



Oral Pathology module

Immune-mediated conditions

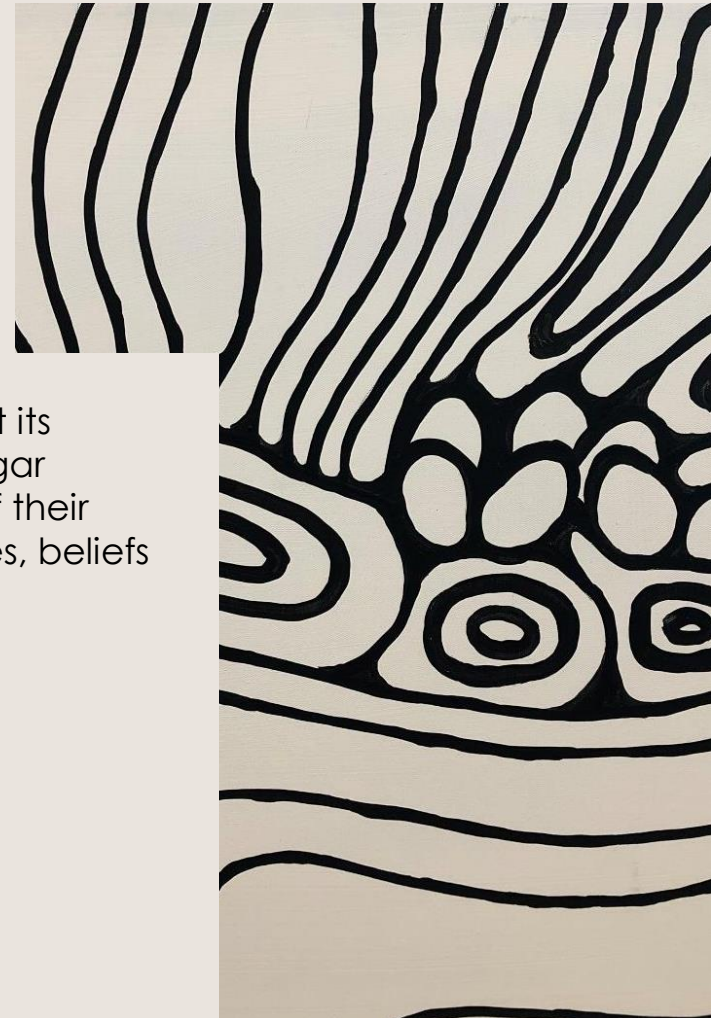
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DENT4217

BDS DipOPath MSc MFDS RCPS FHEA FRCPath PhD FFOMP RCPA

Acknowledgement of country

The University of Western Australia acknowledges that its campus is situated on Noongar land, and that Noongar people remain the spiritual and cultural custodians of their land, and continue to practise their values, languages, beliefs and knowledge.



Artist: Dr Richard Barry Walley OAM

Learning outcomes

1. To recognize the clinical features of allergic disorders including contact dermatitis, contact stomatitis, plasma cell gingivitis, cinnamon stomatitis, and hypersensitivity to dental restorative materials.
2. To differentiate among the key features of minor recurrent aphthous ulcers and herpetiform aphthous ulcers.
3. To learn lichen planus

The central function of the immune system

- to distinguish foreign antigens from self-components of body tissues.
- Sometimes there is failure to discriminate between harmful and harmless antigens. Also, there can be failure to discriminate between self and nonself body proteins.
- Inappropriate immune responses are responsible for a wide variety of conditions.
- Depending on the inappropriate reaction, there can be a variety of clinically apparent signs and symptoms, ranging from a skin rash to failure of a major organ system.

Allergic Contact Mucositis/dermatitis

- **Contact mucositis** is inflammation of mucous membranes (mucositis) caused by direct contact of an offending allergen.
- When inflammation is the result of direct exposure to an allergen, it is termed allergic contact mucositis.



Substances that cause allergic contact mucositis may include [dental materials](#) such as [denture base acrylic](#), [latex rubber dam material](#), or [orthodontic elastics](#); [oral hygiene products](#) such as flavoring agents; detergent additives; or foods.

Often the allergen remains unknown until the patient undergoes allergy testing.

Contact mucositis/dermatitis

- Clinically, contact mucositis appears as an erythematous, edematous, or atrophic zone of mucosa at the point of contact.
- When the source is toothpaste or mouth rinses, patients will complain of a generalized discomfort and burning sensation, with mild swelling, erythema, and superficial sloughing of the surface epithelium.
- Deep ulcers or blisters generally do not occur.



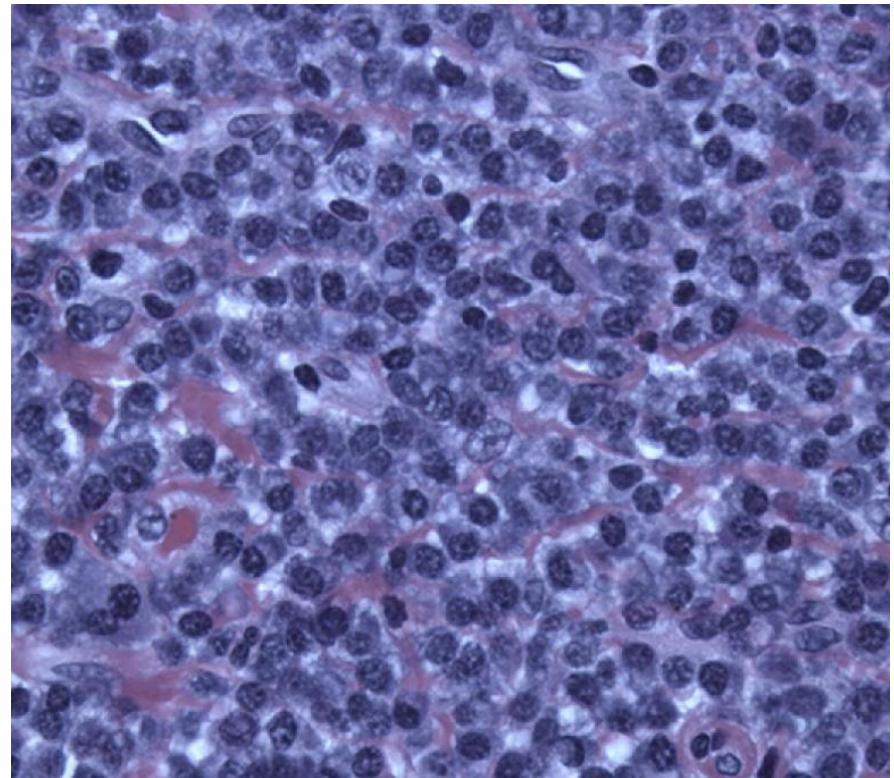
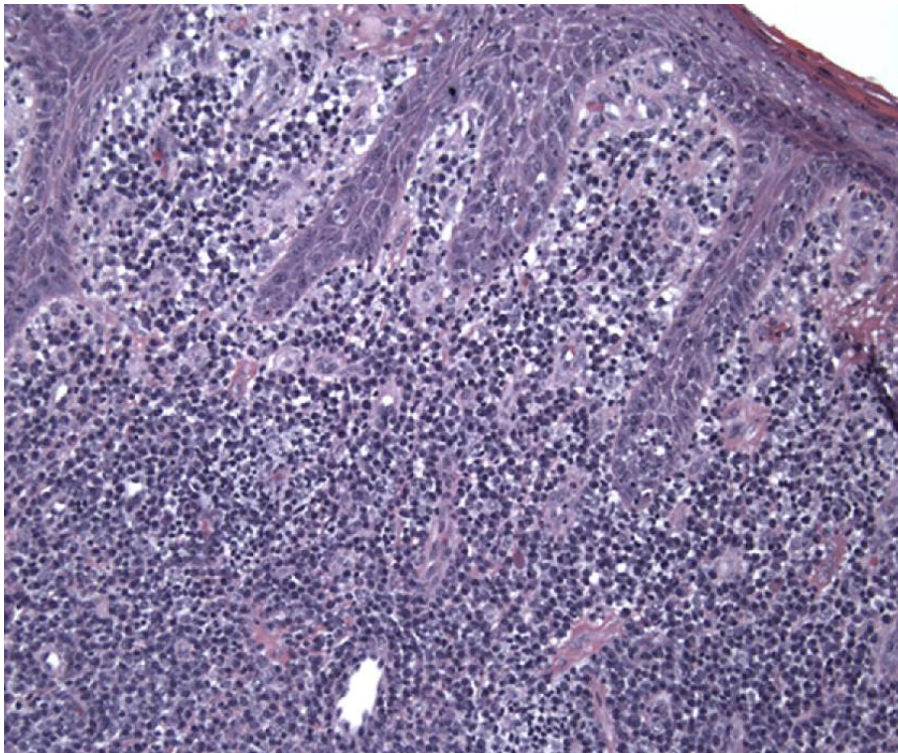
Plasma Cell Gingivitis

- *Plasma cell gingivitis* has become relatively common since oral health-care products containing essential oils, herbal additives, whitening, and anti-calculus agents are readily available. Although their therapeutic effect is often beneficial to patients, they may cause a hypersensitivity reaction.
- Plasma cell gingivitis appears as a diffuse enlargement of the free and attached gingiva characterized by erythema and loss of stippling. Other intraoral sites may also demonstrate areas of tenderness and erythema.



Plasma Cell Gingivitis

Microscopically, many plasma cells are present when the tissue is biopsied. Treatment involves discontinuing the use of the allergen. Topical anti-inflammatory agents may be needed to resolve the mucositis.



Cinnamon Stomatitis

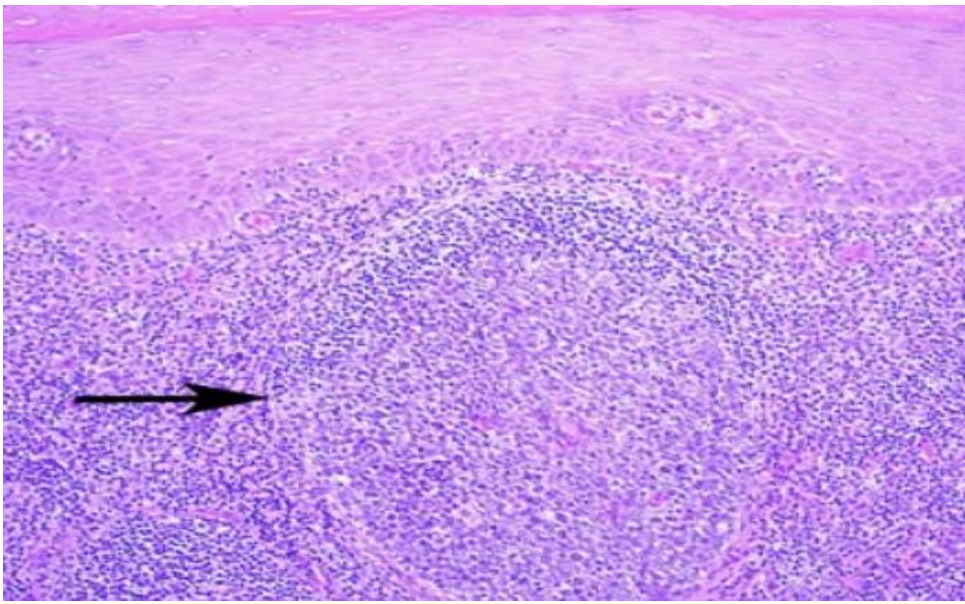
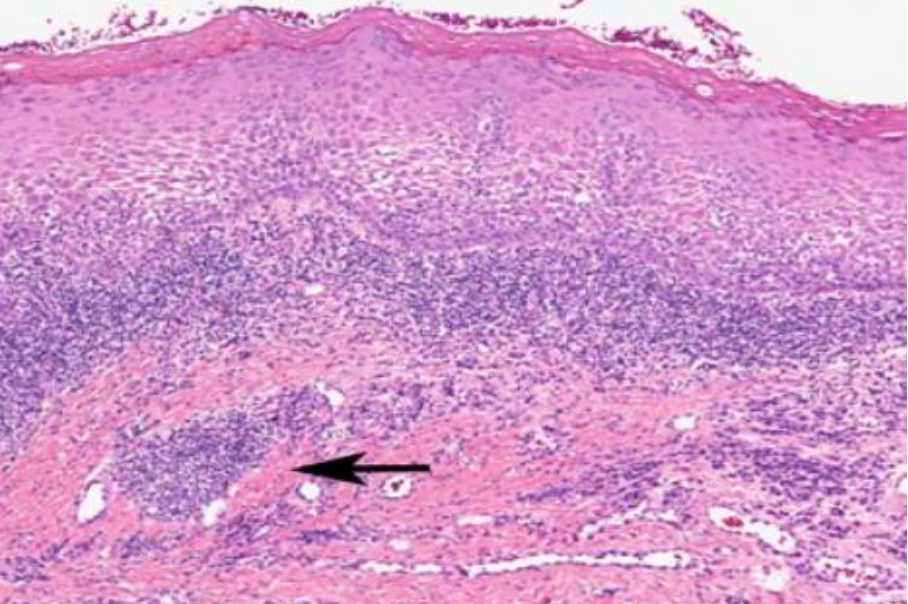
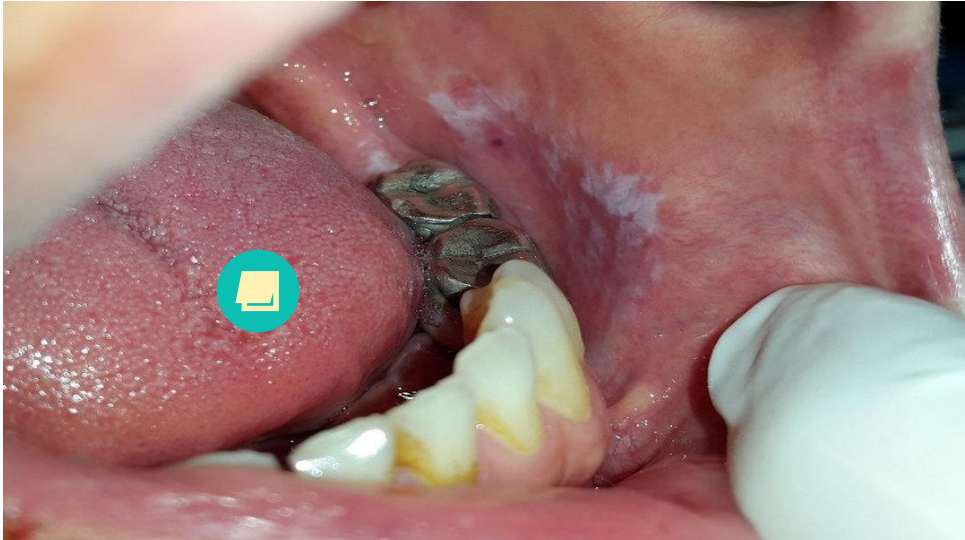
- *Cinnamon stomatitis* is an allergic reaction to cinnamon oil (cinnamon aldehyde) used as a flavoring agent in many red-colored cinnamon-flavored gums, candies, and oral health-care products.
- Patients present with tender or painful “burning” mucosa to which the agent has contact, such as a focal area of buccal mucosa, diffuse gingival lesions, or “chapped” lips.



Hypersensitivity Reaction to Dental Restorative Materials

- *Hypersensitivity reaction to dental amalgam* is seen in about 1% to 2% of individuals with amalgam restorations.
- Dental amalgams are composed of silver, copper, zinc, beryllium, nickel, mercury, or other materials in varying quantities depending on the manufacturer's specifications.
- Patients who experience allergic reactions to dental metals may also react to base metals in jewelry.
- Other dental restorations, such as crowns, bridges, and removable partial dentures (RPDs), use metals such as nickel, titanium, gold, chromium cobalt, and palladium. Up to 17% of women and 3% of men are allergic to nickel and 1% to 3% are allergic to cobalt and chromium. Porcelain-fused to-metal (PFM) crowns and RPD frameworks contain many of these metals.

Hypersensitivity Reaction to Dental Restorative Materials

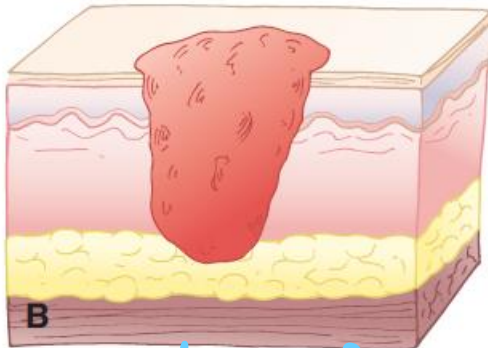


Ulcerative Conditions

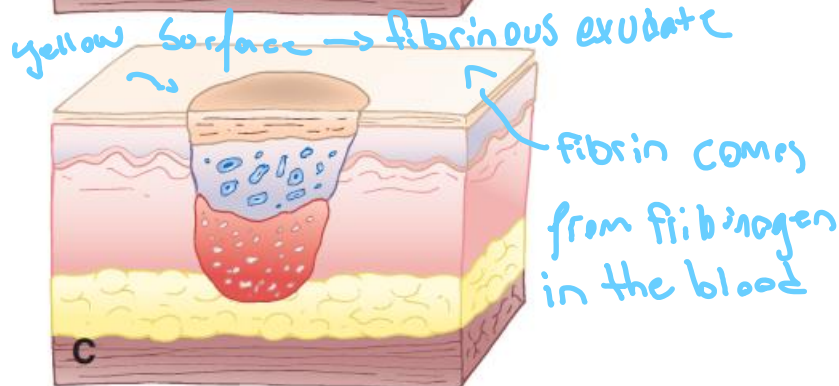


- An **ulcer** is defined as the loss of epithelial continuity with exposure of the underlying connective tissue.

complete loss of connective tissue is why patients feel pain!



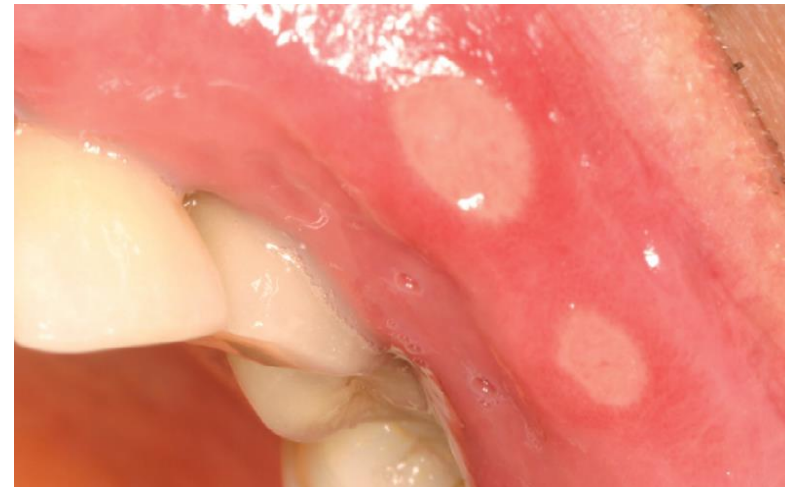
- Ulcers are caused mainly by
 - Trauma
 - viruses
 - common immune-related ulcerative conditions



Ulcers surrounded by red "halos" means that it is most likely an aphthous ulcer

Aphthous Ulcers

- Most cases of *recurrent aphthous ulcers* are idiopathic and occur in **15% to 25% of the population**, usually children, teenagers, and young adults.
- Trauma and stress, both physical and emotional, bring on episodes in susceptible individuals. However, *aphthous-like* lesions are seen in many systemic diseases and oral hypersensitivity reactions but unlike idiopathic aphthous ulcers that are episodic for a few decades of the patient's life, *aphthous-like* ulcers associated with systemic disease generally resolve when the systemic disease is well-controlled.



↳ round well defined ulcer - yellow
↳ red halo

Aphthous Ulcers

- Onset is generally in the second and third decades of life with a 2:1 female predilection, and lesions diminish in severity with age with complete resolution by age 50 in most cases.
- Ulcers are episodic but may be continuous in severe/complex cases, be single or multiple, and occur almost exclusively on the nonkeratinized mucosa. They are sharply demarcated and painful, and composed of a yellow fibrin membrane with surrounding erythema

There are three principal forms of RAUs: **minor**, **herpetiform**, and **major**.



Aphthous Ulcers

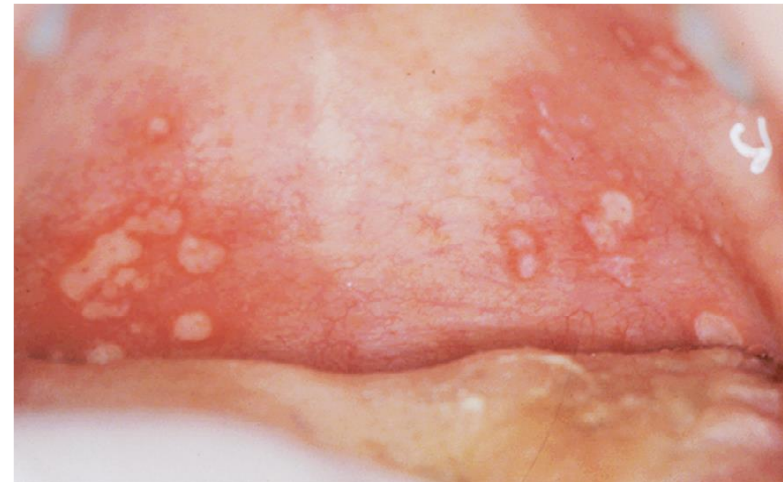
- **Minor** ulcers are the most common (80%), are ≤ 1 cm in size, and last 1 to 2 weeks; the number of episodes each year varies depending on the individual.

↳ if its more frequent → systemic cause

Minor ulcers usually happen in non-keratinized epithelium

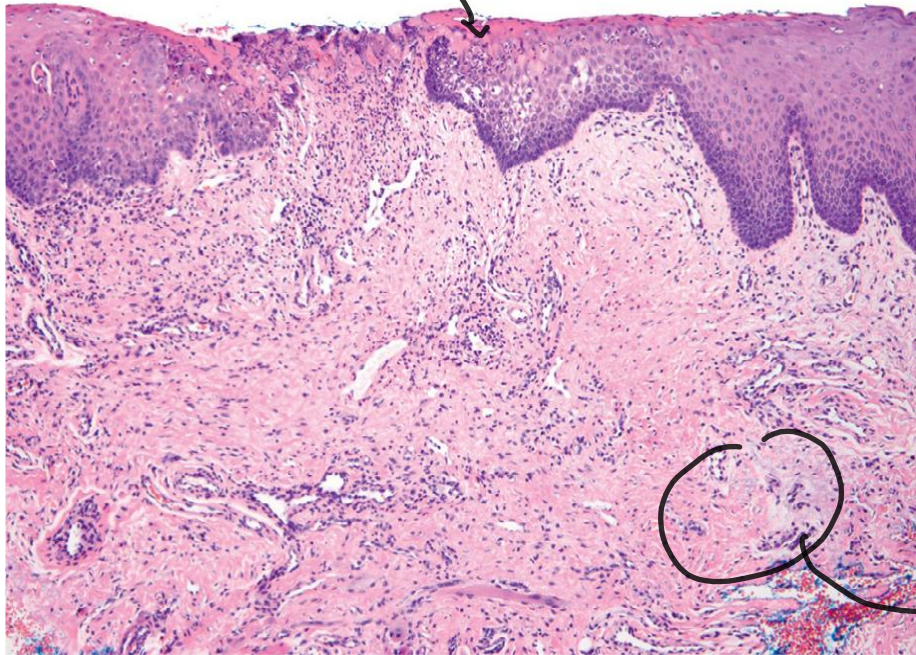
- **Herpetiform** ulcers are uncommon and number more than 10 small ulcers (usually 0.1–0.5 cm) at each episode and last 1 to 2 weeks.

- **Major** ulcers are the least common, are larger than 1 cm in size, last for weeks or months, and may be associated with scarring.

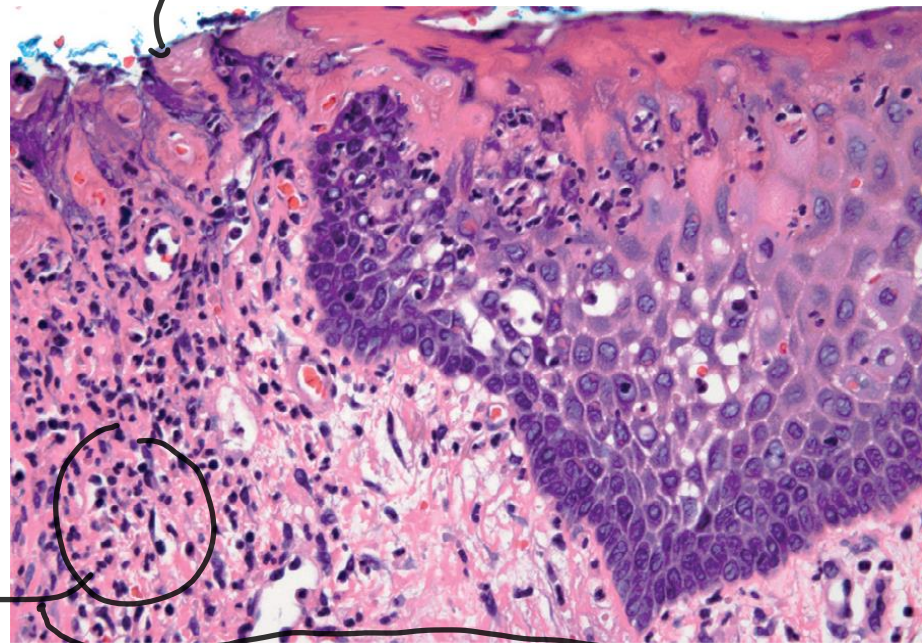


Apthous Ulcers

fibrinous exudate



fibrinous exudate



- Ulcers consist of a fibrin membrane with enmeshed neutrophils and underlying granulation tissue with acute and chronic inflammatory cells confined to the lamina propria and sometimes involving superficial skeletal muscle fibers.

- The adjacent epithelium exhibits spongiotic pustules and reactive atypia such as basal cell hyperplasia, nuclear hyperchromasia, and slight pleomorphism.

granular tissue
↳ blood vessels ↳ fibroblasts
↳ epithelial cells

Aphthous Ulcers

Clinical notes

- Traumatic ulcers should clearly be distinguished from RAUs based on the patient's history. The patient will report injuring himself or herself in the area of the ulcer or the clinician might observe a defective restoration or prosthesis contacting the ulcer.
- Treating a traumatic ulcer with topical anti-inflammatory medication, an acceptable treatment for RAU, may lead to delayed healing and possible infection in a traumatic ulcer.
- Ulcers on the gingiva or hard palate are not recurrent aphthous ulcers. RAUs only occur on nonkeratinized tissue. The gingiva and hard palate are keratinized.

Aphthous Ulcers

TABLE 7.1 Conditions Associated With Aphthous-Like Ulcers

Behçet disease → genetic disorder (east med area/silkroad) reflects eyes & genital

Inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis, celiac disease)

Hematinic deficiencies

Food hypersensitivities

HIV/AIDS

Drug-induced ulcers (e.g., nonsteroidal antiinflammatory medications, mechanistic target of rapamycin [mTOR] inhibitors, checkpoint inhibitors)

Chemotherapy ulcerations

Neutropenic ulcers (qualitative and quantitative neutropenia), including from cyclic neutropenia

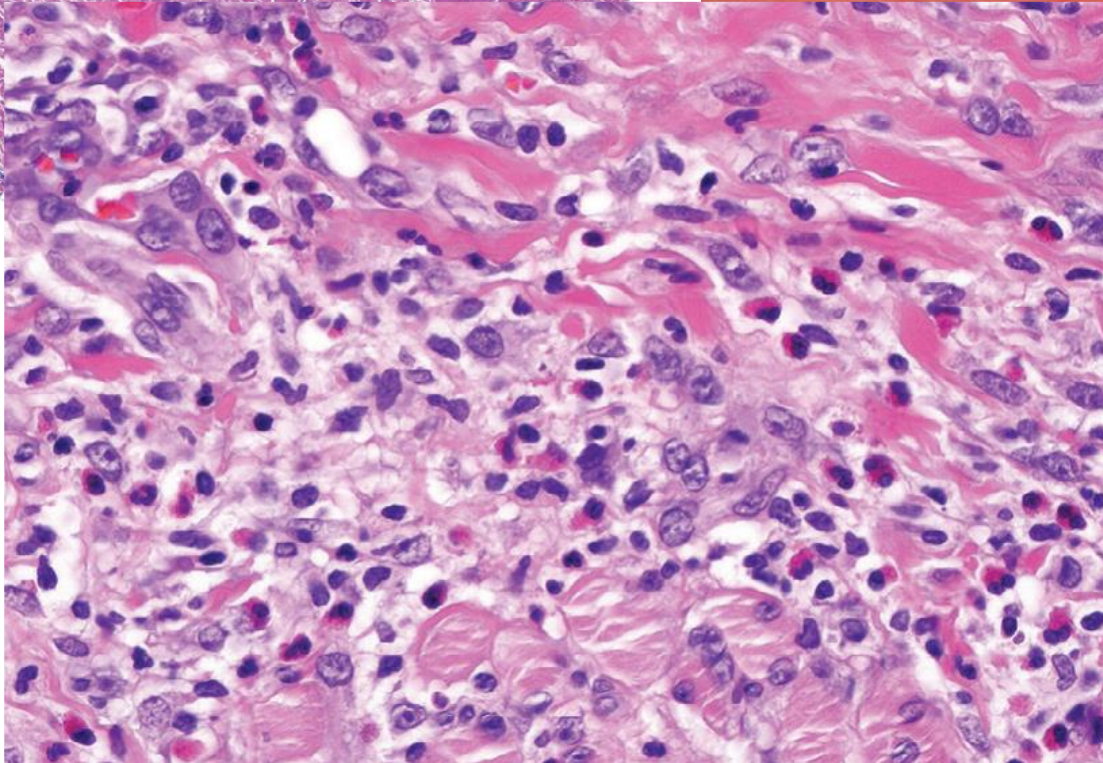
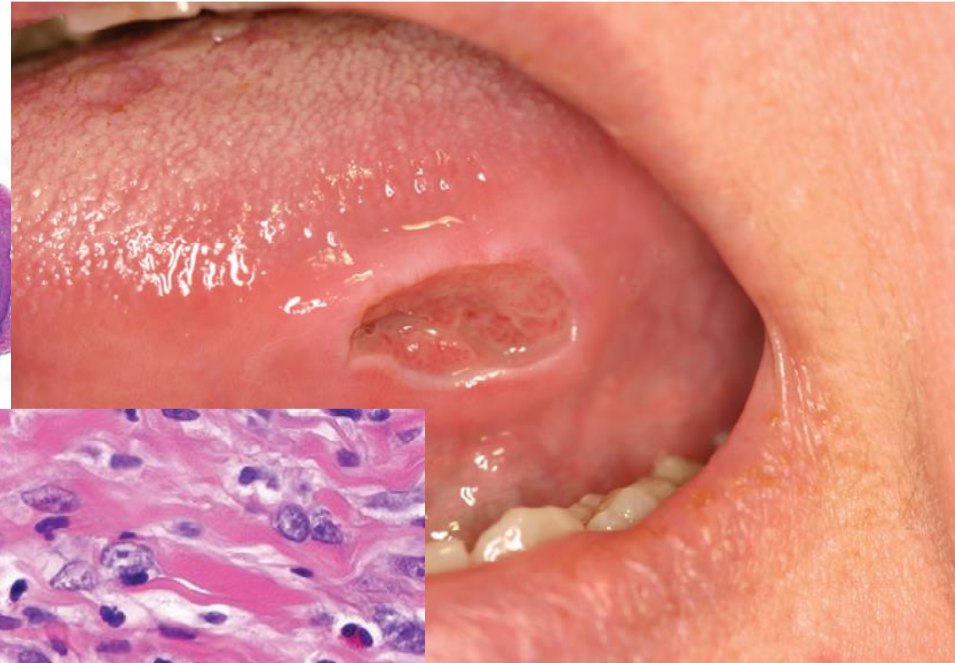
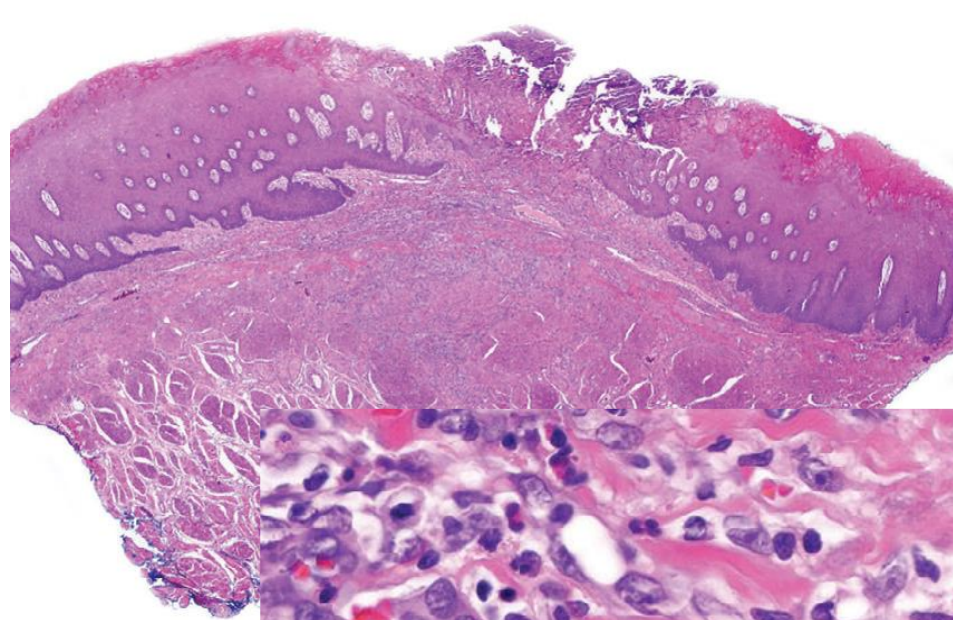
Periodic fever, adenopathy, pharyngitis, aphthae (PFAPA) syndrome

Autoimmune vesiculobullous disease

Herpes simplex virus ulcers in immunocompromised patients

Leukemia

TRAUMATIC ULCERATIVE GRANULOMA WITH STROMAL EOSINOPHILS, EOSINOPHILIC ULCER OF TONGUE



you see lots of
eosinophils and
granulation tissue in
this condition

- Traumatic ulcerative granuloma is secondary to deeply penetrating inflammation involving the underlying skeletal muscle and is most often associated with trauma although less than 50% of patients report such a history. It may be primary or secondary to trauma to another preexisting condition.
- There is an ulcer with acute and chronic inflammation that penetrates into the muscle with separation and degeneration of muscle fibers, sometimes with a “checkerboard” pattern, proliferation of macrophages, and many eosinophils. However, eosinophils may be sparse or even absent, depending on the stage of the ulcer.

Erythema Multiforme

- *Erythema multiforme (EM)* a self-limiting disease that causes a characteristic skin rash and often severe outbreaks of painful ulcerations of the mucous membranes.
- EM most commonly occurs in young adults and affect males more often than females. EM differs from the three forms of RAU in that EM has a more generalized distribution of ulcerations and erosions accompanied by severe pain.
- A severe form of EM is *Stevens-Johnson syndrome*, also called *erythema multiforme major*. In addition to the skin and oral lesions, patients develop eye and genital lesions



ulcers affect system as well

Lichen Planus

Controversial!
↳ some believe benign
↳ others OPMD
↳ Ocular LP = OPMD with CCC chance

• can affect
any tissue

- Lichen planus is a common disease of both skin and mucous membranes. Its name is derived from the appearance of the *reticular form* of the disorder that resembles lichens that grow on rocks and trees.
- It is most commonly seen in middle-aged women, but men comprise many patients.
- OLP is a common condition, with a prevalence of between 0.5-2.2% of the population.
- The aetiology of lichen planus is still under investigation.
- Typical age of presentation is between 30-60 years of age.
- Various forms of clinical presentation are encountered:
 - Reticular
 - Linear
 - Papular
 - Plaque-like
 - Atrophic
 - Erosive/ulcerative
 - Bullous



Lichen Planus

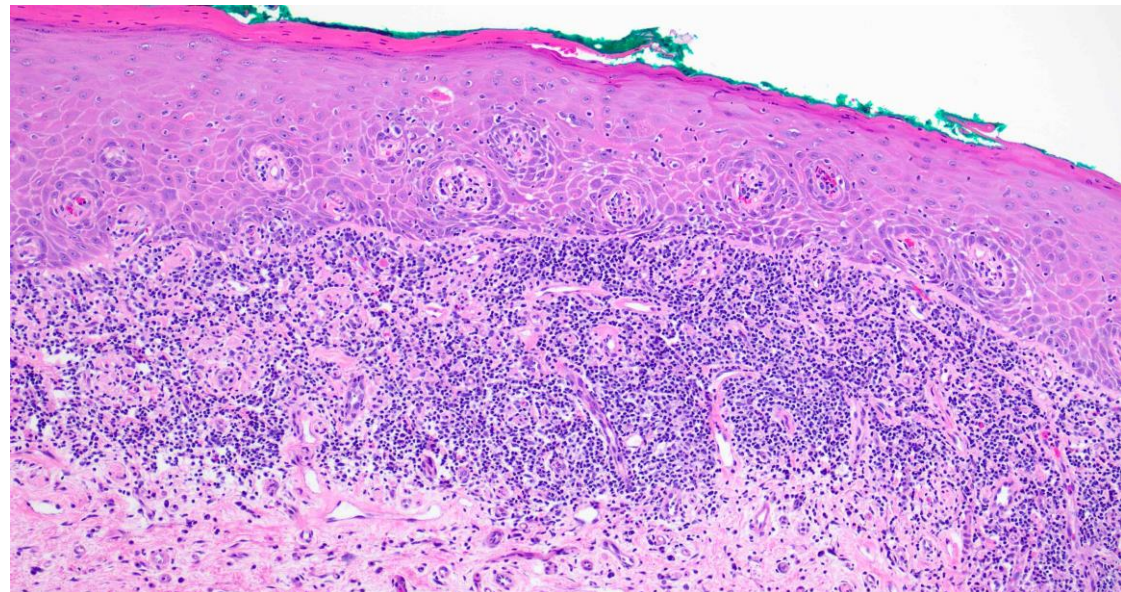
A chronic inflammatory disorder of unknown etiology with characteristic relapses and remissions, displaying white reticular lesions, accompanied or not by atrophic, erosive and ulcerative and/or plaque type areas. Lesions are frequently bilaterally symmetrical. Desquamative gingivitis may be a feature



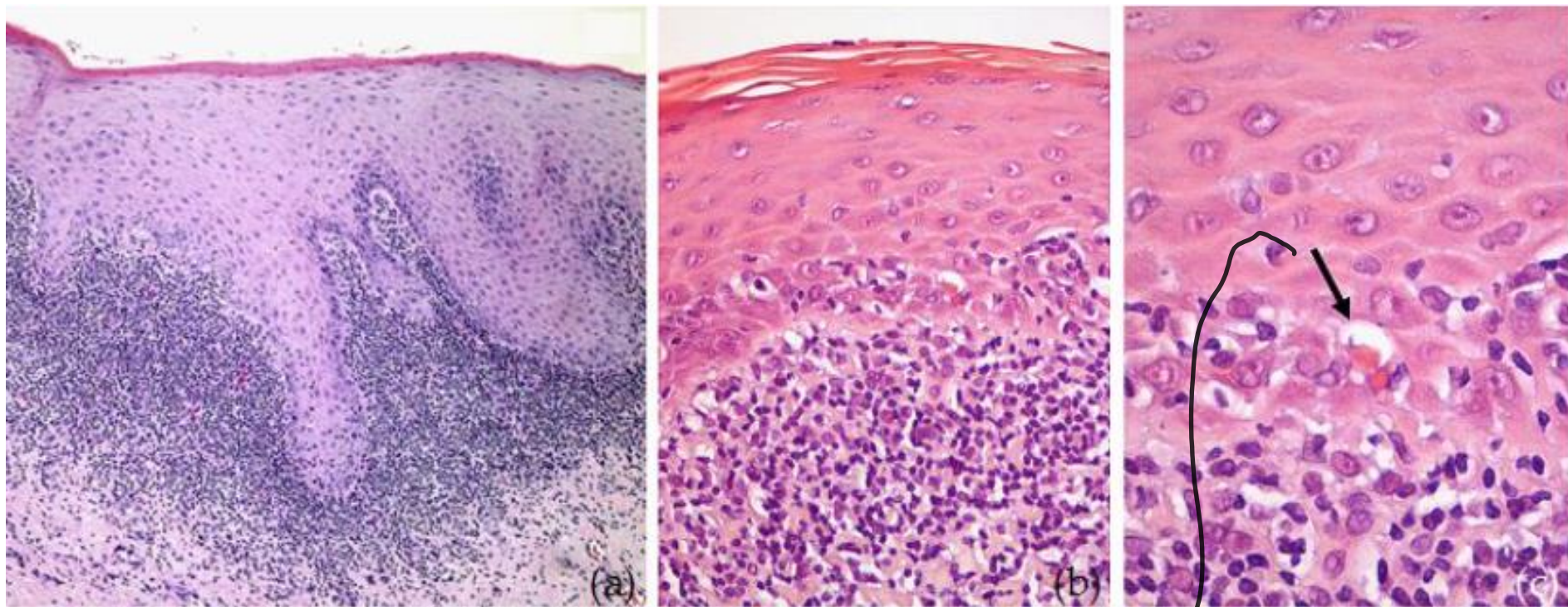
Lichen Planus

The mechanisms involved in the aetio-pathogenesis of OLP are multifactorial and likely to be synergistic:

- cell-mediated immune response (Type IV hypersensitivity)
- role of the humoral immune response
- non-specific immune mechanisms;
- genetic factors.



Lichen Planus



Degeneration of basal cell layer

Apoptotic bodies (seva bodies)

Condensation of the basement membrane

Observer agreement in the diagnosis of oral lichen planus using the proposed criteria of the American Academy of Oral and Maxillofacial Pathology

Majdy Idrees¹ | Camile S. Farah^{2,3,4} | Syed Ali Khurram⁵ | Norman Firth⁶ | Merva Soluk-Tekkesin⁷ | Omar Kujan¹

Clinical criteria	<ul style="list-style-type: none"> • Presence of bilateral, more or less symmetrical white lesions affecting buccal mucosa, and/or tongue, and/or lip, and/or gingiva • Presence of a white papular lesions and lace-like network of slightly raised white lines (reticular, annular, or linear pattern) with or without erosions and ulcerations • Sometimes presents as desquamative gingivitis
Histopathological criteria	<ul style="list-style-type: none"> • Presence of a well-defined band-like predominantly lymphocytic infiltrate that is confined to the superficial part of the connective tissue • Signs of vacuolar degeneration of the basal and/or supra basal cell layers with keratinocyte apoptosis • In the atrophic type, there is epithelial thinning and sometimes ulceration caused by failure of epithelial regeneration as a result of basal cell destruction. A mixed inflammatory infiltrate may be found

Oral lichen planus has a very low malignant transformation rate: A systematic review and meta-analysis using strict diagnostic and inclusion criteria

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Abstract

Background: The malignant transformation (MT) potential of oral lichen planus (OLP) has sparked heated debates for almost a century, despite the fact that global figures of OLP prevalence and oral cancer incidence do not support an association mathematically. In this study, we performed a systematic review and meta-analysis, using strict inclusion criteria, to more precisely assess the malignant potential rate of OLP and the influence of associated risk factors.

Methods: All reports that documented MT of OLP and published in the English language until January 2020 were included if they met the following strict criteria: (a) the presence of a properly verified OLP diagnosis, (b) a clear description of the cancerous lesion developing at the same site as the verified OLP lesion; and (c) a follow-up period of a minimum of 6 months prior to carcinoma development.

Results: Thirty-three studies were included in this analysis with a total of 12 838 OLP patients. Of these, 151 cases were initially considered to have progressed to carcinoma (1.2%). However, after applying strict criteria, only 56 cases were considered to have undergone MT from OLP (0.44%). The risk of MT was significantly higher among OLP patients who smoked (OR = 4.62), consumed alcohol (OR = 3.22), were seropositive for HCV (OR = 3.77) and/or displayed a red OLP subtype (OR = 0.37).

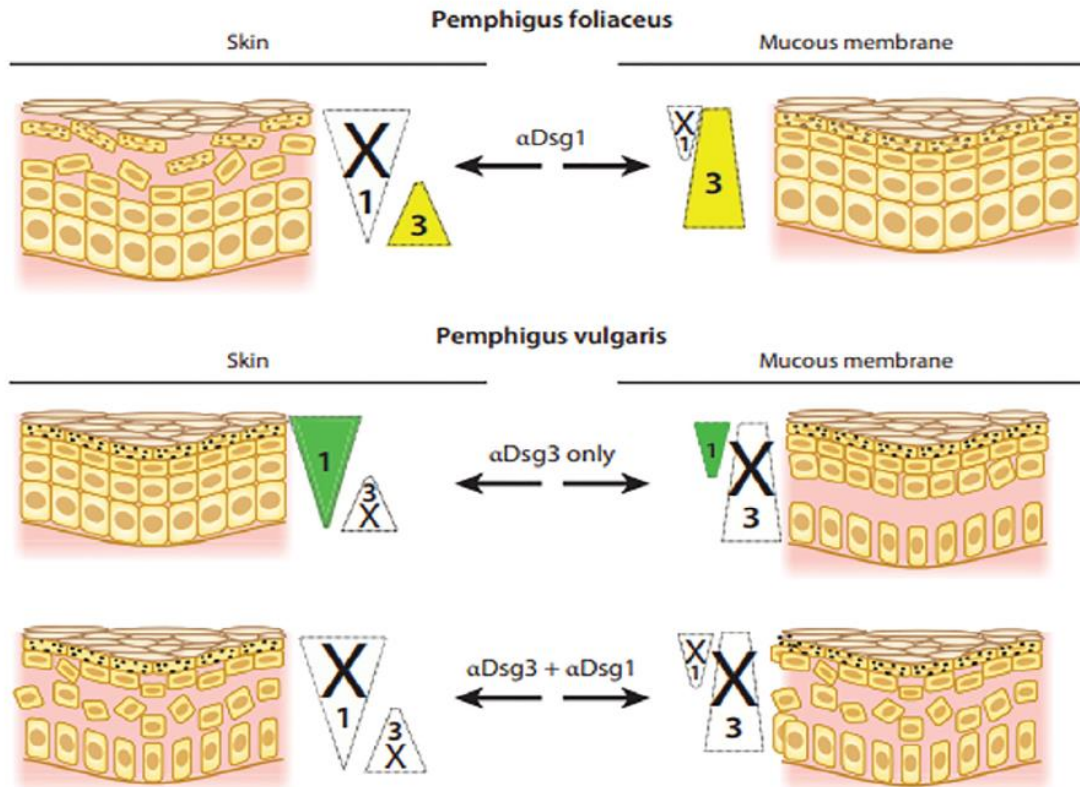
Conclusions: Our results suggest that the reported OLP malignant transformation rates are exaggerated, and these do not reflect the actual clinical course of the disease according to strict clinical and histopathological criteria.

Pemphigus vulgaris

- The term *pemphigus* refers to a group of autoimmune blistering diseases of the skin and mucous membranes.
- The most common form, *pemphigus vulgaris*, is a potentially life-threatening mucocutaneous (both skin and mucous membranes) disorder that often manifests initially in the oral cavity.
 - ↳ steroids + immunosuppressive meds have greatly improved prognosis!
- Pemphigus is derived from the Greek word *pemphix*, meaning bubble or blister.



Pemphigus vulgaris

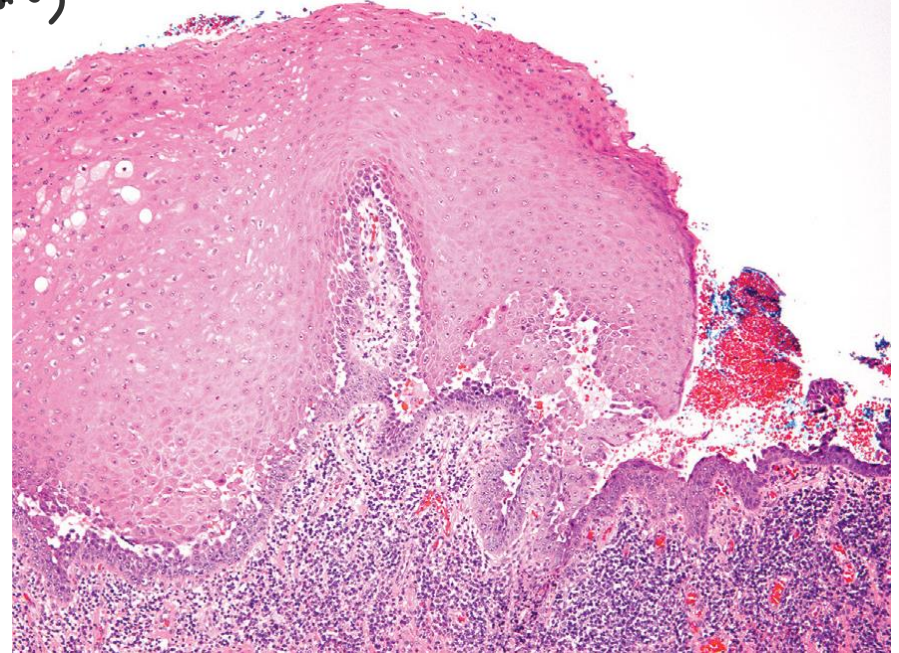
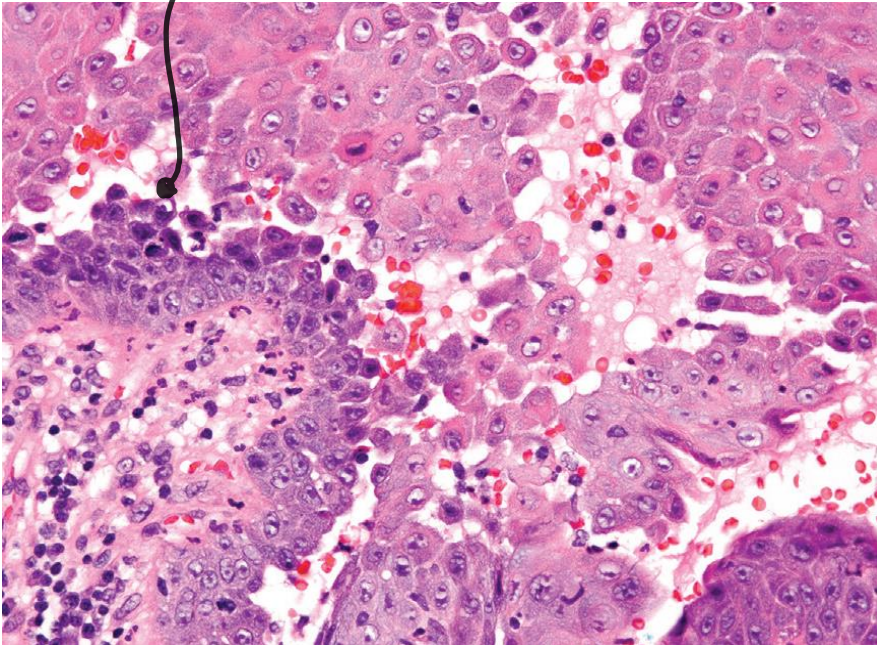


- Autoantibodies are produced against proteins called *desmogleins*, which form the desmosomes, the structural units that bind epithelial cells to each other.
- When the autoantibodies attack the desmosomes, individual epithelial cells lose the ability to adhere to each other. Hemidesmosomes are not affected.

Pemphigus vulgaris

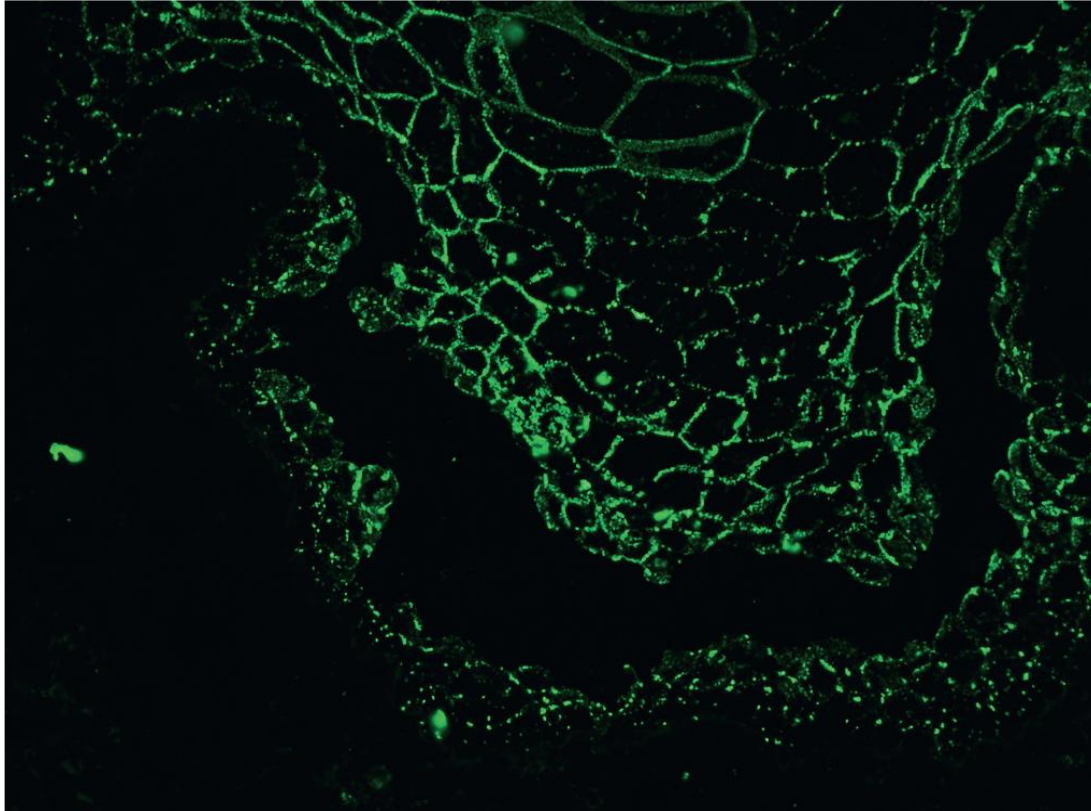
loss of epithelial attachment

↳ intraepithelial blister → ruptures easily



- Biopsy of pemphigus vulgaris shows a split in the epidermis above the basal layer. Individual keratinocytes, referred to as *Tzanck cells*, appear to be floating away from each other, providing evidence that the desmosomes have been destroyed.
- Mild trauma to the area may induce vesicle and bulla formation, leading to tissue sloughing similar to the Nikolsky's sign seen in mucous membrane pemphigoid.
- More than 50 % of patients with pemphigus vulgaris have oral lesions before they develop skin lesions.
- Oral lesions may affect any anatomic surface, but tend to appear on the buccal mucosa, palate, and gingiva.

Pemphigus vulgaris



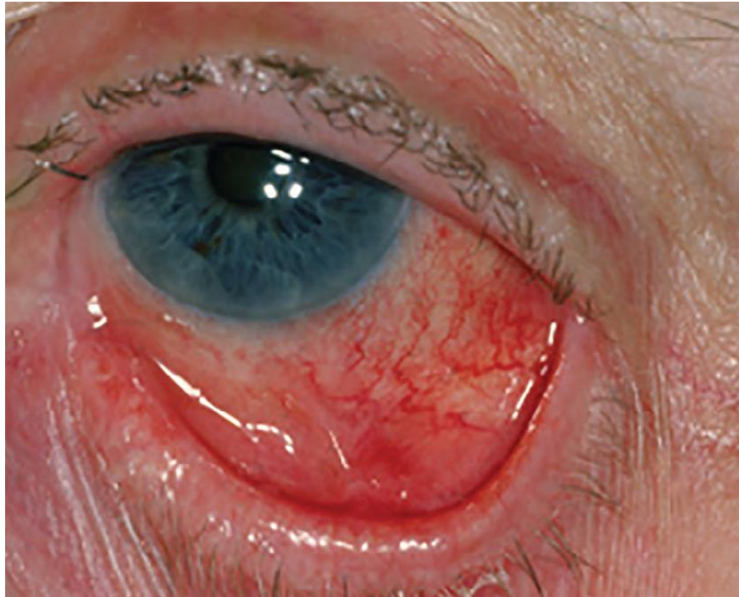
- Direct immunofluorescence shows intercellular deposition of IgG in a distinctive mesh- or netlike pattern. Epitope spread may account for the production of antibodies against multiple antigens.
- Indirect immunofluorescence studies for circulating autoantibodies performed on monkey esophagus or human skin, and enzyme-linked immunosorbent assay (ELISA) to identify autoantibodies against Dsg-1 and/or Dsg-3 should be performed because ³¹ levels correlate with disease activity and as such, are useful for monitoring response to therapy.

Mucous membrane pemphigoid

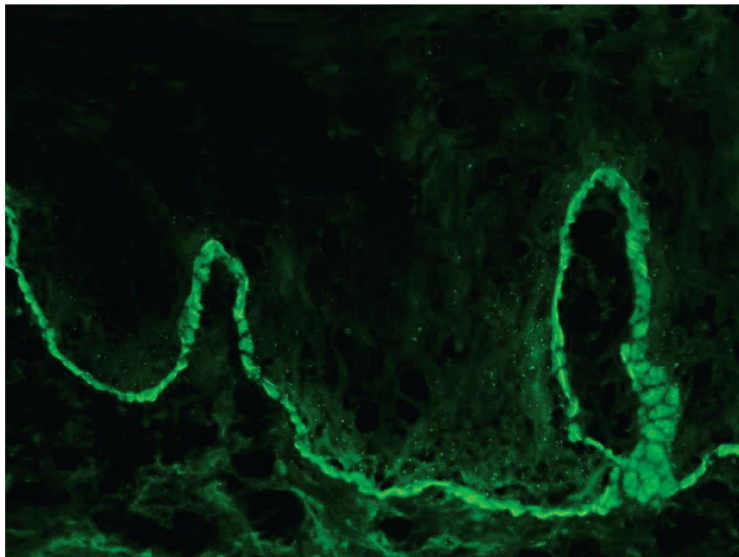


- *Mucous membrane pemphigoid (MMP)* is a type 2 hypersensitivity reaction to specific hemidesmosomal proteins in the basement membrane of the epithelium called *laminins*. Autoantibodies produced by plasma cells destroy this hemidesmosomal “glue” that holds the epithelium to the underlying connective tissue.

Mucous membrane pemphigoid



- Biopsy of mucous membrane pemphigoid shows a split between the full thickness of epithelium and the underlying connective tissue. Connective tissue and nerves are exposed to the oral environment, resulting in significant pain for the patient. Direct immunofluorescence is essential to confirm the diagnosis where IgG antibodies and C3 deposits are found on the basement membrane.
- Mild trauma may induce vesicle and bulla formation, leading to tissue sloughing, a phenomenon referred to as **Nikolsky's sign**.



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Questions

