpaste. The brush should have a small head that and relatively soft bristles. A variety of tooth brushing techniques can be used (e.g. a gentle up-and-down rolling or figure of eight action), but importantly the teeth should not be scrubbed in a horizontal direction as this increases the risk of damage to the gums and any exposed root surfaces. Brushing should include gentle massage of the gum margin, as this will help to remove any plaque trapped beneath this site. There are no specified guidelines for tooth cleaning in relation to SLE but it would seem sensible for each patient to find a method that suits themselves.
Toothbrushes only remove the plaque and debris from the upper and exposed (smooth) surfaces of teeth, hence the areas between teeth (interdental sites) require to be cleaned separately. A variety of interdental aids are available particularly floss, interdental brushes and interdental sticks. Floss needs to be used carefully to avoid traumatising the gums. Floss holders can aid flossing, particularly if individuals have difficulties in reaching the posterior teeth.

Use fluorides

Fluoride in toothpastes and mouthwashes will lessen the resistance of decay of only the surface layer of enamel. Twice daily use of a fluoride-containing toothpaste is recommended. Fluoride mouthwashes can also be helpful although are probably not needed if a patient is already using a fluoridated toothpaste.

Antimicrobial mouthwashes

Antimicrobial mouthwashes may reduce the risk of gingivitis and periodontitis and may lessen oral malodour. A wide range of mouthwashes are available; these should be used on a daily basis. There is no strong evidence that alcohol-containing mouthwashes increase the risk of mouth cancer.

Attend a dentist regularly

Dentists manage common dental disease. In addition they will be able to arrange referral to appropriate specialists if a patient has complex disease or possible oral manifestations of SLE that warrants further investigation or treatment. Advice about the availability of dentists can be obtained from NHS Direct. Dentists with a limited knowledge of SLE and its implications upon oral health and dental care should refer the patient to an appropriate specialist for advice.

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