Practical Anatomic Pathology
Series Editors: Fan Lin · Ximing J. Yang

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Xiaoyin "Sara" Jiang
Editors

Practical Head and Neck Pathology

Frequently Asked Questions

Springer

Practical Anatomic Pathology

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The proposed Book Series will be designed to provide a comprehensive, practical and state-of-the art review and update of the major issues and challenges specific to each subspecialty field of surgical pathology in a question and answer (Q&A) format. Making an accurate diagnosis especially from a limited sample can be quite challenging, yet crucial to patient care. The proposed Book Series, using the most current and evidence-based resources, will

1) focus on frequently asked questions in surgical pathology in day-to-day practice;
2) provide quick, accurate, terse, and useful answers to many practical questions encountered in daily practice;
3) emphasize the importance of a triple test (clinical, radiologic, and histologic correlation);
4) delineate how to appropriately utilize immunohistochemistry, in situ hybridization and molecular tests; and
5) minimize any potential diagnostic pitfalls in surgical pathology.

These books will also include highly practical presentations of typical case scenarios seen in an anatomic pathology laboratory. These will be in the form of case presentations with step-by-step expert analysis. Sample cases would include common but challenging situations, such as evaluation of well-differentiated malignant tumors vs. benign/reactive lesions; distinction of two benign entities; sub-classification of a malignant tumor; identification of newly described tumor and non-tumor entities; workup of a tumor of unknown origin; and implementation of best practice in immunohistochemistry and molecular testing in a difficult case. The Q&A format will be well accepted, especially by junior pathologists, for several reasons:

1) this is the most practical and effective way to deliver information to a new generation of pathologists accustomed to using the Internet as a resource and, therefore, comfortable and familiar with a Q&A learning environment;
2) it's impossible to memorialize and digest massive amounts of new information about new entities, new and revised classifications, molecular pathology, diagnostic IHC, and the therapeutic implications of each entity by reading large textbooks;
3) sub-specialization is a very popular practice model highly demanded by many clinicians; and
4) time is very precious for a practicing pathologist because of increasing workloads in recent years following U.S. health care reforms. This Book Series will meet all of the above expectations. These books will be written by established and recognized experts in their specialty fields and will provide a unique and valuable resource in the field of surgical pathology, both for those currently in training and for those already in clinical practice at various skill levels. It does not seek to duplicate or completely replace other large standard textbooks; rather, it will be a new, comprehensive yet concise and practical resource on these timely and critical topics.

More information about this series at http://www.springer.com/series/13808

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To my husband, Gary, and my mother, Brenda – you did everything else, so that I could do this. Thank you.

To my father, Jeffrey – I am here *because you fought hard to get me there, so long ago.*

To my girls, Cheyenne, Grace, and Lynda – I hope this work will inspire and inform you of the great things you are capable of.

Danielle Elliott Range

To my mentors, learners, and colleagues, past and future. To my first teachers – my parents, Huamei and Haixiang. To my dearest Chris, Harrison, and Clark.

Xiaoyin "Sara" Jiang

Preface

As an anatomic region, the head and neck is home to entities that range from common to roundly fascinating and vanishingly rare. Even the more pedestrian lesions have their own unique qualities. The challenge in writing this book was in addressing the frequently asked questions without neglecting the frequently encountered entities that are the foundation of any good textbook. We hope we've achieved a balance between the two.

This book comes at a time of many changes in head and neck pathology. In 2018, the new World Health Organization classification system of head and neck tumors was published after over a decade since the last edition. Several tumors were newly described or reclassified (e.g., salivary gland and sinonasal carcinomas). In addition, the 2018 American Joint Committee on Cancer staging system introduced new and significant changes to the pathologic staging of some head and neck malignancies. Most notably, a new staging system was developed for oropharyngeal carcinomas. Here, we tried to include the highlights of these important changes and their impact on diagnosis, prognosis, and management.

The format of this book centers around frequently asked questions but is not meant to be comprehensive in its approach. Instead, it aims to touch on all major or commonly encountered entities. Each chapter begins with a list of questions typically ordered from basic histologic knowledge to inflammatory processes, primary tumors, and secondary tumor types. The tables are the foundation of the book, offering a quick reference guide for salient features of various entities and differential diagnoses. However, tables are inherently limited in their scope, summarizing the preponderance of features, but unable to be comprehensive *or* nuanced. They should be regarded as a starting point for readers to expand their knowledge when necessary. Great effort was put into providing a comprehensive set of references after each question that can be used to supplement the information provided and give the reader a foundation for further learning.

In the end, the task of answering frequently asked questions of head and neck pathology has been a labor of love and a lesson in the succinct. We hope we have served both the readers and the discipline well in our effort.

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Oral Cavity

1

Sasha Jane Betz and Ricardo J. Padilla

Frequently Asked Questions

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1. *What are the most common developmental lesions of the oral cavity?*

Common developmental lesions of the oral cavity include choristomas, tori and exostoses, and dermoid cysts.

- Bony exostoses are the most common developmental lesions of the oral cavity. They represent bony growths that arise from the cortical plates. The torus palatinus and torus mandibularis are found in approximately 20% and 6% of the population, respectively. The cause of tori is thought to be multifactorial, including genetic and environmental factors such as diet and bruxism. They may be removed for denture-planning procedures or to rule out more ominous pathologies. Not infrequently, tori become traumatized and infected, leading to bony necrosis and sequestration.
  - The histology is of normal-appearing, dense, lamellar bone.
    - Torus palatinus is a solitary bony protrusion located in the midline of the hard palate.
    - Torus mandibularis is located on the lingual surface of the mandible and usually occurs bilaterally.
    - Less frequent, is the torus maxillaris, found bilaterally in the buccal, maxillary, and premolar regions.
- Choristomas are defined as normal tissue that is found in abnormal locations, where such tissue does not normally exist. In the oral cavity, they include lesions containing glial, gastrointestinal, and adnexal tissue. Choristomas typically present in the posterior dorsal tongue.
  - Females are affected twice as frequently as males with a wide age range from birth to the elderly.
  - The lesions present as smooth-surfaced, firm, sessile, or pedunculated masses. Gagging or dysphagia may be associated.
  - The most common tissue type in the oral cavity is bone or cartilage.
  - Histologically, mature bone or cartilage lies within connective tissue, deep to a normal epithelium. Haversian canals and marrow spaces may be identified.
  - Fordyce granules are another common lesion in this group. They are ectopic sebaceous glands (Fig. 1.1) usually found in the mucosa of the upper lip and cheek. Fordyce granules rarely form a mass. They are seldom biopsied given the classic clinical appearance of evenly distributed yellow-white, submucosal papules.
- Ectopic thyroid tissue results from a disturbance in the descent of the thyroid from the foramen cecum to the anterior neck during embryogenesis. It presents early in life as a painless mass.

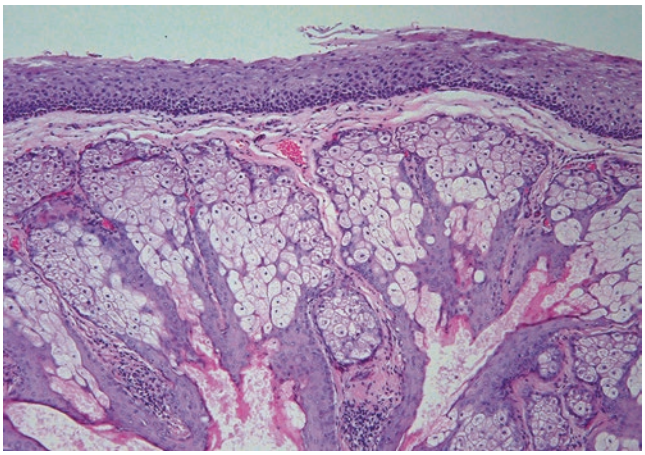

Fig. 1.1 Fordyce granules. Ectopic sebaceous glands underlie a normal squamous epithelium and show aggregates of pale, finely vacuolated cells with central, small nuclei

  - Females are affected four times more frequently than males.
  - 90% occur in the posterior tongue.
  - In 75% of cases, a normal thyroid gland in the neck is absent, and patients require thyroid replacement therapy.
  - Histologically, normal-appearing thyroid follicles with colloid are identified in the lamina propria with possible extension into skeletal muscle. A capsule is usually absent. The tissue may undergo pathologic changes, including thyroiditis, nodular hyperplasia, and rarely, carcinoma.
- Dermoid cysts most often occur in the midline floor of the mouth and are typically diagnosed within the first two decades of life.
  - Dermoid cysts located above the mylohyoid muscle present as a sublingual swelling and those located below the muscle present as a submental swelling.
  - Dermoid cysts contain tissue arising from both ectodermal and endodermal elements. Histologically, stratified, keratinized squamous epithelium lines a cystic lumen. The cyst wall contains dermal adnexa including hair follicles, sebaceous and sweat glands (Fig. 1.2).
  - The differential diagnosis includes an epidermal inclusion cyst which has a similar squamous lining but lacks adnexal structures and tends to occur in adults.

References: [1–6]

2. *What is the differential diagnosis of vascular lesions of the oral cavity?*

Vascular lesions of the oral cavity range from localized caliber-persistent arteries to large hemangiomas. Vascular lesions are broadly divided into tumors and malformations (Table 1.1). A more comprehensive discussion of vascular lesions and how they are characterized can be found in Chap. 10.

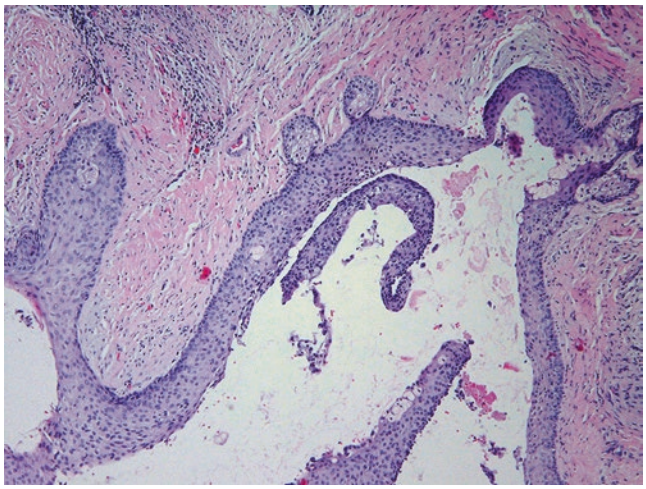

Fig. 1.2 Dermoid cyst. The cystic lumen is lined by stratified squamous epithelium with keratinization and adnexal structures in the cyst wall

- Vascular tumors are characterized by a proliferation of endothelial cells. They may enlarge and later regress.
- Vascular malformations are characterized by abnormal vascular channels. They are rare and typically do not regress.
- The most common vascular lesions of the head and neck, in order of frequency, are:
  1. Infantile hemangioma.
  2. Lymphatic malformation – also known as cystic hygroma or lymphangioma. 75% occur in the head and neck.
  3. Venous malformation.

References: [7–14]

3. *What is lichen planus and which entities are in the differential diagnosis of lichenoid lesions of the oral cavity?*

A lichenoid inflammatory infiltrate in oral mucosa biopsies (lichenoid mucositis) is a frequent finding with

Table 1.1 Vascular lesions of the oral cavity

Lesion	Most affected demographic	Most common oral site	Clinical description	Characteristic histologic features
Vascular tumors				
Lobular capillary hemangioma (Fig. 1.3)	Any age Common in pregnancy	Gingiva	Solitary, exophytic, erythematous, painless mass Often ulcerated, bleeds easily with manipulation	Hypercellular proliferation of variably sized vascular spaces with a lobular pattern Loose stroma with plump, tightly packed endothelial cells, ±inflammatory cells Overlying epithelium may be ulcerated ± Scattered mitotic figures
Infantile capillary hemangioma	Infants	Skin and soft tissue of H/N, lip, larynx	Deep or superficial masses, red or blue in color. Segmental variants follow a dermatome distribution and may be associated with syndromes	Proliferation of immature endothelial cells and disorganized vessels in a lobular arrangement Mitotic figures may be numerous but not atypical GLUT-1+ (congenital hemangiomas are negative)
Kaposi sarcoma	Classic: Mediterranean or Eastern European middle-aged men AIDS-related/iatrogenic: immunosuppressed Endemic: children in sub-Saharan Africa	Palate, gingiva, dorsal tongue	Depends on stage. Early: asymptomatic, flat, blue- or red-hued, often resembles an ecchymosis Late: raised, nodular, may be painful	Early: proliferation of irregular vascular channels in superficial lamina propria. Endothelial cells show mild atypia. Promontory sign – neoplastic vessels surround pre-existing vessels Late: sheets and fascicles of spindle cells. Slit-like vascular spaces and prominent extravasation of RBCs. Numerous mitotic figures. HHV-8+, LANA-1+
Vascular malformations				
Lesion	Most affected demographic	Location(s)	Clinical description	Characteristic histologic features
Lymphatic malformation (lymphangioma, cystic hygroma)	Children, usually <2 years old	Tongue	Submucosal, microcystic fluid-filled spaces May present as macroglossia	Thin-walled, endothelial-lined, ectatic vessels with varying luminal sizes No appreciable smooth muscle wall Stroma may have lymphocytes, fat, fibroblasts Admixed with normal tissues, enlarges with infection

(continued)

Table 1.1 (continued)

Lesion	Most affected demographic	Most common oral site	Clinical description	Characteristic histologic features
Venous malformation	Congenital, but may be diagnosed in adults due to continued growth	Any oral cavity site	Soft, compressible, blue submucosal mass	Aberrant, tortuous, thin-walled venous channels without internal elastica Disorganized smooth muscle in walls May dissect through normal tissue Intravascular papillary endothelial hyperplasia ±Few RBCs, ±thrombi due to stasis
Arteriovenous malformation	Children	Any oral cavity site May be associated with syndromes	Red, pulsatile mass with bruit or murmur	Venules and arterioles of variable sizes distributed throughout normal, native connective tissue
Other vascular anomalies				
Lesion	Most affected demographic	Location(s)	Clinical description	Characteristic histologic features
Caliber-persistent artery	Elderly	Lower lip	Soft, raised, blue-hued or mucosa-colored nodule. Often pulsatile	Normal, medium-caliber artery with a thick smooth muscle wall located in the superficial lamina propria
Oral varices	Middle-aged to elderly	Ventral tongue, lip	Blue, tortuous, compressible veins	Thin-walled, dilated venules coursing through normal lamina propria. Organizing thrombi or phleboliths may be present

H/N head and neck, *GLUT* glucose transporter, *RBC* red blood cell, *HHV* human herpes virus, *LANA* latency-associated nuclear antigen

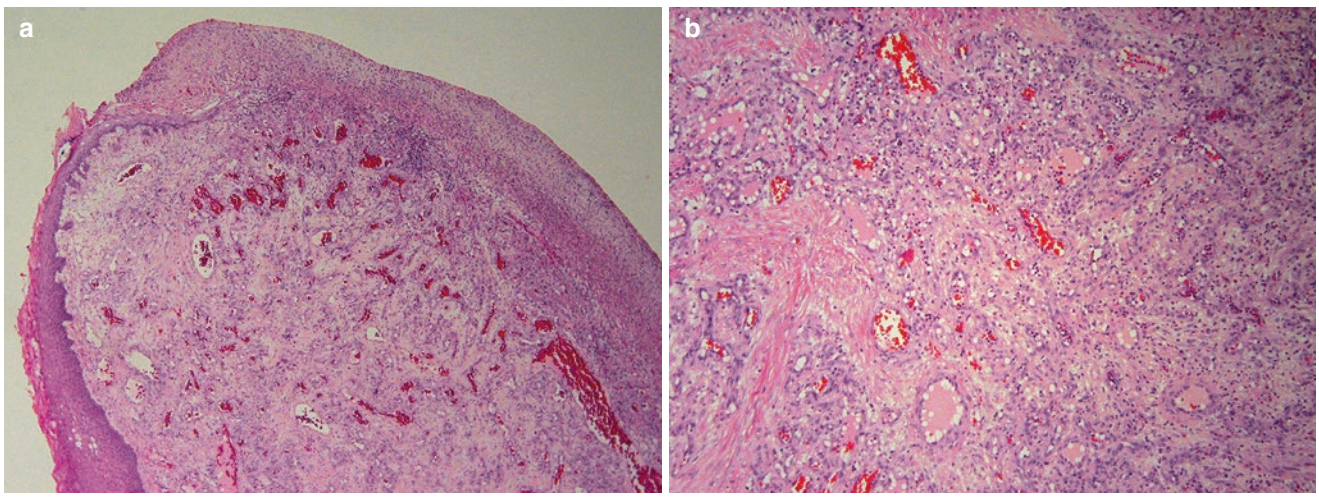

Fig. 1.3 Lobular capillary hemangioma. (**a**) A vascular proliferation with surface ulceration and a (**b**) vaguely lobular pattern

various etiologies and is characterized by a band-like inflammatory infiltrate in the lamina propria.

- The classic lichenoid lesion of the oral cavity is lichen planus (LP). LP is a mucocutaneous, immune-mediated inflammatory process (Fig. 1.4). It affects middle-aged patients and shows a female predominance.
  - Patients present with erythematous, inflamed mucosal lesions, and ulcers which vary in appearance depending on type (Table 1.2).
  - As many as 25% of patients with mucosal lesions will have skin involvement.
  - The histologic features of LP are summarized in Table 1.3 and are characterized by a band-like, lichenoid chronic inflammatory infiltrate with interface mucositis and basal, vacuolar change (Fig. 1.4).
  - Dysplasia is not a feature of LP. However, there is conflicting data on the risk of malignancy in these patients which is reported to approximate 2%.

Table 1.2 Clinicopathologic features of the different types of lichen planus

Type of lichen planus	Oral site	Clinical	Histology
Reticular	Buccal, buccal sulcus, tongue Usually asymptomatic Bilateral	Thin, raised white lines arranged in a lace-like/reticular pattern on an erythematous or non-erythematous background	Orthokeratosis and parakeratosis Acanthosis Admixed areas of atrophic epithelium Thick basement membrane
Erosive	May be restricted to gingiva	Erythematous mucosa alternating with irregular areas of ulceration White pseudomembranes	Thin, ulcerated epithelium Loss of rete ridges Infiltrate extends to mid-level of epithelium
Plaque-like	Tongue	Slightly raised white area Resembles leukoplakia	Orthokeratosis and parakeratosis Acanthosis No admixed atrophic epithelium Thick basement membrane
Bullous	Posterior buccal	Large bulla that rupture and expose an erythematous, inflamed ulcer base	Subepithelial bulla Lifting of the epithelium off the basement membrane Typical epithelial changes of LP

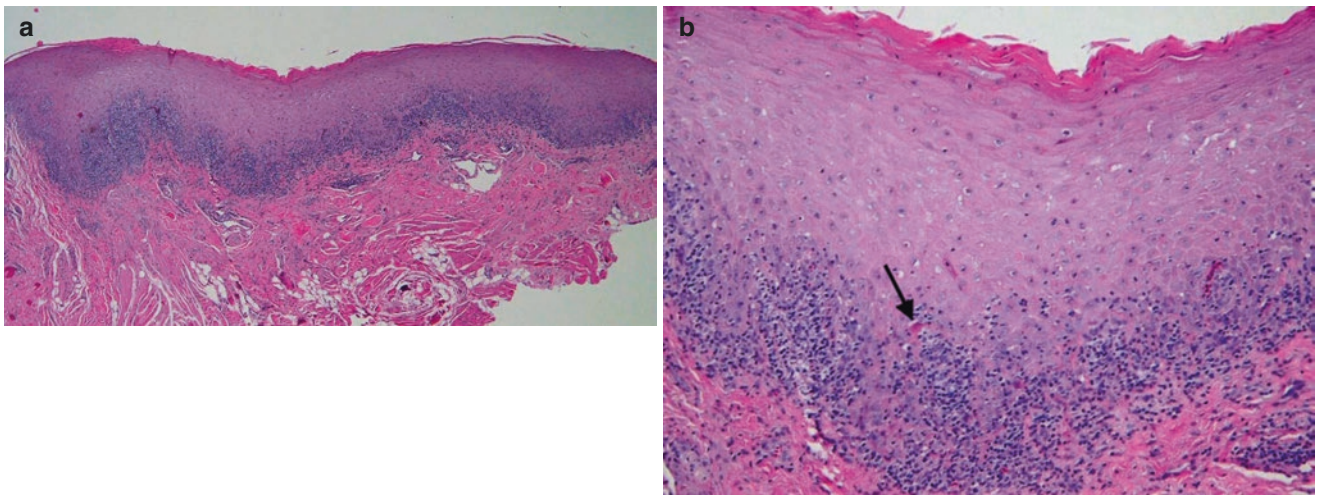

Fig. 1.4 Oral lichen planus. (**a**) Acanthotic squamous mucosa with a band-like lymphocytic infiltrate along the interface between the epithelium and lamina propria. (**b**) The lymphocytes obscure the basement membrane, eroding the basal keratinocytes. Exocytosis into the epithelium is present, and a dyskeratotic keratinocyte (Civatte body) is present (arrow)

  - Direct immunofluorescence shows an irregular band of fibrinogen deposition on the basement membrane in nearly all cases.
- There are a host of drugs and systemic conditions that can elicit a lichenoid mucositis and mimic LP (Table 1.4). Clinical history and careful application of diagnostic criteria can aid in arriving at the correct diagnosis.

References: [15–19]

4. *What is geographic tongue and its key histologic features?*

Geographic tongue, also known as benign migratory glossitis, is a chronic, immune-mediated inflammatory process that affects approximately 3% of the population. It is the most common oral lesion associated with psoriasis.

- The majority of cases are asymptomatic and present clinically as migrating areas of sharply demarcated erythematous mucosa rimmed by white, scalloped mucosa. The changes represent loss of filiform papillae.
- Biopsies show a psoriasiform mucositis (Fig. 1.5). The white areas represent acanthosis with mild hyperparakeratosis, neutrophilic transmigration, and pseudo-abscesses filled with neutrophils within the upper half of the epithelium. The red areas cor-

Table 1.3 Histologic features of lichen planus

Feature	Histologic findings
Lichenoid infiltrate	Dense, band-like, chronic inflammatory infiltrate in the lamina propria
Interface inflammation	Inflammation at the epithelial-submucosal junction which usually obscures the basement membrane
Vacuolar change	Degeneration of the basal epithelial layer with individual cell necrosis and liquefaction
Exocytosis	Migration of lymphocytes into the epithelium
Civatte bodies	Dyskeratotic squamous cells with shrunken, deeply eosinophilic cytoplasm and hyperchromatic nuclei
Sawtooth rete ridges	Thickening of the spinous layer with elongated, pointed rete ridges and overlying orthokeratosis or parakeratosis

Table 1.4 Lichenoid conditions of the oral cavity

	Lichen planus	Lichenoid drug reaction	Contact hypersensitivity lichenoid reaction	Lupus erythematosus	Chronic graft-versus-host disease
Patients	F:M = 2–3:1 Middle-aged adults	Variable Common drugs: methyldopa, interferon-alpha, TKI, beta-blockers, antihypertensives	Adults, F > M	F > M SLE > discoid lupus	Allogenic stem cell transplant patients > > BMT Chronic – 100 days after transplant
Pathogenesis	Presumed autoimmune condition	Immune mediated (antibody and/or T-cell mediated)	Type IV/contact hypersensitivity reaction to dental materials: amalgam, acrylic, flavorings	Autoimmune, immune complex type 3 reaction	HLA incompatibility between donor and recipient 70% of GVHD patients will have oral disease
Clinical presentation	Bilateral, symmetric White, reticular areas on mucosa Red, painful areas and ulcers Cheek, tongue, gingiva	Painful, erythematous or white mucosal lesions Similar to LP but more erosive and unilateral Buccal > lips > tongue	Erythematous, white, ulcerative lesions localized to the area of contact Cheek, ventral and lateral tongue	Oral lesions almost always occur with skin lesions Aphthous ulcer, reticulated, red, keratotic lesions of cheek, palate, lip	Gingivitis, mucositis, erythema, pain Hyperkeratotic plaques, limited oral opening due to sclerosis
Histology	Dense, lichenoid inflammation Degeneration of basal layer with single cell necrosis, vacuolar change Obscured interface Exocytosis Sawtooth rete ridges OK, PK	Similar to LP with more mixed infiltrate of lymphocytes, plasma cells, eosinophils Deeper extension into lamina propria, ±perivascular Exocytosis in all layers of epithelium ±Granulomatous inflammation ±PK, spongiosis, acanthosis	Acanthosis, HK, spongiosis Predominantly lymphocytes with plasma cells, histiocytes, eosinophils Papillary vessels are dilated, with a perivascular lymphohistiocytic infiltrate ±Deep perivascular plasma cells ±Neutrophils	Alternating acanthosis and atrophy Degeneration of basal cell layer Interface lichenoid inflammation Thick BM, mucin in lamina propria Occasionally, a deeper perivascular infiltrate with lymphocytes and scattered plasma cells	Acanthosis, exocytosis, thick BM with sclerosis is most often present Epithelium may be normal or atrophic Variable severity of lichenoid T-cell infiltrate Basal vacuolization, severe forms show clefts between epithelium and lamina propria Dyskeratosis, apoptosis
Other laboratory findings	DIF: Linear fibrinogen and granular C3 at BM	Positive basal cell cytoplasmic antibody	Skin patch test can confirm diagnosis Basal cell cytoplasmic antibody usually negative	DIF: Linear, granular IgG, M, A at BM Serum: anti-Smith, anti-dsDNA, anti-RNP	

TKI tyrosine kinase inhibitors, *SLE* systemic lupus erythematosus, *BMT* bone marrow transplant, *HLA* human leukocyte antigen, *GVHD* graft-versus-host disease, *OK* orthokeratosis, *PK* parakeratosis, *LP* lichen planus, *HK* hyperkeratosis, *BM* basement membrane, *DIF* direct immunofluorescence, *dsDNA* double-stranded DNA, *RNP* ribonucleic protein

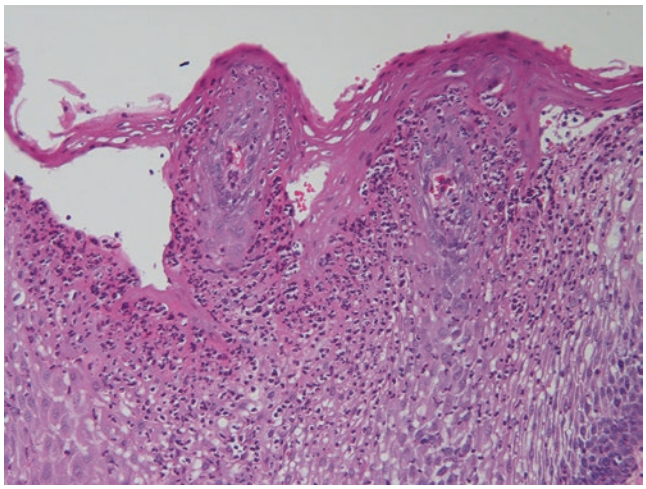

Fig. 1.5 Geographic tongue. The surface epithelium exhibits acanthosis, collections of neutrophils, and the absence of the usual filiform papillae of the dorsal tongue

respond to areas of epithelial atrophy and loss of the filiform papillae. A mixed inflammatory cell infiltrate is usually seen in the lamina propria.

- There is no premalignant potential associated with geographic tongue, but it is frequently biopsied and must not be confused with epithelial dysplasia.

Reference: [20]

5. *Which oral lesions are associated with a prominent eosinophilic infiltrate?*

Eosinophils in the oral mucosa are associated with a host of lesions (Table 1.5) including, infectious, inflammatory, and neoplastic.

References: [17, 21]

6. *What is the differential diagnosis of granulomatous inflammation of the oral cavity?*

Granulomatous inflammation can be encountered in oral biopsies as a result of local and systemic causes (Table 1.6).

- The most frequently encountered lesion is secondary to foreign body implantation (Fig. 1.7).
  - Examination of all specimens under polarized light is mandatory.
  - In the absence of a foreign body, special stains for microorganisms should be performed.
- Orofacial granulomatosis is a hypersensitivity reaction typically seen in young adults. Patients present with swelling of the lips and gingiva.
  - Histologic sections show non-necrotizing granulomas in the lamina propria with edema and chronic inflammation. Eosinophils may be seen. The granulomas may be subtle.

References: [22–24]

Table 1.5 Lesions of the oral cavity with prominent eosinophilia

Condition	Features
Traumatic ulcerative granuloma with stromal eosinophilia (Fig. 1.6)	Striated muscle destruction, usually due to trauma, elicits an eosinophilic inflammatory response. Histiocytic proliferation is also present. The mucosa shows ulceration with hyperplastic epithelium at the edges and abundant granulation tissue which can be hyperplastic and makes the surface appear elevated.
Lichenoid drug reactions and other antigen-related responses	The exposure to antigens triggers an inflammatory/immune response that may include a significant number of eosinophils, in addition to mast cells, plasma cells, and lymphocytes.
	Vesiculobullous diseases like pemphigus and pemphigoid of the oral cavity have a relative paucity of eosinophils compared to skin biopsies.
Infectious processes	Similar to other sites, the presence of microorganisms triggers an eosinophilic response. Examples are parasites, nematodes, and fungal infections.
Neoplasms	The most frequently encountered is squamous cell carcinoma, but other neoplasms such as mucoepidermoid carcinoma and Hodgkin lymphoma may have prominent eosinophilia.

7. *What is the differential diagnosis of vesiculobullous conditions of the oral cavity, and which ancillary tests are used to diagnose them?*

The oral mucosa is a frequent site of vesiculobullous diseases. The most common are mucous membrane pemphigoid and pemphigus vulgaris (Table 1.7).

- Mucous membrane pemphigoid (Fig. 1.8) is the most common variant of a group known as the immune-mediated subepithelial blistering disorders.
  - Entities such as bullous pemphigoid, linear IgA disease, and pemphigoid gestationis are included in this group.
- Pemphigus refers to a group of rare, autoimmune blistering disorders which include several variants. Pemphigus vulgaris (Fig. 1.9) is the most common. Other variants include:
  - Pemphigus foliaceus, IgA pemphigus, and paraneoplastic pemphigus
- Diagnosis of vesiculobullous disorders relies on histologic confirmation with the aid of direct immunofluorescence (DIF).
- Oral biopsies rarely include intact blisters due to the fragility of the oral mucosa.
- If a blistering process is diagnosed, the patient must have a second biopsy of peri-lesional tissue for direct immunofluorescent studies in order to properly classify the disease and provide appropriate management.

References: [25–30]

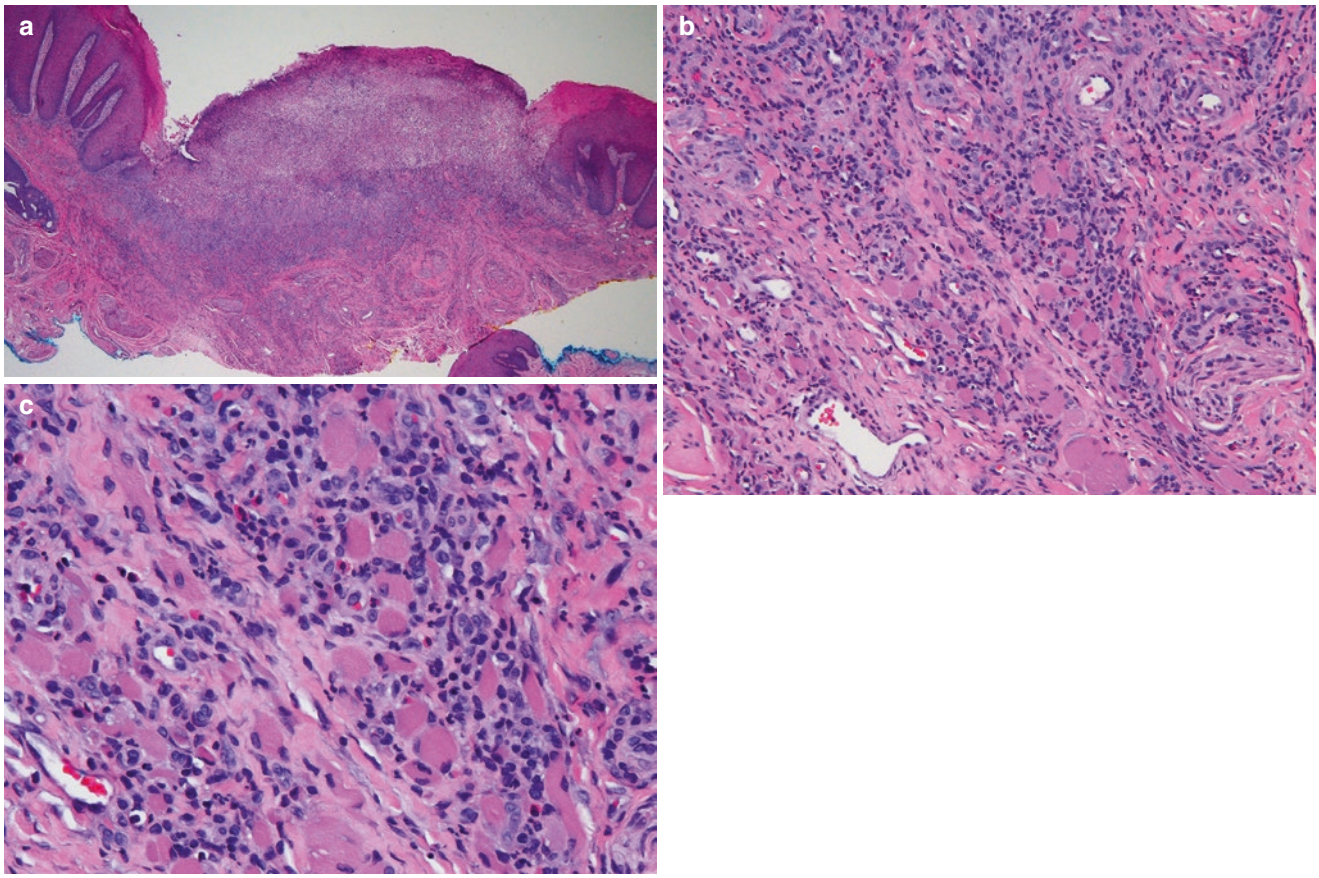

Fig. 1.6 Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE). (**a**) The ulcerated oral mucosa is rimmed by reactive epithelium. (**b**) The granulation tissue extends into the underlying striated muscle and contains enlarged fibroblasts, endothelial cells, and (**c**) eosinophils which may vary in number but are a constant feature

Table 1.6 Disorders that present as granulomatous lesions of the oral cavity

Localized	Systemic
Foreign body reaction to dental materials: Amalgam Composite Impression materials Food particles Crystals found in dental materials and dentifrice Foreign body reaction to cosmetic fillers	Sarcoidosis Crohn's disease Deep fungal infections (histoplasmosis, etc.) Mycobacterial infections Granulomatosis with polyangiitis Orofacial granulomatosis

8. *What is the differential diagnosis of ulcers of the oral cavity?*

Oral ulcers can broadly be clinically divided into multiple ulcers and solitary ulcers.

- Common conditions that manifest as multiple oral mucosal ulcerations are summarized in Table 1.8. Some of them have characteristic histologic features, but the majority require clinical correlation.
  - When reporting histologic findings in oral mucosal ulcers, it is important to:
    - Rule out infectious causes (fungal, viral, mycobacteria, etc.).

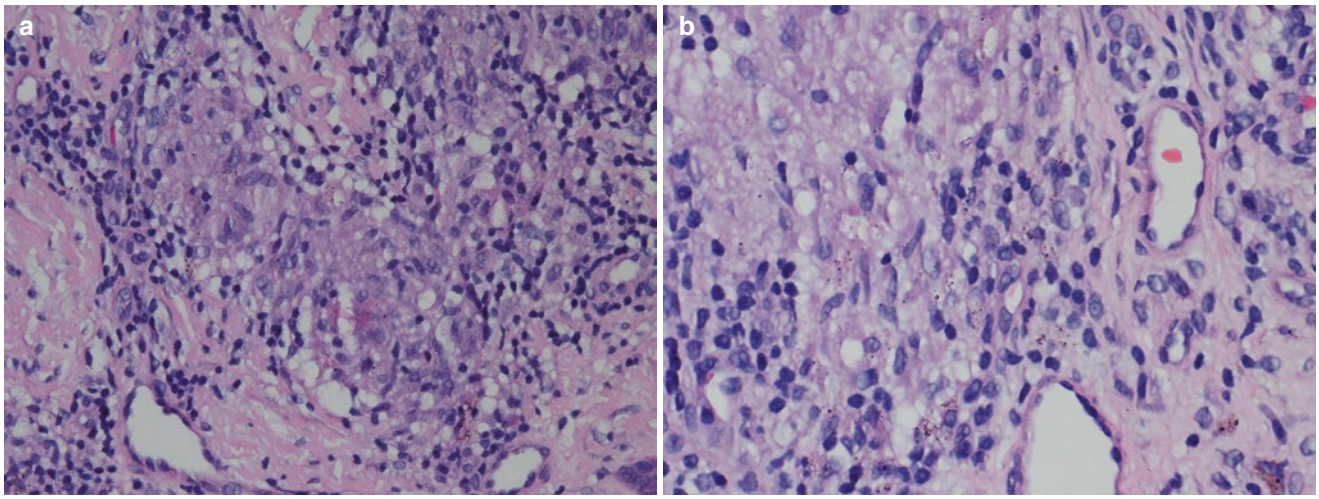

Fig. 1.7 Foreign body granulomatous inflammation. (**a**) The lamina propria has non-necrotizing granulomas that lack microorganisms. (**b**) Fragments of pigmented, finely granular foreign body material are present

Table 1.7 Vesiculobullous conditions of the oral cavity

	Mucous membrane pemphigoid	Pemphigus vulgaris
Bulla and antigen location	Subepithelial Basement membrane	Suprabasal Cell surface desmosomes
Oral sites	Palate, gingiva, lip, tongue Most common variant encountered in oral mucosa	Cheek, palate, ventral tongue
Clinical	Desquamative gingivitis Ocular disease	Multiple persistent oral lesions, followed by skin lesions
Morphology	Subepithelial cleft with preservation of basal cell layer Minimal spongiosis Predominantly lymphocytes Rarely eosinophils	Suprabasal blister with severe acantholysis Acantholytic basal cells have "tombstone" appearance, rounded Tzanck cells are present in the blister No inflammation in early lesions Rarely presents with intact vesicles in oral mucosa The mixed inflammatory infiltrate is scarce
DIF	Continuous, linear IgG, C3, ±IgA on basement membrane	Intercellular, granular IgG and C3

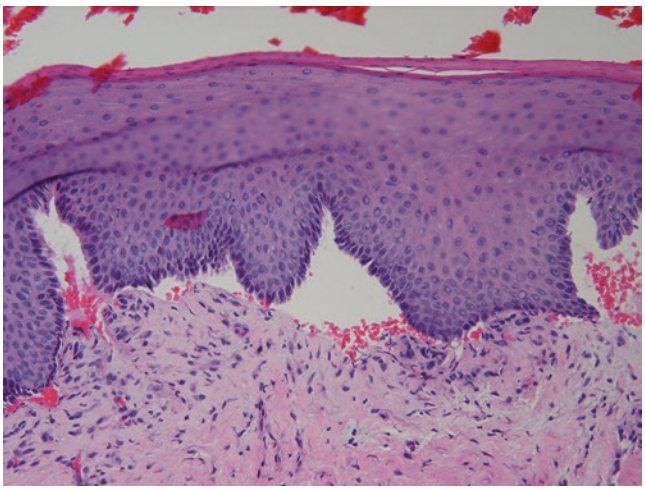

Fig. 1.8 Mucous membrane pemphigoid. The mucosa shows separation of the entire epithelium at the basement membrane level with subepithelial bulla formation and no evidence of acantholysis

    - Characterize the type of the inflammatory infiltrate (chronic, granulomatous, etc.).
- Recurrent aphthous ulcers have a variety of causes and associations. Diagnosis relies on clinical history and presentation. Treatment depends on the etiology, and unresolved lesions may be biopsied.

- The ulcers will have a tan-gray pseudomembrane on examination.
- Histology shows non-specific changes.
- The mucosa is ulcerated with overlying fibrin and neutrophils.
- Adjacent epithelium is spongiotic with inflammation.
- The edge of the lesions may show granulation tissue and hyperkeratosis or parakeratosis.

- Encountering single ulcerations of the oral mucosa is a frequent clinical situation. Most single ulcers are traumatic in origin.
  - In many occasions, the greatest value of pathologic examination of single ulcers is to rule out infectious processes or malignancy.
  - Entities in the differential diagnosis of a single aphthous ulcer includes:
    - CMV-associated mucosal ulcer (Fig. 1.10).
    - Syphilitic chancre.
    - Deep fungal infection.
    - Mucosal ulcer secondary to jaw disease or malignancy.
    - EBV-associated mucocutaneous ulcer – this is a hematolymphoid entity which is discussed later in question 29.

References: [31, 32]

9. *What is the differential diagnosis of inflammatory gingival masses?*
   - Inflammatory masses of the gingiva are common (Table 1.9). The pluripotent capacity of gingival cells results in a spectrum of inflammatory lesions comprising reactive proliferations of bone, vessels, and mesenchymal cells.
     - The most common of these lesions is a pyogenic granuloma. This lesion differs from lobular capillary hemangioma in that the vascular proliferation is not organized in a lobular arrangement but instead grows in a radiating fashion from a central stalk or area.

References: [33–35]

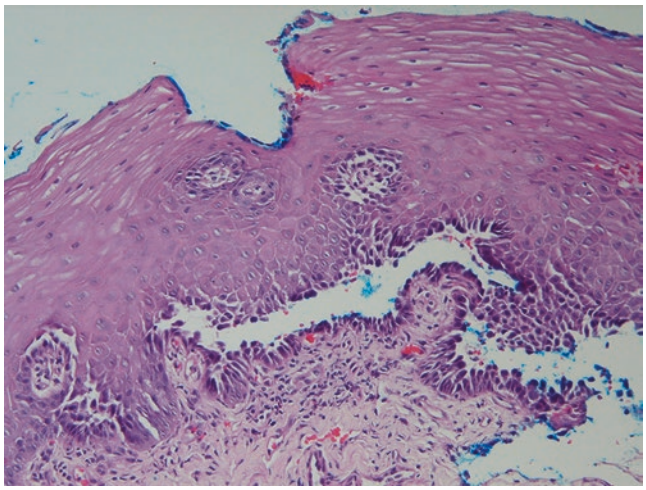

Fig. 1.9 Pemphigus vulgaris. The mucosa shows acantholysis with retention of the basal keratinocytes along the basement membrane and suprabasal blistering

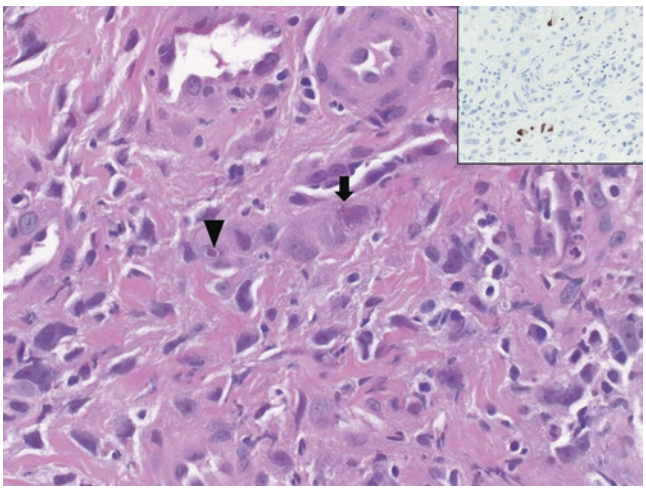

Fig. 1.10 CMV ulcer base. Large, infected stromal cells show intracytoplasmic granules (arrow) and intranuclear inclusions with the characteristic clear halo (arrowhead). An immunohistochemical stain for CMV is positive in scattered cells (inset)

Table 1.8 Conditions presenting with multiple oral ulcers

	Recurrent aphthous ulcers	Recurrent intraoral herpes	Ulcerative lichen planus
Clinical associations	Bechet disease, Crohn's disease, anemia, zinc deficiency, celiac disease	Herpes infection	Lichen planus
Features	Non-specific histology, usually located on mucosa that is not bound to bone and has a thin parakeratin layer. Not often seen in orthokeratinized mucosa.	Initially presents as a blistering condition. Later, the lesions rupture and create ulcers. Viral cytopathic changes are in the epithelial cells adjacent to the ulcers. Most frequently in oral mucosa bound to the bone but seen anywhere in immunosuppressed patients.	Lichen planus can have a predominantly ulcerative presentation with large shallow ulcers. The lichenoid features are not present in areas of ulceration but may be found in the adjacent mucosa.

Table 1.9 Inflammatory gingival masses

	Peripheral ossifying fibromas	Peripheral giant cell granuloma	Epulis fissuratum (inflammatory fibrous hyperplasia)	Parulis (sinus tract)
Patient gender, age	F > M, 2nd–3rd decades	F = M 4th–6th decades	F > M Elderly, denture-wearing	Any
Oral site	Exclusively gingiva	Gingiva, alveolar mucosa	Alveolar mucosa	Gingiva, alveolar mucosa
Clinical	Solitary, red or mucosa-colored, firm, well-circumscribed, exophytic mass	Red, purple, or blue-hued, painless, soft, exophytic mass	Sessile or pedunculated Firm and pink, or erythematous and ulcerated Grooved due to denture placement	Red or purple raised mass with a central punctum May be tender and associated with infected tooth
Pathology	Hypercellular proliferation of spindle cells with woven bone, osteoid or cementum-like material **(Fig. 1.11)** Nuclei are plump, ovoid with fine chromatin, small nucleoli Lamellar bone in older lesions ±Giant cells	Hypercellular proliferation of mesenchymal cells with a prominent vascular component **(Fig. 1.12)** Numerous multinucleated giant cells ±Scattered mitotic figures Normal or ulcerated overlying epithelium	Subepithelial fibrous proliferation Overlying hyperkeratotic and acanthotic epithelium, often with ulceration Variable chronic inflammation and vascular proliferation ±Osseous or chondroid metaplasia	Floridly inflamed granulation tissue Linear, sinus tract that is lined with neutrophils Overlying epithelium may be spongiotic and acanthotic with focal ulceration

Table 1.10 Conditions associated with generalized gingival enlargement

Entity	Clinical findings	Histologic features
Drug-induced gingival overgrowth	Most commonly associated with calcium channel blockers, anticonvulsants, and cyclosporin	Acanthotic epithelium with thin, elongated rete pegs Fibrous hyperplasia with collagen bundles of varying densities Mild to moderate chronic inflammation
Plasma cell gingivitis	Probably a hypersensitivity reaction, but the causative agent is not identified in many cases	Epithelium may show inflammatory changes and acanthosis (Fig. 1.13) Dense sheets of plasma cells in the connective tissue
Vitamin C deficiency (scurvy)	Patients with limited dietary intake Presents as enlarged, erythematous gingiva that bleeds with gentle manipulation	Mixed inflammatory cell infiltrate with marked epithelial acanthosis
Hereditary gingival fibromatosis	Autosomal dominant or recessive inheritance May occur in isolation or as part of several rare syndromes (e.g., Zimmermann-Laband syndrome, oculo-dental syndrome)	Similar to drug-induced gingival overgrowth with fibrous hyperplasia with haphazardly arranged collagen bundles of varying densities, mild to moderate chronic inflammation Surface epithelium is often acanthotic with thin, elongated rete pegs
Granulomatosis with polyangiitis	Necrotizing granulomatous inflammation, usually affecting the respiratory tract and vasculitis of small to medium vessels. Necrotizing glomerulonephritis and ocular vasculitis are common. Intraoral lesions may be ulcerations and red, enlarged gingiva termed, "strawberry gingivitis"	Ill-defined granulomatous inflammation of lamina propria comprising multinucleate giant cells, epithelioid histiocytes and T-lymphocytes Leukocytoclastic vasculitis or classic vasculitis with fibrinoid necrosis may be present
Leukemias	Neutropenic ulcerations, spontaneous gingival hemorrhage, palatal petechiae, and gingival enlargement	Malignant infiltrates of immature hematopoietic cells, most often myeloid leukemias

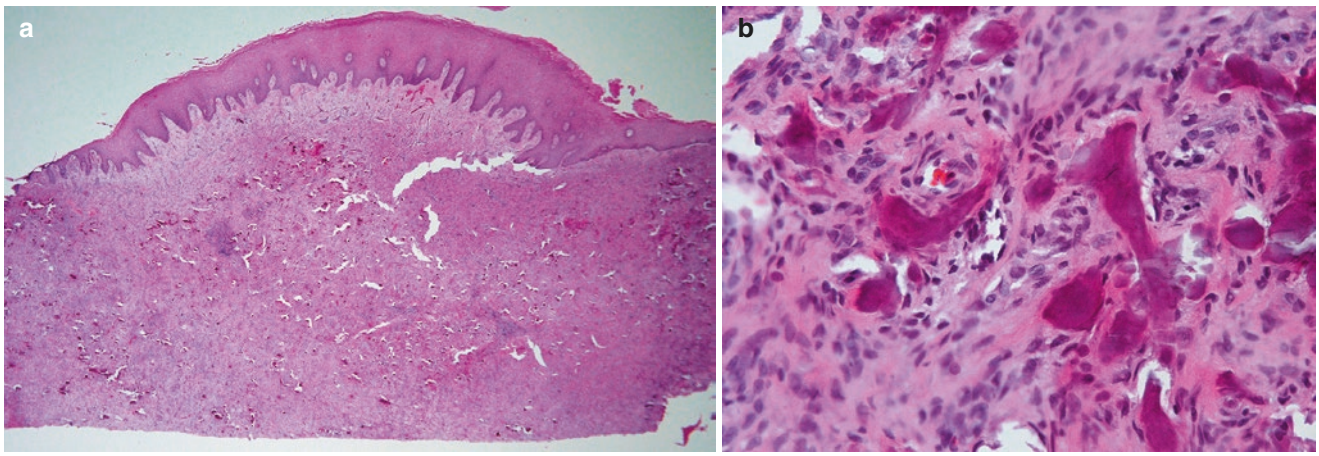

Fig. 1.11 Peripheral ossifying fibroma. (**a**) Sessile, hypercellular nodule composed of (**b**) bland fibroblasts and deposition of cementum and calcifications

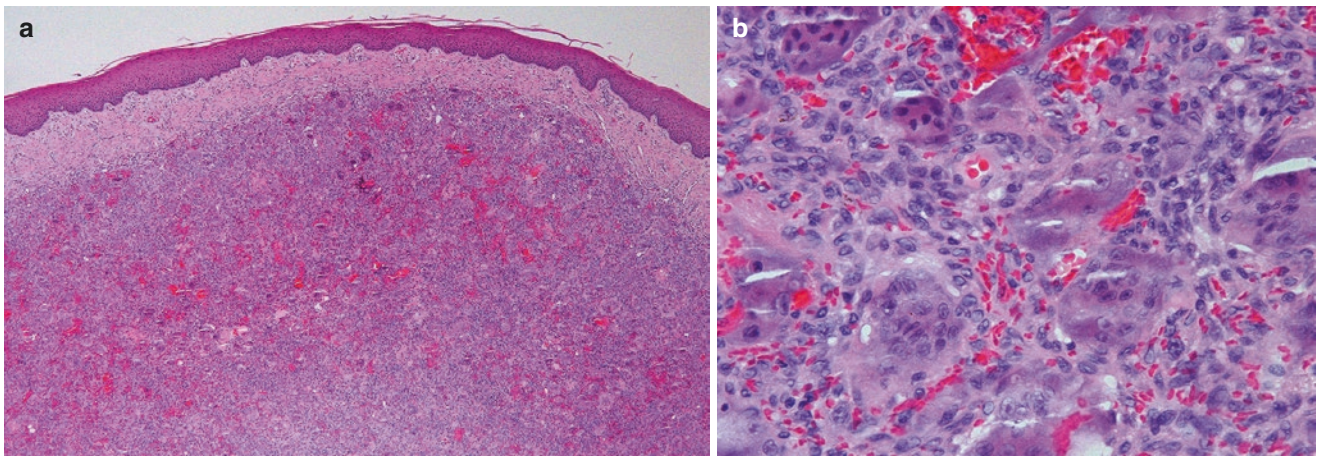

Fig. 1.12 Peripheral giant cell granuloma. (**a**) Hypercellular, sessile lesion composed of (**b**) plump, monotonous spindle cells and multinucleated giant cells in a vascular stroma

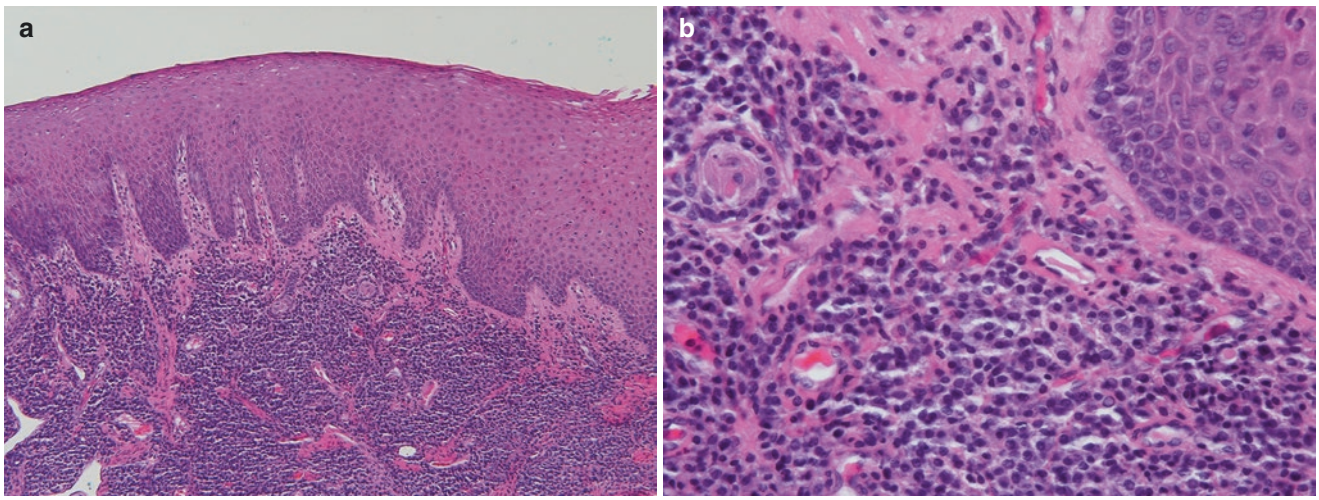

Fig. 1.13 Plasma cell gingivitis. (**a**) Slightly hyperplastic epithelium with sheets of inflammatory cells that do not efface the normal lamina propria architecture. (**b**) The inflammatory cell infiltrate is composed of mature, reactive plasma cells with no atypical features

10. *What conditions are associated with generalized gingival enlargement and what are their histological features?*

    Gingival overgrowth is usually triggered by an inflammatory response to dental plaque and poor oral hygiene. If the inflammatory response is clinically exaggerated, clinicians may biopsy these lesions to rule out other etiologies. There are multiple causes of gingival hyperplasia (Table 1.10); the histologic findings can be non-specific, and clinical correlation is usually required to arrive at a specific diagnosis.

    References: [36–42]

11. *What systemic conditions may present with multiple oral masses?*

    Oral soft tissue masses may be manifestations of inherited syndromes, immune-mediated conditions, infections, or systemic diseases. Multiple oral lesions should raise suspicion for systemic diseases and prompt further clinical workup based on the histologic findings.

    - Inherited syndromes presenting with oral masses are highlighted in Table 1.11.
    - Immune-mediated conditions, specifically the granulomatous disorders, vary in their clinical manifestation of oral masses (see question 6).
      - Sarcoidosis may present as submucosal nodules, while Crohn's disease may present with mucosal tags.
      - Biopsies of both reveal noncaseating granulomatous inflammation.
    - Among the infectious processes, multifocal epithelial hyperplasia (Heck's disease) is most commonly associated with multiple oral masses.
      - Other HPV-associated lesions occurring in multiples may be seen in immune-deficient states, such as HIV-infected patients.
    - Amyloidosis can appear in the oral cavity as multiple oral masses, macroglossia, or induration of the buccal mucosa, lips, or tongue (see question 12).

    References: [43–48]

12. *What are the etiologies, presentations, and histologic features of amyloidosis? What stains aid in the diagnosis?*

    Amyloid deposits comprise proteinaceous material with a variety of biochemical compositions. Amyloidosis of the oral cavity most commonly results from monoclonal gammopathies and the overproduction of immunoglobulin light chains (AL amyloid). Other etiologies include infection and rheumatic disease as a result of overproduction of acute phase proteins (AA amyloid). Rarely, amyloidosis is associated with familial syndromes.

    - Patients may present with induration, generalized nodularity, or isolated nodules of the oral mucosa.

Table 1.11 Inherited syndromes presenting with multiple oral masses

	Multiple endocrine neoplasia 2B	Cowden syndrome	Neurofibromatosis type 1	Tuberous sclerosis
Inheritance	Autosomal dominant	Autosomal dominant or sporadic	Autosomal dominant	Autosomal dominant or sporadic
Genetics	Germline mutation in RET proto-oncogene	Germline PTEN (phosphate and tensin homolog) mutations	Mutation in tumor suppressor gene NF1 which codes for a RAS GTPase-activating protein	Mutations in TSC1 and TSC2 (tuberous sclerosis-1 and 2)
Head and neck presentation	Multiple oral neuromas Medullary thyroid carcinoma in childhood	Oral papillomas, neuromas Facial trichilemmomas	Intraoral neurofibromas (NF)	Multiple intraoral, facial, ungal fibromas Enamel pitting of the teeth Desmoplastic fibromas of the jaws
Other lesions	Pheochromocytomas Marfanoid habitus Intestinal ganglioneuromatosis	Dysplastic gangliocytoma of cerebellum Macrocephaly Mucocutaneous and GI hamartomas Multiple trichilemmomas High risk for thyroid, breast, endometrial tumors	Plexiform neurofibroma Café au lait macules Multiple neurofibromas Lisch nodules of the iris Optic gliomas Osseous dysplasia	Cutaneous hypomelanotic macules Fibrous plaques of the forehead or scalp Retinal hamartomas Lymphangioleiomyomatosis of the lungs Renal angiomyolipomas Cardiac rhabdomyoma Cortical dysplasias Subependymal nodules and giant cell astrocytoma

GI gastrointestinal

- The tongue is affected in 20% of patients with amyloidosis and presents as macroglossia with reduced mobility.
- Histologic sections show amorphous, paucicellular, pale pink depositions within the lamina propria. The deposits may appear globular or diffuse, and perivascular or perineural patterns may be identified. Plasma cell infiltrates and a multinucleated giant cell reaction may be seen in association with the deposits.
- Amyloid deposits stained with Congo red demonstrate apple-green birefringence under polarized light microscopy. If plasma cell infiltrates are identified, kappa and lambda immunohistochemistry (IHC) may be used to demonstrate monoclonal light chain restriction.

References: [49, 50]

13. *What is the differential diagnosis of intraoral soft tissue masses in infants?*

The most common intraoral soft tissue masses in infants are vascular (see question 4). Others include ectopic thyroid tissue and hamartomas (see question 3), as well as congenital epulis of the newborn.

- Congenital epulis of the newborn shows a female predominance and presents as a slightly red or mucosa-colored, pedunculated soft tissue mass. It is usually located on the mucosa of the anterior alveolus, with occurrence in maxilla approximately twice as frequent as the mandible.
- Histologically, unencapsulated sheets of large cells with abundant, eosinophilic, granular cytoplasm and small, eccentric nuclei lie within normal adjacent connective tissue. The cells are morphologically identical to those of a granular cell tumor; however, S100 and SOX10 staining is negative. Excision is curative.

References: [51, 52]

14. *What is the differential diagnosis of benign neural tumors of the oral cavity?*

Benign neural tumors of the oral cavity are not uncommon (Table 1.12). They may be trauma-induced, neoplastic, or syndrome-related. They are seen in various head and neck sites including soft tissues, ear, and salivary gland. With overlapping histologic features and immunohistochemical profiles, achieving the correct diagnosis may be challenging.

References: [53–57]

15. *What are the common muscle tumors of the oral cavity and which immunohistochemical studies differentiate them?*

- Angioleiomyoma is the most common oral smooth muscle tumor. It arises from the smooth muscle of vessel walls. In the oral cavity, it is most commonly

Table 1.12 Histologic features and immunohistochemical profiles of benign neural tumors of the oral cavity

Entity	Description	Histologic features	IHC
Traumatic neuroma	Non-neoplastic neural proliferation representing attempts at nerve regrowth after trauma Presents as a variably painful submucosal nodule	Small, tangled bundles of multiple mature nerves separated by dense connective tissue	S100+, EMA+ perineurium
Mucosal neuroma	Associated with multiple endocrine neoplasia type 2B	Hyperplastic nerve bundles, often with prominent thickening of the perineurium, within a normal to loose stroma	S100+, EMA+ perineurium
Schwannoma	Benign proliferation of Schwann cells. Associated with neurofibromatosis type 2 (vestibular schwannomas)	Encapsulated proliferation of spindled Schwann cells with hypo- and hypercellular areas Verocay bodies – palisaded nuclei polarized away from a central, eosinophilic area containing cytoplasmic processes	Diffuse S100+, str SOX10+, EMA+ capsular tissue
Neurofibroma	Usually solitary. Multiple or plexiform variants are associated with neurofibromatosis type 1	Circumscribed, unencapsulated proliferation of fusiform, spindle, "comma-shaped" nuclei Loose, variably myxomatous stroma with wavy collagen Plexiform variant has tangled bundles of tumor cells, each representing a nerve that is distended by tumor cells	S100+, focal SOX10+, var CD34+, var EMA+
Palisaded encapsulated neuroma	Benign proliferation of axons and Schwann cells (also known as solitary circumscribed neuroma)	Circumscribed, variably encapsulated. Spindled cells with elongated nuclei may show streaming and palisading reminiscent of poorly formed Verocay bodies of schwannomas (Fig. 1.14)	S100+, var EMA+ in capsular and peri-tumoral tissue
Nerve sheath myxoma	Proliferation of Schwann cells in an abundant myxomatous stroma	Multiple myxoid lobules of scattered spindle and stellate cells separated by loose connective tissue Sparse collagen fibers and mast cells may be present	S100+, NSE+, EMA–

var variable, *str* strong

found on the lower lip and presents as a painless or painful, mucosa-colored mass.

- Myofibromas occur less frequently but may overlap in clinical and histological presentations. Rarely, multiple lesions are seen in infants and termed myofibromatosis.
- Rhabdomyoma occurs in adults and children. It is a benign tumor derived from skeletal muscle. There is an adult and fetal type. Most are solitary but multifocal disease has been described.
  - The head and neck account for over 85% of the extracardiac rhabdomyomas.
  - The head and neck variant is *not* associated with tuberous sclerosis.
- A comparison of the clinical, histologic, and immunohistochemical features of these lesions is outlined in Table 1.13.

References: [58–60]

16. *What types of pigmented lesions are encountered in the oral mucosa?*

Pigmented lesions of the oral cavity may represent foreign body deposition, vascular lesions with hemorrhage, or melanocytic lesions. They are typically biop-

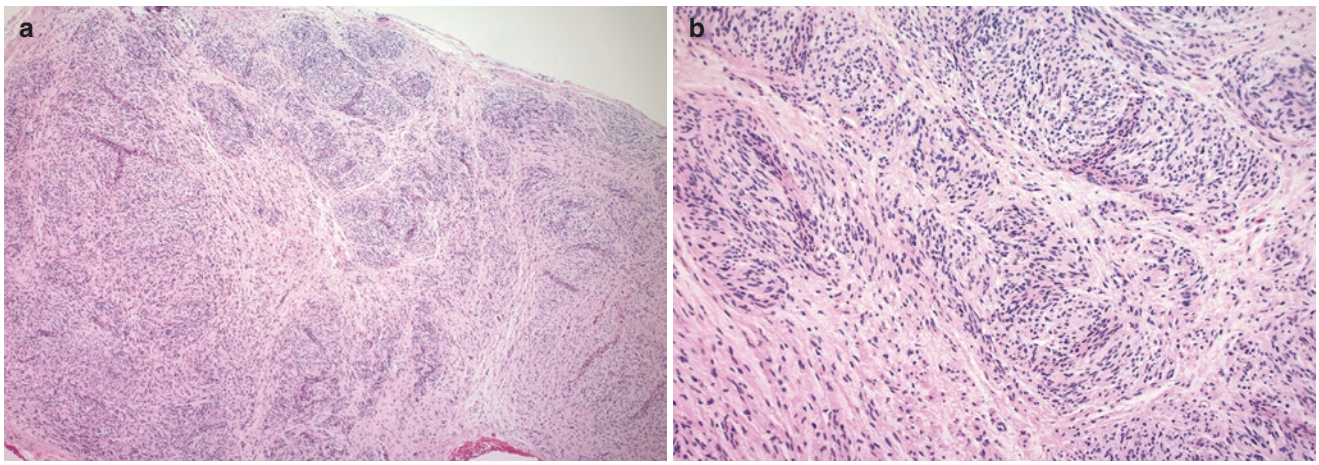

Fig. 1.14 Palisaded encapsulated neuroma. (**a**) A well-circumscribed spindle cell proliferation arranged in a vaguely lobular pattern with areas of tissue clefting. (**b**) Higher magnification shows short, plump, spindled cells with vague palisading and indistinct cell borders

Table 1.13 Clinicopathologic features of muscle tumors of the oral cavity

	Angioleiomyoma	Myofibroma	Adult rhabdomyoma	Fetal rhabdomyoma
Age (years), gender	Wide range (mean 45) F > M	Birth to 20 (mean 23) M > F	Adult type: 60–70, M:F=3:1	Birth to 60
Oral site	Lower lip, palate	Buccal mucosa, tongue	Solitary FOM, tongue, palate	Solitary or multiple Tongue, cheek, palate
Morphology	Well-circumscribed, variably encapsulated spindle cell proliferation Bland nuclei are elongated and "cigar-shaped" with blunt ends Prominent vascular spaces Fascicles of spindled cells course between thick-walled vessels	Unencapsulated, circumscribed spindle cell proliferation with a biphasic pattern Lighter zones contain short fascicles or whorls of myofibroblastic cells with glassy, blue-hued stroma Darker zones have increased cellularity with larger nuclei Slit-like blood vessels may be seen ±infiltrative border Mitoses may be frequent	Sheets of polygonal cells with abundant, pink, granular cytoplasm Cross striations in cytoplasm "Jackstraw-like" intracytoplasmic, rod-shaped crystals ±"Spider" cells with vacuolated cytoplasm Bland, small vesicular nuclei	Myxoid type: spindle cells with short, bland, oval nuclei Occasional striated, muscle cells Myxoid stroma Intermediate type: spindled areas and areas with differentiated muscle cells Less myxoid stroma, no mitoses
Positive IHC	Desmin, SMA	SMA, MSA	MSA, desmin, myoglobin, S100	MSA, desmin, myoglobin, ±S100, ±SMA
Negative IHC	S100, CK	Desmin, S100	CK, CD68, GFAP	CK, CD68

FOM floor of mouth, *SMA* smooth muscle actin, *MSA* muscle-specific actin, *CK* cytokeratin, *GFAP* glial fibrillary acidic protein

sied to exclude atypical and malignant melanocytic tumors.

- Amalgam tattoos represent foreign body deposition of amalgam debris from silver-colored dental fillings.
  - Tissue sections show black to brown coarse, granular material tracking along collagen fibers and within vessels of the lamina propria (Fig. 1.15). Minimal to no inflammatory response is elicited.
- Vascular pigmentation results from bleeding of vascular lesions and extravasation of blood.
  - Lesions show hemosiderin-laden macrophages singly or in clusters, resulting in clinical ecchymoses.
  - Traumatic lesions are often on the palate as a result of heavy snoring and emesis; inflammation may be present
- Localized melanocytic lesions and their histologic findings are outlined in Table 1.14.
- Generalized melanocytic lesions are usually associated with increased melanin production (melanosis) rather than melanocyte hyperplasia or proliferation.
  - The histologic findings are non-specific and typically show increased melanin in the basal layers of epithelium.
  - Causes of generalized melanocytic lesions include racial pigmentation, smoker's melanosis, Addison's disease, and various inherited syndromes that result in melanotic macules.

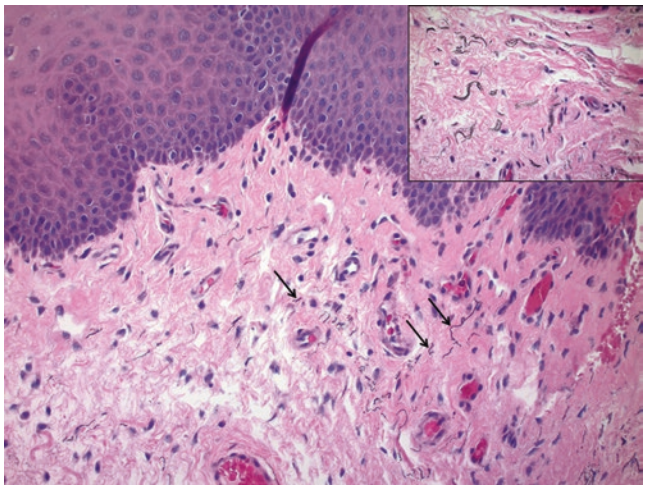

Fig. 1.15 Amalgam tattoo. Normal-appearing squamous epithelium with coarse, black granules (arrows, inset) deposited in the collagen of the lamina propria. The absence of a tissue reaction is typical

References: [61–63]

17. *What are the features of oral cavity melanomas and how do they differ from cutaneous melanomas?*

Mucosal melanomas of the head and neck are most common in the nasal cavity and sinuses. Oral melanomas are rare and commonly affect the maxillary gingiva and hard palate. Patients are typically in the fifth to seventh decades.

- The majority of cases show a radial growth phase in the form of a pigmented macule with or without a nodular component.

Table 1.14 Localized melanocytic lesions of the oral cavity

Entity	Clinical features	Histologic features
Melanoacanthoma	Young, black females Traumatic or reactive in nature Solitary or multiple brown to black lesions, usually on the buccal mucosa Usually painless, may be associated with burning sensation Remarkable for a rapid increase in size	Epithelial acanthosis and spongiosis Melanocytes with long, dendritic processes are dispersed throughout the epithelium Melanin is present in melanocytes and their processes Mild to moderate chronic inflammation with melanin incontinence and melanophages may be present in the lamina propria **(Fig. 1.16)**
Melanotic macule	F:M = 2:1 Solitary, well-defined and homogenous in color. Typically on the vermillion border and gingiva	Normal epithelium with increased melanin in the basal layer, no increase in melanocytes Melanophages and melanin incontinence may be present in the lamina propria **(Fig. 1.17)**
Melanocytic nevi	Palate > buccal mucosa, gingiva Well-circumscribed, round macules or papules, homogenous in color	Proliferation of bland melanocytes in nests in the epithelium and/or lamina propria, based on type: Intramucosal > blue nevi > compound nevi
Mucosal melanoma	Palate and maxillary alveolus are most common M:F = 2.5–3:1 Rare in the oral cavity (<1% of all melanomas) Irregular pigmentation and ill-defined borders Amelanotic melanomas present as an ill-defined mass	Proliferation of atypical, pleomorphic epithelioid or spindled melanocytes in sheets and irregular nests ±Prominent nucleoli, pseudoinclusions, pagetoid spread within epithelium

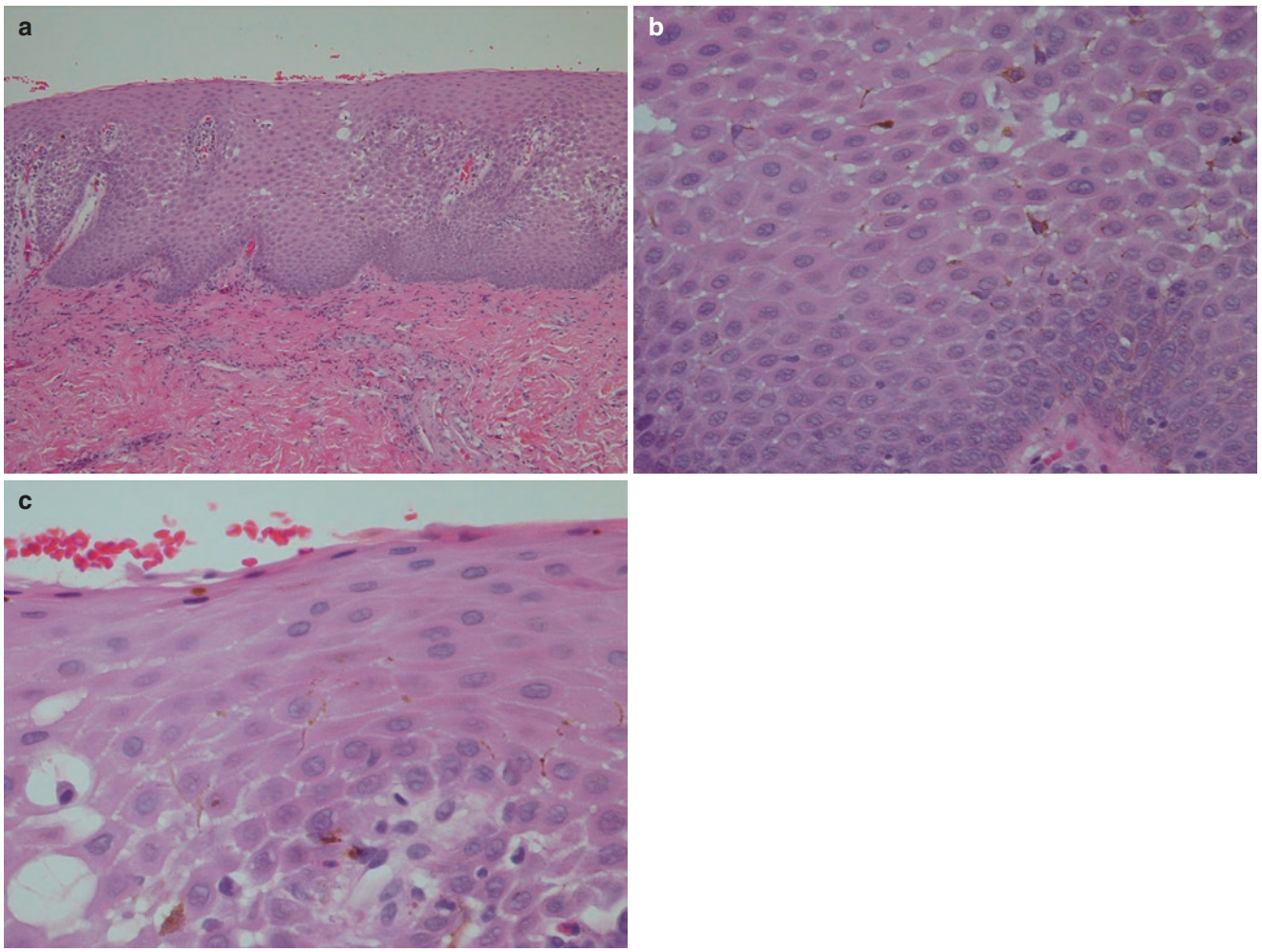

Fig. 1.16 Oral melanoacanthoma. (**a**) The surface epithelium appears slightly acanthotic and (**b**) contains multiple dendritic melanocytes with bland nuclear features. Focal acantholysis is present, and occasional eosinophils (not shown) can be seen

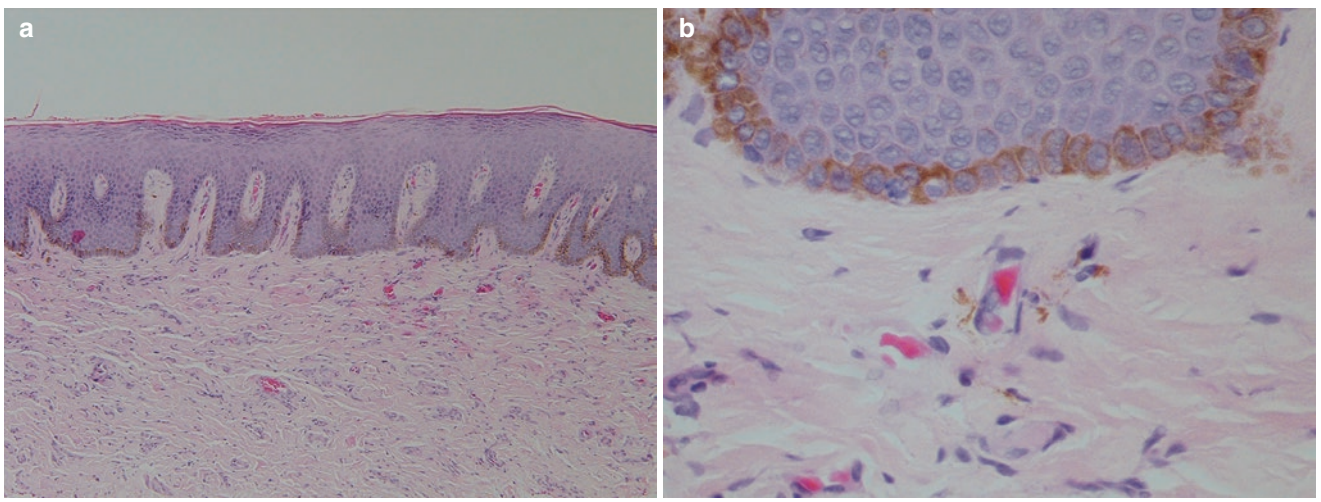

Fig. 1.17 Melanotic macule. (**a**) The mucosa exhibits increased accumulation of melanin, restricted to the basal keratinocytes. (**b**) Melanocytic hyperplasia and atypia are absent, but melanin incontinence in the lamina propria can be seen (center)

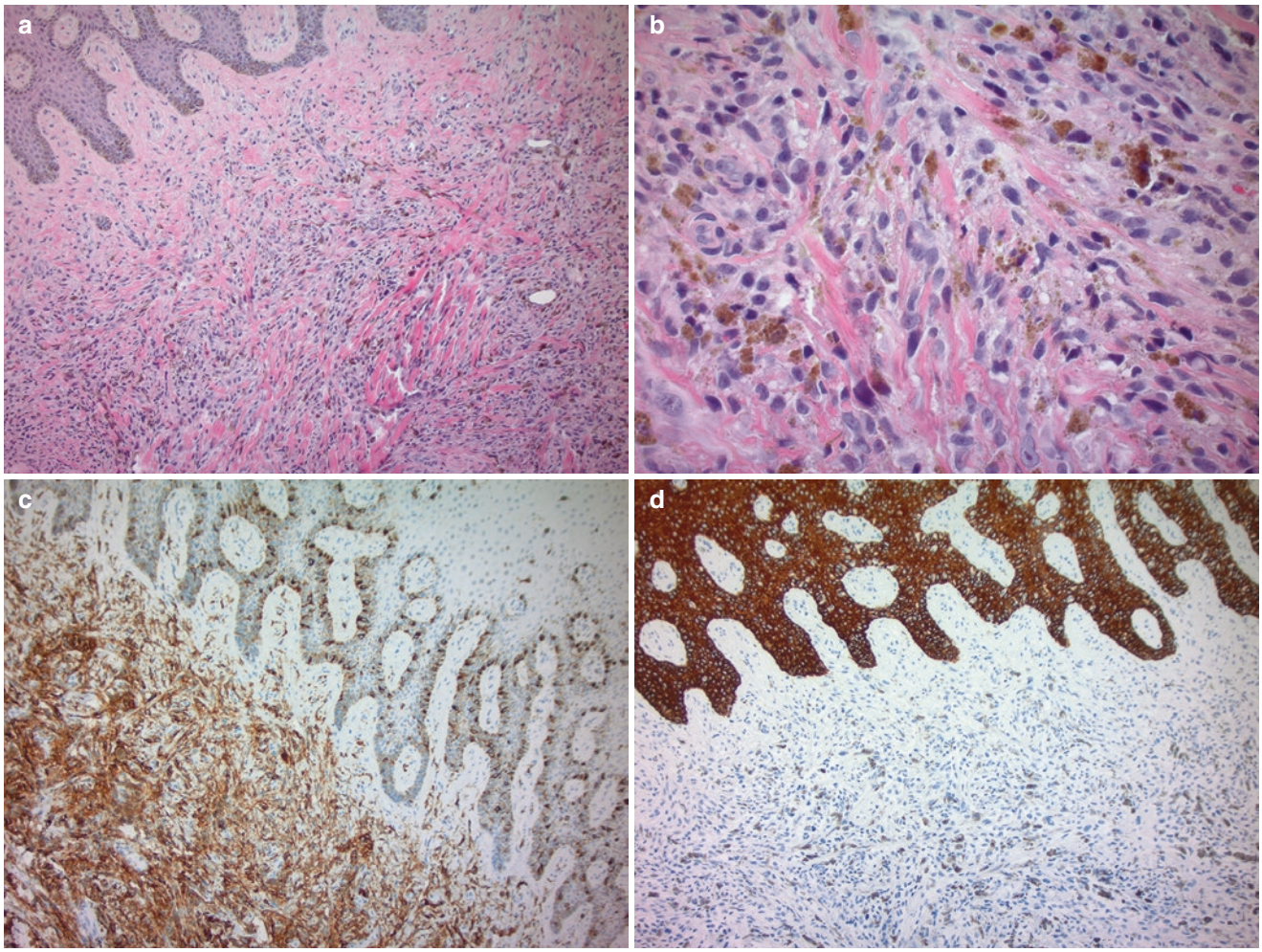

Fig. 1.18 Melanoma of hard palate. (**a**) Atypical pigmented cells infiltrate the lamina propria, overlying squamous epithelium has a pigmented basal layer. (**b**) Higher magnification shows spindled and epithelioid cells with amphophilic cytoplasm, fine and coarse intracytoplasmic pigment, pleomorphic nuclei with variably sized nucleoli. The tumor cells are positive for (**c**) HMB-45 and negative for (**d**) cytokeratin by immunohistochemistry

- The radial proliferation comprises basally located atypical melanocytes. The vertical growth phase shows invasive nests of atypical melanocytes in the lamina propria.
- Tumor cells show a variety of morphologies, as in other sites, including spindled, epithelioid, pleomorphic, and small round blue cells. Nuclei range from round to spindled with prominent nucleoli and brisk mitotic activity. Cells are generally pleomorphic and may contain fine, dusty brown, or coarse intracytoplasmic pigment and intranuclear inclusions (Fig. 1.18).
- Melanin production is seen in about two-thirds of cases.
- In contrast to cutaneous melanomas, oral melanomas:
  - Are not associated with ultraviolet light exposure as a risk factor.
  - Do not harbor BRAF-V600E mutations.
  - Uniformly have a poor prognosis that is not related to histologic parameters commonly identified in skin melanomas (e.g., depth, ulceration, etc.).
  - Usually arises de novo and is not preceded by a pre-existing, noninvasive pigmented lesion.
- Five-year disease-free survival rates range from 0% to 20%. Over 50% of mucosal melanoma patients have nodal metastases at diagnosis, and over 25% present with distant metastases.

References: [61, 64, 65]

18. *What is the differential diagnosis of benign papillary and verrucous lesions of the oral cavity?*

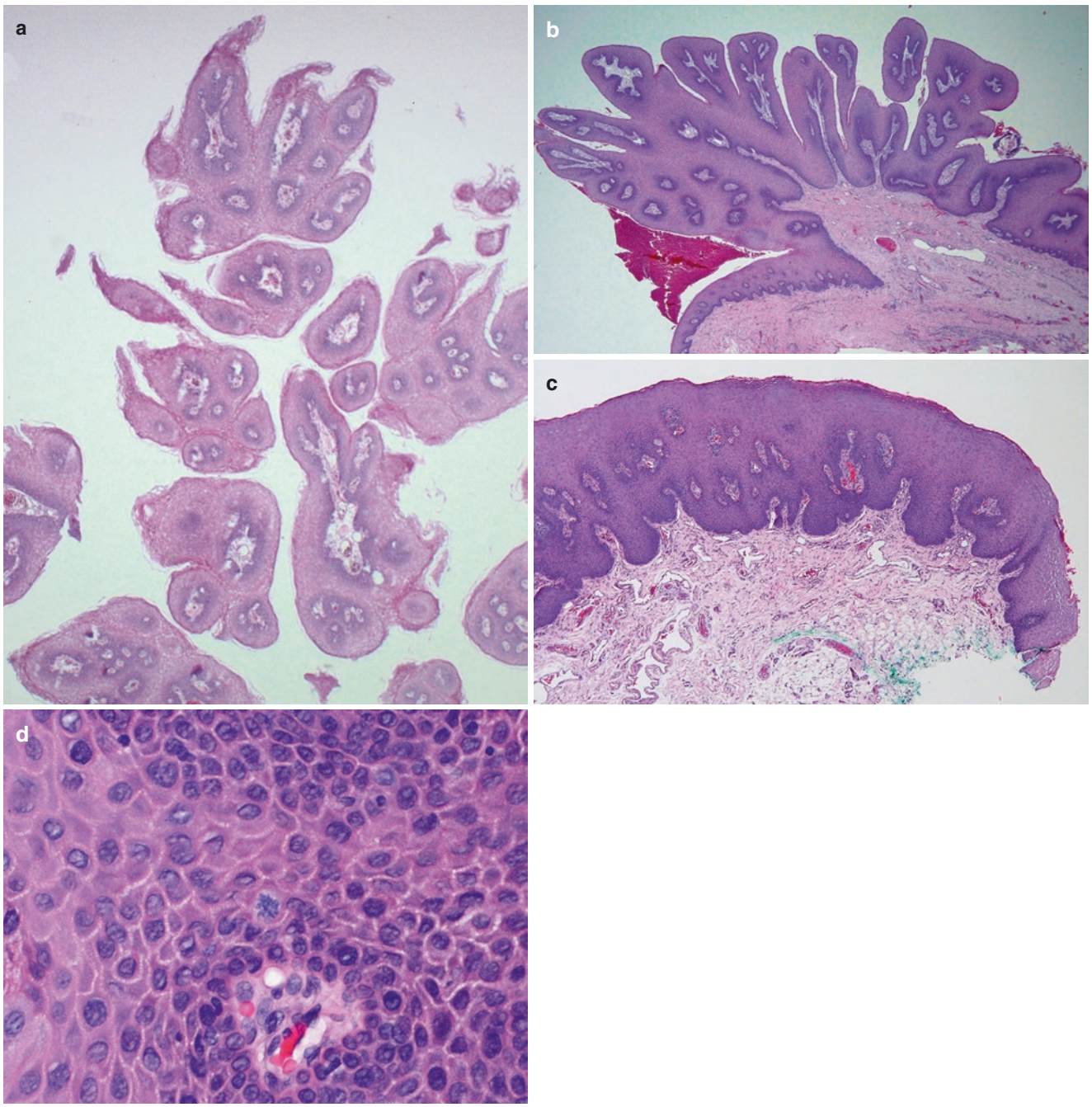

Fig. 1.19 Benign HPV-associated lesions. (**a**) Squamous papilloma with delicate, pointed hyperkeratotic papillary projections. (**b**) Condyloma acuminatum with a more sessile base and blunt papillary projections. (**c**) Multifocal epithelial hyperplasia showing papule-type lesions with acanthosis and (**d**) mitosoid body (center)

The descriptive terms verrucous and papillary overlap clinically and histologically in that both depict an exophytic architecture with surface projections. Due to the overlap, these lesions may be considered together for the purposes of generating a differential diagnosis.

- Verrucous lesions are generally spikey and hyperkeratotic, appearing white clinically.
- Papillary lesions have more rounded projections with parakeratosis and typically have fibrovascular cores imparting a more pink color on clinical inspection.
- The etiologies of papillary and verrucous lesions of the oral cavity (Fig. 1.19) include human papillomavirus (HPV), inflammatory reactions, and neoplasia.

- HPV-related lesions are commonly associated with low-risk subtypes including types 2, 4, 6, 11, and 32. The histological and clinical presentations vary widely (Table 1.15).
- Inflammatory reactions with a papillary appearance may mimic the HPV-associated lesions clinically (Table 1.16).
- Premalignant lesions and carcinomas with papillary or verrucous architecture are also in the differential diagnosis and will be discussed separately in question 24. They include lesions such as proliferative verrucous hyperplasia as well as papillary and verrucous carcinomas.

References: [66–72]

19. *Should lesions of the oral cavity be tested for HPV?*

While the incidence of HPV-related squamous cell carcinoma is rising in the oropharynx, the majority of squamous cell carcinomas (SCC) of the oral cavity remain tobacco- and alcohol-related. It is estimated that

Table 1.15 Benign HPV-associated lesions of the oral cavity

	Squamous papilloma	Condyloma acuminatum	Multifocal epithelial hyperplasia	Verruca vulgaris
HPV subtype	6, 11	6, 11 (±16, 18)	13, 32	2, 4
Oral site	Soft palate, tongue	Lip, soft palate	Lips, buccal mucosa, tongue	Lips, hard palate, anterior tongue
Affected demographic	Any	Peak incidence in adolescents Sexually transmitted	Children (unsanitary conditions) Adults (immunocompromised)	Any
Clinical	Solitary Small, <1 cm Sessile or pedunculated	Usually multiple, confluent Large 1–2 cm Sessile or pedunculated with a cauliflower-like surface	Multiple 0.5–1 cm Broad, sessile papules with a pebbly surface	Solitary Sessile or pedunculated
Koilocytes	Uncommon	Common, always present	Common	Common
Papillae	Delicate, rounded papillae, extend from a narrow base Edematous fibrovascular cores	Large, blunt papillae on a broad base	Papillae not prominent Bulbous rete ridges Acanthotic	Pointed, elongated papillae Extensive hyperkeratosis
Characteristic histologic features	Papillary projections extend from narrow base	Minimal keratin Basal cell hyperplasia	Hyperplasia with parakeratosis Mitosoid bodies: karyorrhectic and apoptotic cells with coarse chromatin	Coarse keratohyaline granules in prominent granular cell layer Rete ridges point inwards

Table 1.16 Reactive papillary and verrucous lesions of the oral cavity

	Verruciform xanthoma	Inflammatory papillary hyperplasia	Localized juvenile spongiotic gingival hyperplasia
Demographics	Any, seen in patients with LP, lipid storage diseases, immunosuppression	Patients with poorly fitted dentures, poor dentition, and chronic stomatitis	Preteens, teenagers Related to trauma or irritation
Oral site	Gingiva, alveolar	Hard palate	Anterior maxillary gingiva
Clinical	Solitary, mucosa-colored, yellow, white, or gray verrucous lesion Sessile or pedunculated, slightly raised, ±central depression	Multiple, red, papillary overgrowths on the central hard palate	Erythematous papillary or cobblestoned plaque that is painless but bleeds easily
Morphology	Papillary or verrucous epithelial proliferations with central cupping of the rete ridges **(Fig. 1.20)** Distinct orange parakeratin accumulates between papillae. Papillae are filled with large, foamy macrophages Often colonized by *Candida*	Hyperkeratotic papillary epithelial hyperplasia Variably loose to dense lamina propria with moderate to severe chronic inflammation Absence of dysplasia Often colonized by *Candida* species	Nonkeratinizing, hyperplastic epithelium with a papillary architecture Prominent spongiosis and edema with neutrophilic transmigration Lamina propria with acute chronic inflammation