Disorders of the mouth

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Abstract

Disorders of the mouth, whether as a consequence of primary disorders, systemic disease or treatment, may be encountered across most medical specialties. Recurrent aphthous ulceration represents the most common primary oral disease, but oral lesions may indicate active systemic disease at less accessible sites such as the gut. Moreover, oral disease can have a detrimental impact on quality of life. For these reasons, it is important to be aware of the more common lesions affecting the oral cavity and to formulate a differential diagnosis appropriate for each lesion. In this article, we address the more common disorders seen in clinical practice. A distinction is made between primary oral disorders and systemic disease with oral manifestations. We have attempted to categorize systemic disease affecting the oral cavity into the medical specialties where they are likely to be encountered and for ease of reference for the general reader. Finally, we include a table of commonly used therapeutic regimens for oral disease, summarizing their mode of action and indications.

Keywords Drug-induced; MRCP; mucosa; oral disease; primary; systemic

Key points

- Disorder of the oral cavity may represent primary oral disease or systemic disease
- A careful review of systems with a particular focus on dermatological and gastroenterological concerns is key to accurate diagnosis
- Thorough examination of the oral cavity should be included in routine clinical assessments
- Any patient with oral lesions should be encouraged to attend their primary care dentist or be referred to an oral medicine unit for further assessment

Introduction

The oral cavity is not only important for speech, taste and the ability to eat, but also plays an integral part in the body's immune system as it is the first portal to be exposed to a variety of antigens and pathogens. As a result, oral disease often has a detrimental effect on a patient's well-being, quality of life and nutritional status. It is therefore important to undertake a careful examination of the oral cavity during the clinical assessment of many, if not all, patients. This is particularly true in those conditions where the oral status may reflect the disease process at less accessible sites such as the gut.

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Whether from a gastroenterological or a general medical point of view, the approach to oral lesions should be logical and assist in the formulation of a differential diagnosis appropriate for the lesions encountered. In practice, it is often useful to consider three questions when oral pathology is encountered:

- Does it indicate existing or new primary oral disease?
- Is it a consequence of existing or new systemic disease?
- Is it a consequence of treatment?

The following is one approach to assess the oral cavity. Our aim is to provide an overview of the more common oral conditions and their possible systemic associations.

Primary oral disease

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease and is generally divided into three subtypes (minor, major, herpetiform), of which minor accounts for approximately 90% of cases. Minor RAS typically presents during adolescence as crops (1–5) of painful, small (<5 mm), rounded, well-defined shallow ulcers with surrounding erythema and a greyish base.[1] The pathogenesis remains unknown, but it is thought to be an immune-mediated disease with a genetic predisposition (30% of patients have a positive family history). Lesions are self-limiting and usually heal without scarring within 14 days but can recur several times or more per year. Stress, food hypersensitivities and infections may all predispose to RAS.

Treatment consists of symptomatic relief, although topical corticosteroids can be indicated for frequent or debilitating attacks of minor or herpetiform RAS. Major RAS is best managed by appropriate referral for specialist care. Common medications used to treat oral mucosal disease are detailed in Table 1.

Benign migratory glossitis (geographic tongue, erythema migrans) is usually an asymptomatic inflammatory condition of uncertain aetiology involving the epithelium of the tongue. The lesions result from a localized loss of filiform papillae and appear as erythematous patches with a whitish border on the dorsal aspect of the tongue; they can change location and size with time (Figure 1). Most patients do not require treatment, and the value of symptomatic therapy, in the form of local anaesthetic mouthwashes and gels, remains unproven.

Common medications used in oral mucosal disease

Drug	Mode of action	Disease	Regimen
Hydrocortisone sodium succinate 2.5 mg tablets (Corlan®) licensed indication	Topical corticosteroid, multiple anti-inflammatory effects	Aphthae	6-hourly during ulcer episode 12-hourly prophylactically
Betamethasone sodium phosphate 500 microgram tablets (Betnesol®) (licensed indication)	Topical corticosteroid, multiple anti-inflammatory effects	Aphthae Lichen planus	Dissolve tablet in 10 ml of water and use as a mouthwash for 3 minutes 6-hourly
Fluticasone propionate 50 microgram spray (Flixonase®) 125 microgram inhaler (Flixotide®) 400 microgram nasules (Flixonase®) (unlicensed indication)	Topical corticosteroid, multiple anti-inflammatory effects	Aphthae Lichen planus	1—2 puffs 8-hourly 1—2 puffs 12-hourly Dissolve contents of nasule in 10 ml of water and use as a mouthwash for 3 minutes 12-hourly
Doxycycline 100 mg capsule (tetracycline 250 mg capsule if doxycycline unavailable) (unlicensed indication)	Antimicrobial with undefined anti-inflammatory effects	Herpetiform aphthae	Dissolve contents of capsule minutes in 10 ml of water and use as a mouthwash for 3 minutes 8-hourly
Tacrolimus 0.1% ointment (Protopic®) (unlicensed indication)	Calcineurin inhibitor	Lichen planus	Apply sparingly twice daily — review after 6 weeks' use
Colchicine 500 μg tablets (unlicensed indication)	Effect on microtubule function of polymorphs, inhibiting their migration to sites of inflammation	Aphthae Behçet's disease	500 micrograms/mg daily
Prednisolone 1 mg, 5 mg and 10 mg tablets (unlicensed indication)	Systemic corticosteroid, multiple anti-inflammatory effects	Aphthae Lichen planus Orofacial granulomatosis (OFG) Behçet's disease	Reducing dose: 40 mg for 7 days, reducing by 5 mg every 3 days until 5 mg, and then by 1 mg every day until 0
Azathioprine 50 mg tablets (unlicensed indication)	Anti-inflammatory effect, corticosteroid-sparing agent	Aphthae Lichen planus OFG Behçet's disease	1—2 mg/kg daily depending on thiopurine *S*-methyltransferase activity
Thalidomide (available on named-patient basis only) (unlicensed indication)	Anti-tumour necrosis factor action	Severe unresponsive aphthae	50—100 mg daily

Table 1

A fissured tongue is frequently seen in the general population (prevalence of 21%) and varies by country. It is characterized by grooves, varying in depth, on the dorsum of the tongue and is thought to have a polygenic inheritance pattern. A fissured tongue is also seen as part of the Melkersson—Rosenthal syndrome (fissured tongue, cheilitis granulomatosa, VIIth cranial nerve palsy) and is associated with Down's syndrome. Patients are usually asymptomatic, but gentle tongue-brushing may be required if food debris within the grooves causes irritation.

Black hairy tongue (lingua nigra) is a benign condition in which the tongue shows elongated, hypertrophic filiform papillae and can have a yellowish or brownish-black discolouration. Predisposing factors include poor oral hygiene, antibiotic use, heavy smoking, candidiasis and corticosteroid therapy. Management consists of removal of predisposing factors, effervescent vitamin C tablets and regular brushing of the tongue with a toothbrush.

Oral disease secondary to underlying systemic disease

A number of medical conditions can present or be associated with oral manifestations. Some of the more common of these are described below, grouped by specialty for ease of reference.

Dermatological

Erythema multiforme is an acute immune-mediated mucocutaneous disease. It is often idiopathic (50%) but can be related to infections (e.g. herpes simplex, mycoplasma) or medications (e.g. sulfonamides, phenytoin, non-steroidal anti-inflammatory drugs). Oral involvement occurs in up to 70% of cases and consists of blisters, which often rupture leaving a painful denuded surface. Cutaneous involvement presents with target lesions, often involving the acral areas symmetrically. Management involves the withdrawal of any causative agent or treatment of the potential infective trigger. Supportive care includes analgesics and fluids. Corticosteroids, both topical and systemic, can play a role. Approximately 30% of cases are recurrent and can be managed with prophylactic antiviral therapy or immunosuppressants.

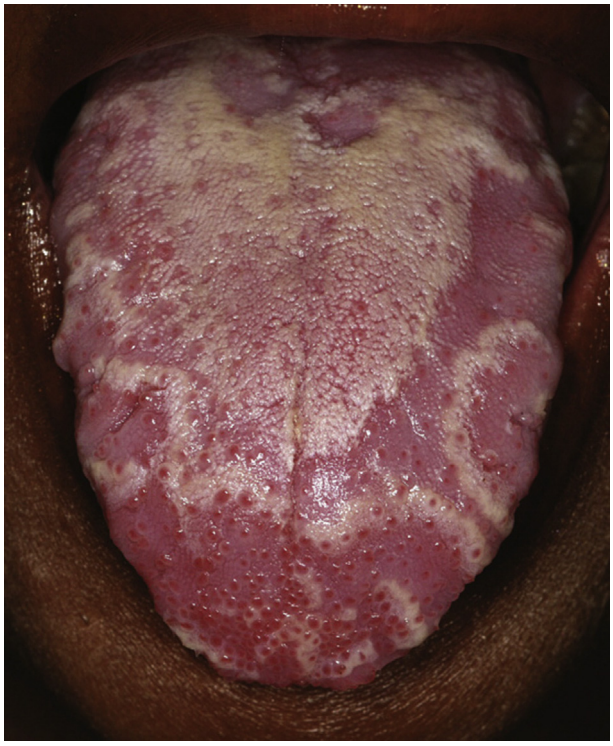

Figure 1 Benign migratory glossitis demonstrating the erythematous patches with a whitish border on the dorsum of the tongue.

Stevens–Johnson syndrome/toxic epidermal necrolysis is a spectrum of more extensive lesions with haemorrhage and necrosis. Lip involvement manifests as oedema and erythema. Mucosal surfaces are usually involved (oral 90%, ocular 85%). It is a drug-induced cytotoxic reaction, the most commonly implicated drugs being allopurinol, carbamazepine and sulfonamides. Most patients require admission and management within an intensive care setting. Treatment consists of supportive care, including removal of all possible precipitating drugs, pain control and fluid management, and treatment of any superinfections.

Immunobullous disorders includes several immunobullous blistering diseases, of which pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) are the most common.[2] Autoantibodies in these diseases are targeted against specific antigens within the epidermal structure (e.g. intraepithelial in PV, subepithelial in MMP). PV usually presents with pain and easily ruptured blisters in the oropharynx and can also involve the skin. MMP may be associated with ocular, pharyngeal, laryngeal or genital involvement. In both cases, diagnosis requires a biopsy and the demonstration of the appropriate autoantibody, at the appropriate site, on direct immunofluorescence. Treatment often requires systemic corticosteroids and subsequent maintenance immunomodulatory agents, such as azathioprine, mycophenolate mofetil and cyclophosphamide. Rituximab, a chimaeric anti-CD20 monoclonal antibody, is also used.

Lichen planus is an uncommon disease of unknown aetiology that mostly affects middle-aged adults. An autoimmune mechanism has been proposed, with cytotoxic CD8 T cells, responsible for epithelial apoptosis, and human leucocyte antigen (HLA) class II involvement.

LP affects the nails, skin and mucosal surfaces. Most cutaneous disease resolves in 1–2 years, but oral disease tends to be chronic. When mucosal surfaces are involved, associated pain can cause significant morbidity. Lesions in the mouth can accompany skin disease or be the only manifestation. The most common lesions are white keratotic striations (Wickham's striae), seen particularly on the buccal mucosa. Lesions can also be atrophic, erosive, plaque-like or desquamative, and involve the tongue and/or gingivae (Figure 2). Histological features consist of a band-like subepithelial mononuclear infiltrate consisting of T cells, histiocytes and increased numbers of intraepithelial lymphocytes with degeneration of basal keratinocytes.

Topical corticosteroids are often beneficial for less severe cases, although their use is not evidence-based, whereas recalcitrant disease may require systemic therapy (e.g. corticosteroids, azathioprine). Patients should be informed of the small increased risk of developing squamous cell carcinoma, particularly with plaque or erosive disease, and regular follow-up is advisable.[3]

Gastroenterological

Coeliac disease is an immune-mediated enteropathy initiated by ingestion of gluten in individuals who are genetically susceptible. This leads to characteristic small bowel histological changes, which revert to normal once a gluten-free diet has been established. Oral signs consist of recurrent oral ulceration, usually similar in appearance to herpetiform aphthous stomatitis. Resultant enamel defects have been described if it is present during dental development. Non-specific oral lesions such as glossitis are also seen and are related to haematinic deficiencies.

Gardner's syndrome is the occurrence of familial adenomatous polyposis (FAP) and multiple extra-colonic growths, first described in the1950s. The gastrointestinal polyposis and gastric cancer risks in Gardner's syndrome are the same as those in FAP, suggesting that Gardner's syndrome is a variant of FAP. Osteomas are found in 20% of patients and commonly involve the mandible. Dental abnormalities, consisting of odontomes (supernumerary and/or unerupted teeth) are also seen. Orthodontic management can be required if dental problems arise.

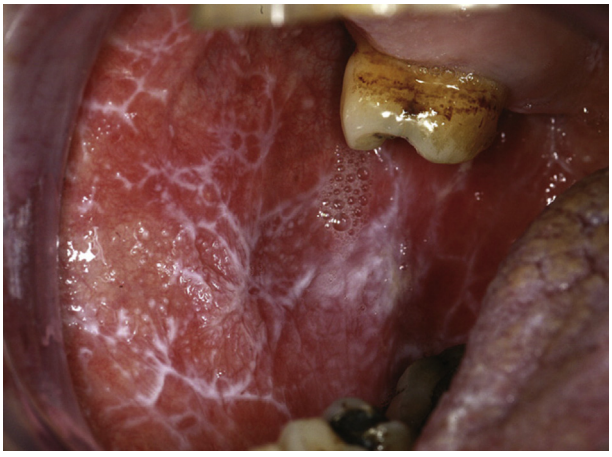

Figure 2 Oral lichen planus showing white keratotic striations (Wickham's striae) on the buccal mucosa.

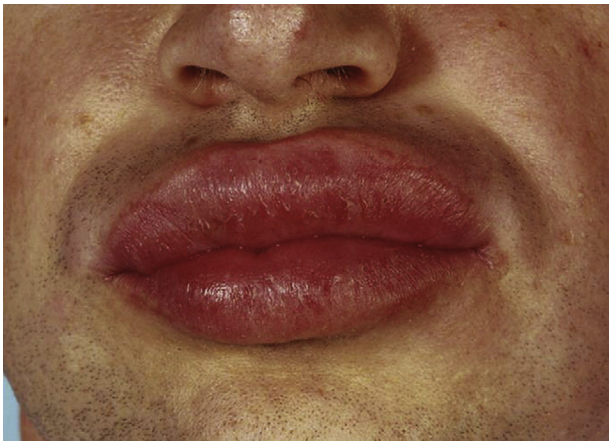

Figure 3 OFG presenting with involvement of the upper lip with swelling and mild erythema.

Orofacial granulomatosis (OFG) and Crohn's disease form another category. OFG is a rare chronic inflammatory disease of unknown aetiology, usually presenting during childhood or young adult life (Figure 3).[4] The differential diagnosis includes Crohn's disease, sarcoidosis, chronic granulomatous disease, Melkersson–Rosenthal syndrome and, rarely, tuberculosis. Up to 60% of patients have asymptomatic gut involvement with histological evidence of intestinal granulomatosis. In a small number of cases, OFG appears to have preceded gut Crohn's disease by a number of years, but no definitive link has been demonstrated. Lip swelling is the most common presentation, but intraoral involvement in the form of buccal cobblestoning, deep linear sulcal ulceration, mucosal tags and gingival hyperplasia can be part of the clinical presentation, as can angular cheilitis. Histologically, OFG is characterized by non-caseating epithelioid granulomas.

Treatment remains a challenge, but evidence suggests that dietary manipulation in the form of a cinnamon- and benzoate-free diet is beneficial for a subgroup of patients. Corticosteroid mouthwashes can help, but some preparations contain benzoates, which can worsen the underlying disease. Intralesional corticosteroids provide benefit in a number of cases. Patients with more severe disease or concurrent Crohn's disease usually require an immunosuppressant regimen, comprising a thiopurine or methotrexate with or without a biological agent (e.g. infliximab, adalimumab). Associated angular cheilitis is often infective and can be helped by topical agents (e.g. miconazole, fucidin) to address candidal and/or staphylococcal infection.

Peutz-Jeghers syndrome is defined as the association between distinctive mucocutaneous pigmentation and multiple gastrointestinal hamartomatous polyps. It has an autosomal dominant inheritance with the gene usually mapped to 19p13.3. Male and female patients are equally affected. The mucocutaneous pigmentation is present in approximately 95% of cases, and the lesions are typically flat brown/blue spots up to 5 mm in diameter. Histologically, they consist of pigment-laden macrophages within the dermis. These lesions are most commonly seen on the lips and perioral area, but are also found on the buccal mucosa, hands and feet. Patients with Peutz–Jeghers syndrome have an increased risk of malignancy, with an estimated risk of around 50% when in their 60s. Most malignancies are gastrointestinal in origin, but breast cancer is also increased in female patients.

Gastro-oesophageal reflux disease is common but its impact on the oral cavity is frequently underestimated. Gastro-oesophageal reflux disease lowers the pH within the oral cavity, often to <5.5, resulting in erosion of dental enamel. The erosions are seen on the palatal surface of the teeth, with the upper teeth more often involved as the tongue protected the lower teeth. The exposed dentine can become discoloured with time, and in severe cases the teeth are destroyed. Treatment consists of addressing the underlying condition and involving a dental practitioner as necessary.

Ulcerative colitis is also seen. Pyostomatitis vegetans is a rare oral presentation of inflammatory bowel disease (primarily ulcerative colitis). It is characterized by multiple small yellowish pustules on an erythematous mucosa and can be accompanied by small vegetating lesions. The lesions may ulcerate, suppurate or become necrotic, and often demonstrate a snail-track pattern. Most areas of the oral cavity can be involved, although the dorsum of the tongue is rarely affected. Treatment remains difficult but ultimately focuses on the management of the underlying gut disease. Management includes topical and systemic corticosteroids, and immunosuppressants.

Haematological

Anaemia, whether caused by iron, vitamin B_{12} or folate deficiency, can manifest with oral signs. Glossitis can be the first sign of vitamin B_{12} or folate deficiency. The tongue appears smooth and erythematous, and can be painful. Other lesions that can coexist include angular cheilitis, recurrent oral ulceration and pale mucosae. Angular cheilitis is more often seen with iron deficiency, and not infrequently as a consequence of candidal infection. Haematological malignancies and any cause of bone marrow failure leading to anaemia can present in a similar manner. In addition, patients can present with spontaneous gingival bleeding or gingival hyperplasia as a result of leukaemic infiltration. Management consists of haematinic replacement, treatment of the underlying disease and good oral hygiene.

Infective

Oral candidiasis (thrush): *Candida* is a normal oral commensal but can become pathological when immunocompetency is reduced, for example by:

- diabetes mellitus
- antibiotic use
- immune deficiencies (inherited or acquired)
- inhaled or oral corticosteroids
- chemo-radiotherapy
- old age.

The most common presentation is in the form of removable white plaques on the tongue, palate and buccal mucosa. However, candidiasis can also cause painful sores at the corners of the mouth (angular cheilitis) or present with a sore, erythematous tongue. The diagnosis can be confirmed from a potassium hydroxide preparation using scrapings of the white plaques, looking for budding yeasts. Management consists of removal of predisposing factors, treatment of the underlying medical condition, and topical therapy in the form of nystatin suspension or miconazole gel. Oral

fluconazole or itraconazole preparations can be needed in recalcitrant disease or in patients with immunodeficiency.

Herpes simplex: primary herpes simplex virus type 1 (HSV-1) infection is often asymptomatic, and the first manifestation can be recurrent disease. Approximately 85–90% of adults demonstrate serological evidence of HSV exposure.

Herpetic gingivostomatitis is the most common presentation of primary disease; it manifests as a rapid onset of multiple intraoral, pinhead-sized vesicles with surrounding erythema (Figure 4). The vesicles rupture rapidly to form painful irregular ulcers and typically heal within 14 days. This can be preceded by prodromal symptoms, consisting of fever, irritability and anorexia, and usually requires supportive therapy only. Thereafter the virus remains latent in the neural ganglia, pending reactivation by precipitants such as trauma, emotional stress, sunlight and immunosuppressant therapy. On reactivation, replication and migration to the skin or mucosa occurs, leading to local symptoms of tingling, pain and burning approximately 24 h before eruption of the vesicles (herpes labialis or 'cold sores').

The diagnosis is typically clinical but can be confirmed using culture techniques or a polymerase chain reaction viral swab. Treatment in the form of aciclovir 5% cream is acknowledged to be effective primary therapy. Timing is, however, important, as aciclovir is effective only when active viral replication is occurring (e.g. the prodromal period). Disease can be more extensive and more frequent in immunocompromised patients. Prophylactic aciclovir or valaciclovir can play a role in patients suffering from frequent reactivation.

Vascular

Behçet's disease is characterized by the triad of recurrent oral ulcers, genital ulceration and eye disease (especially iridocyclitis), although a number of other systemic manifestations are also seen.[5] Behçet's disease mainly affects young men, and there is an association with HLA-B51 (B5101).

Features such as arthralgia and leucocytoclastic vasculitis suggest an immune complex-mediated basis, which is supported by finding circulating immune complexes. Although the antigen responsible has not been identified, heat shock proteins have been implicated. An inflammatory disorder, Behçet's disease is now considered a systemic vasculitis, characterized by a very wide spectrum of clinical features and unpredictable exacerbations and remissions.

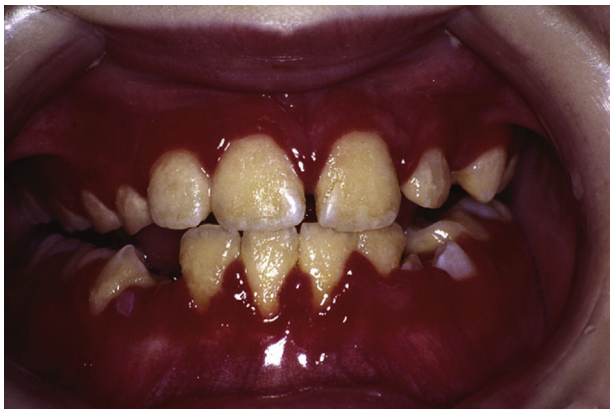

Figure 4 Herpetic gingivostomatitis in a child, showing gingival erythema and small gingival ulcerations.

A variety of treatments, including corticosteroids and azathioprine, have been tried for individuals with the multisystem lesions of Behçet's disease, but results have been variable, especially as the disease is subject to spontaneous transient remission. More recent trials have used biological agents in the management of patients who have failed traditional immunosuppressant therapy. Oral lesions can be managed symptomatically as in RAS, with topical corticosteroids the drug of choice.

Osler-Rendu-Weber syndrome (hereditary haemorrhagic telangiectasia) is an autosomal dominant condition characterized by mucocutaneous telangiectasias. Arteriovenous malformations of various organs also exist. Lesions often start in young adulthood with numerous telangiectasias on the lips, tongue, palate, face, conjunctivae, trunk and arms. Arteriovenous malformations of major organs can present with serious complications, particularly gastrointestinal bleeding.

Miscellaneous

Drug related: many therapeutic agents affect the oral mucosa, and it is worth enquiring about the relationship between the onset of symptoms and the start of any new medication. Among the more common effects are lichenoid reactions (e.g. β-adrenoceptor blockers, oral hypoglycaemics) and ulceration (e.g. nicorandil).

Chemotherapy and/or radiotherapy: cytotoxic chemotherapy has an oral cavity effect that manifests predominantly as oral mucositis. Up to 40% of patients given chemotherapy have mucositis as a consequence. Drugs that are DNA cell-specific, such as cisplatin, fluorouracil and methotrexate, are more stomatotoxic. Clinically, stomatotoxicity begins soon after chemotherapy administration, peaking at 7 days and usually healing after approximately 14 days. Initial symptoms of pain and a burning sensation can precede intraoral signs. Patches of erythema involving the buccal mucosa and palate become desquamative, resulting in eventual sloughing of the mucosa with ulceration. The ulcers coalesce and can have a pseudomembranous appearance. Disruption of the mucous membrane barrier predisposes to superimposed infection, particularly candidiasis.

Management is aimed at prevention and elimination of predisposing factors such as sharp teeth or fillings, underlying poor oral hygiene and pre-existing periodontal disease. Other prophylactic measures include cryotherapy (ice cubes), palifermin (a keratinocyte growth factor), laser therapy and allopurinol mouthwashes. Once oral mucositis is established, management consists of good oral hygiene, chlorhexidine mouthwashes, mucosal coating agents such as carmellose sodium, and local anaesthetic mouthwashes and gels. In more severe cases, systemic analgesia (e.g. opioids) may be indicated, and further chemotherapy may have to be postponed. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 57-year-old man presented with recent recurrent oral ulcers. He also complained of night sweats and lethargy. There was no significant medical history, and he was not taking regular medication.

On clinical examination, there was bilateral cervical lymphadenopathy. Intraorally, there was generalized gingival swelling with spontaneous bleeding. Multiple oral ulcers were noted on the buccal mucosa and lateral tongue.

What is the most likely diagnosis?

A. Recurrent aphthous stomatitis
B. Erythema multiforme
C. Mucous membrane pemphigoid
D. Ulceration secondary to haematological malignancy
E. Orofacial granulomatosis

Question 2

A 21-year-old man presented with a 4-year history of recurrent oral ulcers. He described crops of five ulcers, which healed within 2 weeks before recurring. More recently, he complained of eye pain and blurred vision.

What the most likely diagnosis?

A. Recurrent aphthous stomatitis
B. Erythema multiforme
C. Pemphigus vulgaris
D. Coeliac disease
E. Behçet's disease

Questions 3

A 63-year-old woman presented with a 1-year history of a sore mouth. On further questioning, she reported genital discomfort and ridging of the nails.

On clinical examination, there was ulceration of the lateral aspects of the tongue with white lesions on the buccal mucosa bilaterally. The lesions were not removable.

What the most likely diagnosis?

A. Mucous membrane pemphigoid
B. Recurrent aphthous stomatitis
C. Lichen planus
D. Pemphigus vulgaris
E. Candidiasis