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

Danielle Elliott Range
Xiaoyin "Sara" Jiang
*Editors*

# Practical Head and Neck Pathology

## Frequently Asked Questions

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# 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

Danielle Elliott Range • Xiaoyin "Sara" Jiang
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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

1. What are the most common developmental lesions of the oral cavity?
2. What is the differential diagnosis of vascular lesions of the oral cavity?
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27. What are the common salivary gland tumors of the oral cavity?
28. What are the characteristics of metastases to the oral cavity?
29. Which hematolymphoid lesions show a predilection for the oral cavity?

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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.

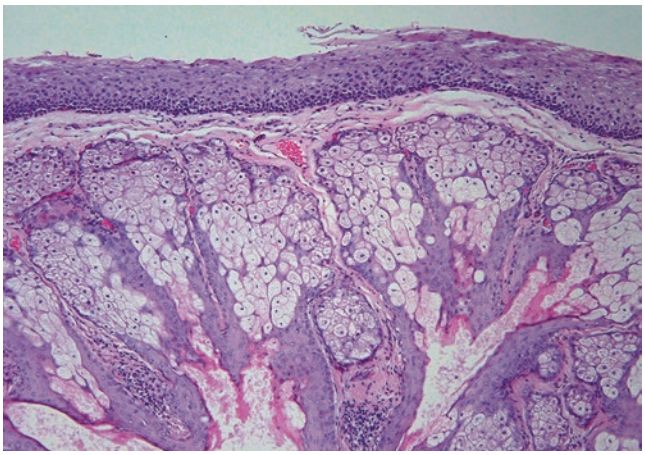

**Fig. 1.1** Fordyce granules. Ectopic sebaceous glands underlie a normal squamous epithelium and show aggregates of pale, finely vacuolated cells with central, small nuclei

  - 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.

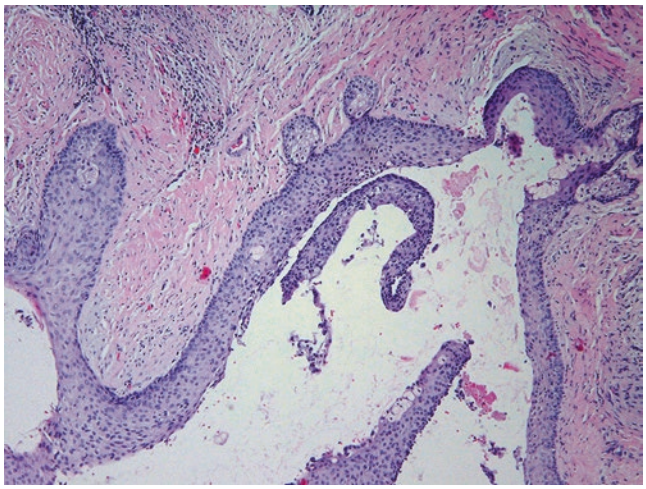

**Fig. 1.2** Dermoid cyst. The cystic lumen is lined by stratified squamous epithelium with keratinization and adnexal structures in the cyst wall

- 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<br>Common in pregnancy | Gingiva | Solitary, exophytic, erythematous, painless mass<br>Often ulcerated, bleeds easily with manipulation | Hypercellular proliferation of variably sized vascular spaces with a lobular pattern<br>Loose stroma with plump, tightly packed endothelial cells, ±inflammatory cells<br>Overlying epithelium may be ulcerated<br>± 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<br>Mitotic figures may be numerous but not atypical<br>GLUT-1+ (congenital hemangiomas are negative) |
| Kaposi sarcoma | Classic: Mediterranean or Eastern European middle-aged men<br>AIDS-related/iatrogenic: immunosuppressed<br>Endemic: children in sub-Saharan Africa | Palate, gingiva, dorsal tongue | Depends on stage.<br>Early: asymptomatic, flat, blue- or red-hued, often resembles an ecchymosis<br>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<br>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<br>May present as macroglossia | Thin-walled, endothelial-lined, ectatic vessels with varying luminal sizes<br>No appreciable smooth muscle wall<br>Stroma may have lymphocytes, fat, fibroblasts<br>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<br>Disorganized smooth muscle in walls<br>May dissect through normal tissue<br>Intravascular papillary endothelial hyperplasia<br>±Few RBCs, ±thrombi due to stasis |
| Arteriovenous malformation | Children | Any oral cavity site<br>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

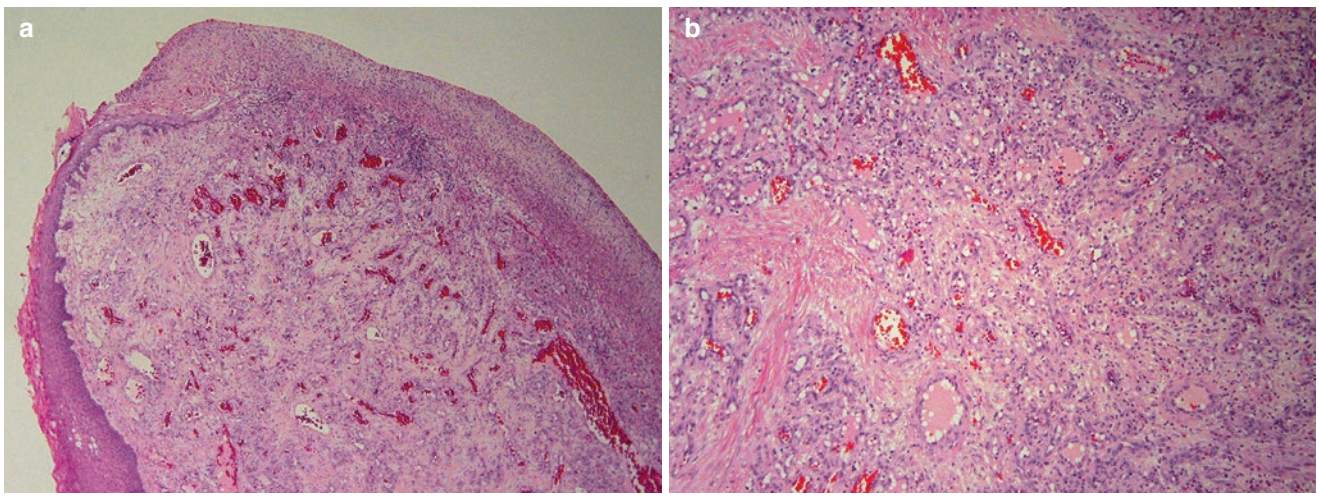


**Fig. 1.3** Lobular capillary hemangioma. (**a**) A vascular proliferation with surface ulceration and a (**b**) vaguely lobular pattern

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

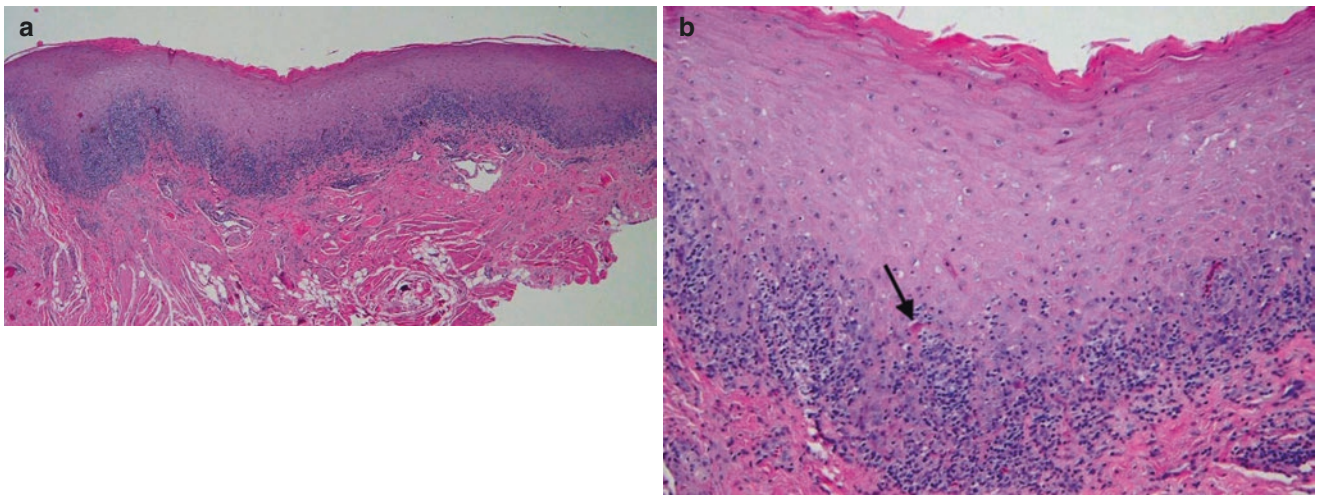


**Fig. 1.4** Oral lichen planus. (**a**) Acanthotic squamous mucosa with a band-like lymphocytic infiltrate along the interface between the epithelium and lamina propria. (**b**) The lymphocytes obscure the basement membrane, eroding the basal keratinocytes. Exocytosis into the epithelium is present, 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<br>Middle-aged adults | Variable<br>Common drugs: methyldopa, interferon-alpha, TKI, beta-blockers, antihypertensives | Adults, F > M | F > M<br>SLE > discoid lupus | Allogenic stem cell transplant<br>patients > > BMT<br>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<br>70% of GVHD patients will have oral disease |
| Clinical presentation | Bilateral, symmetric<br>White, reticular areas on mucosa<br>Red, painful areas and ulcers<br>Cheek, tongue, gingiva | Painful, erythematous or white mucosal lesions<br>Similar to LP but more erosive and unilateral<br>Buccal > lips > tongue | Erythematous, white, ulcerative lesions localized to the area of contact<br>Cheek, ventral and lateral tongue | Oral lesions almost always occur with skin lesions<br>Aphthous ulcer, reticulated, red, keratotic lesions of cheek, palate, lip | Gingivitis, mucositis, erythema, pain<br>Hyperkeratotic plaques, limited oral opening due to sclerosis |
| Histology | Dense, lichenoid inflammation<br>Degeneration of basal layer with single cell necrosis, vacuolar change<br>Obscured interface<br>Exocytosis<br>Sawtooth rete ridges<br>OK, PK | Similar to LP with more mixed infiltrate of lymphocytes, plasma cells, eosinophils<br>Deeper extension into lamina propria, ±perivascular<br>Exocytosis in all layers of epithelium<br>±Granulomatous inflammation<br>±PK, spongiosis, acanthosis | Acanthosis, HK, spongiosis<br>Predominantly lymphocytes with plasma cells, histiocytes, eosinophils<br>Papillary vessels are dilated, with a perivascular lymphohistiocytic infiltrate<br>±Deep perivascular plasma cells<br>±Neutrophils | Alternating acanthosis and atrophy<br>Degeneration of basal cell layer<br>Interface lichenoid inflammation<br>Thick BM, mucin in lamina propria<br>Occasionally, a deeper perivascular infiltrate with lymphocytes and scattered plasma cells | Acanthosis, exocytosis, thick BM with sclerosis is most often present<br>Epithelium may be normal or atrophic<br>Variable severity of lichenoid T-cell infiltrate<br>Basal vacuolization, severe forms show clefts between epithelium and lamina propria<br>Dyskeratosis, apoptosis |
| Other laboratory findings | DIF: Linear fibrinogen and granular C3 at BM | Positive basal cell cytoplasmic antibody | Skin patch test can confirm diagnosis<br>Basal cell cytoplasmic antibody usually negative | DIF: Linear, granular IgG, M, A at BM<br>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

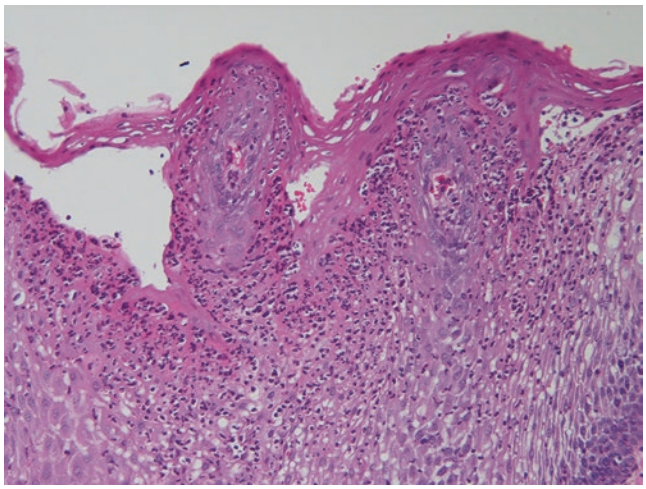

**Fig. 1.5** Geographic tongue. The surface epithelium exhibits acanthosis, collections of neutrophils, and the absence of the usual filiform papillae of the dorsal tongue

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]

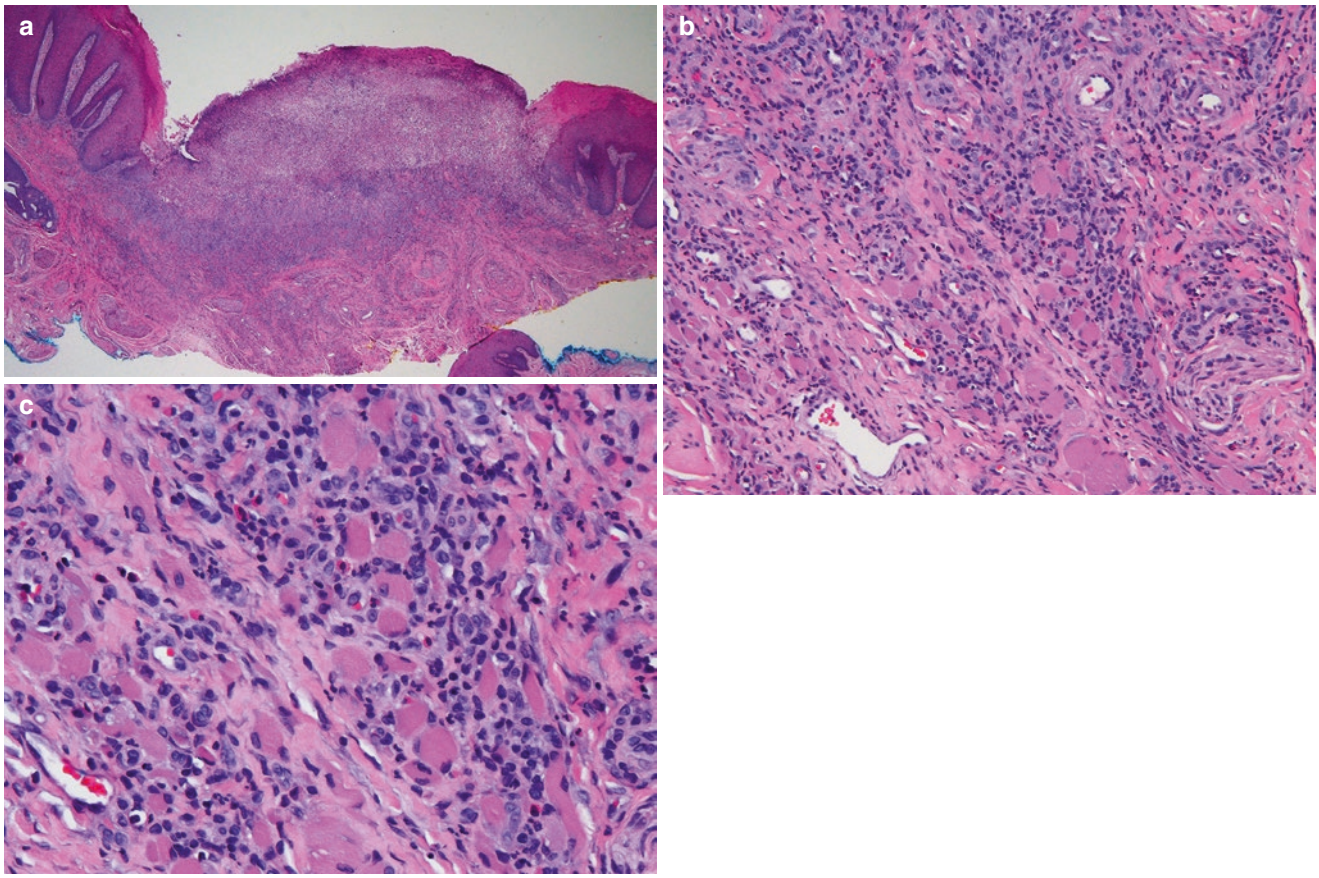


**Fig. 1.6** Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE). (**a**) The ulcerated oral mucosa is rimmed by reactive epithelium. (**b**) The granulation tissue extends into the underlying striated muscle and contains enlarged fibroblasts, endothelial cells, and (**c**) eosinophils which 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:<br>Amalgam<br>Composite<br>Impression materials<br>Food particles<br>Crystals found in dental materials and dentifrice<br>Foreign body reaction to cosmetic fillers | Sarcoidosis<br>Crohn's disease<br>Deep fungal infections (histoplasmosis, etc.)<br>Mycobacterial infections<br>Granulomatosis with polyangiitis<br>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.).

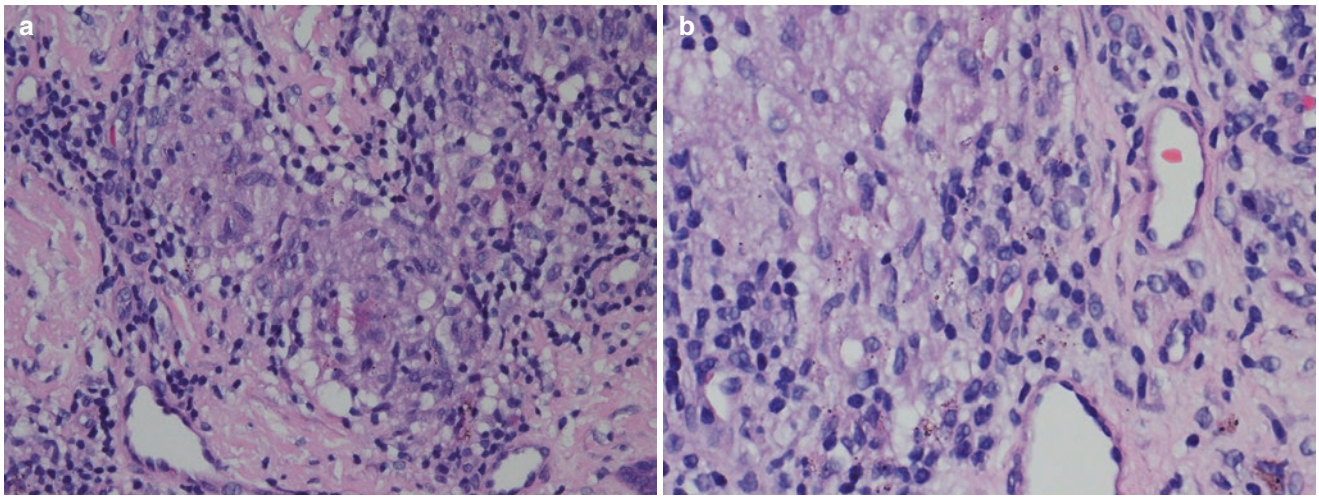


**Fig. 1.7** Foreign body granulomatous inflammation. (**a**) The lamina propria has non-necrotizing granulomas that lack microorganisms. (**b**) Fragments of pigmented, finely granular foreign body material are present

**Table 1.7** Vesiculobullous conditions of the oral cavity

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

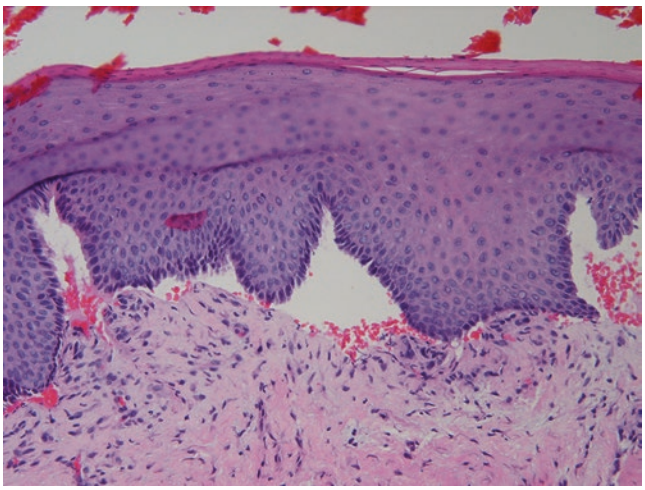

**Fig. 1.8** Mucous membrane pemphigoid. The mucosa shows separation of the entire epithelium at the basement membrane level with subepithelial bulla formation and no evidence of acantholysis

    - 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]

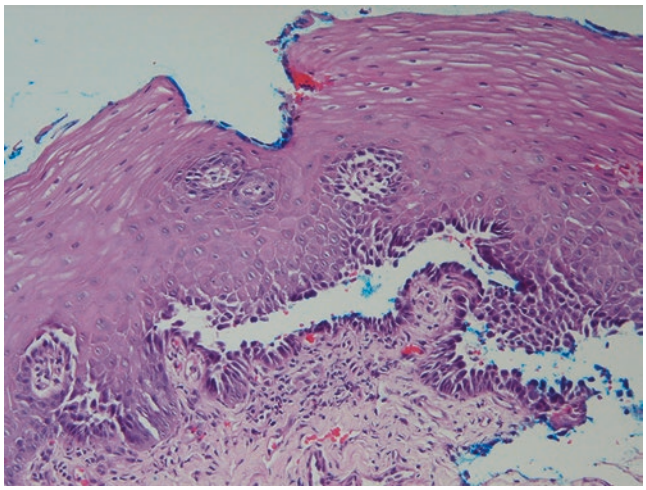

**Fig. 1.9** Pemphigus vulgaris. The mucosa shows acantholysis with retention of the basal keratinocytes along the basement membrane and suprabasal blistering

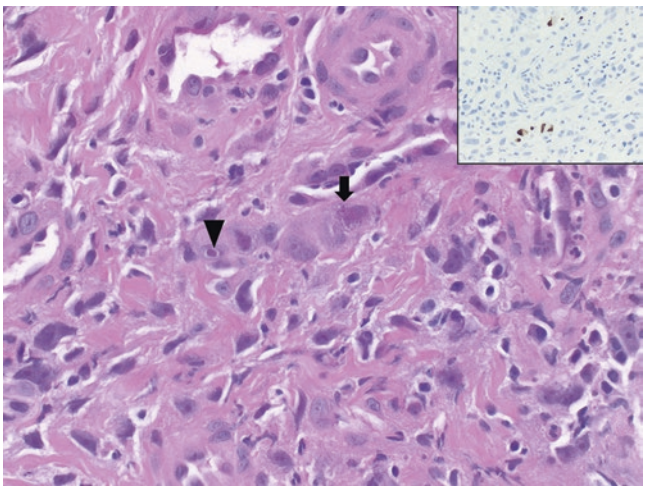

**Fig. 1.10** CMV ulcer base. Large, infected stromal cells show intracytoplasmic granules (arrow) and intranuclear inclusions with the characteristic clear halo (arrowhead). An immunohistochemical stain for CMV is positive in scattered cells (inset)

**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.<br>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<br>4th–6th decades | F > M<br>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<br>Firm and pink, or erythematous and ulcerated<br>Grooved due to denture placement | Red or purple raised mass with a central punctum<br>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)**<br>Nuclei are plump, ovoid with fine chromatin, small nucleoli<br>Lamellar bone in older lesions<br>±Giant cells | Hypercellular proliferation of mesenchymal cells with a prominent vascular component **(Fig. 1.12)**<br>Numerous multinucleated giant cells<br>±Scattered mitotic figures<br>Normal or ulcerated overlying epithelium | Subepithelial fibrous proliferation<br>Overlying hyperkeratotic and acanthotic epithelium, often with ulceration<br>Variable chronic inflammation and vascular proliferation<br>±Osseous or chondroid metaplasia | Floridly inflamed granulation tissue<br>Linear, sinus tract that is lined with neutrophils<br>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<br>Fibrous hyperplasia with collagen bundles of varying densities<br>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)<br>Dense sheets of plasma cells in the connective tissue |
| Vitamin C deficiency (scurvy) | Patients with limited dietary intake<br>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<br>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<br>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<br>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 |

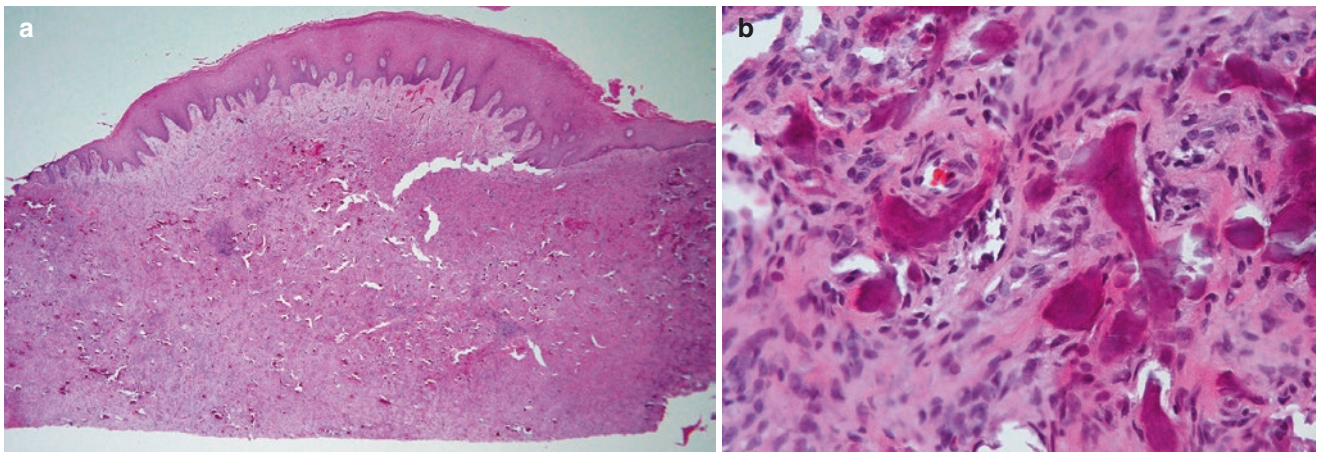


**Fig. 1.11** Peripheral ossifying fibroma. (**a**) Sessile, hypercellular nodule composed of (**b**) bland fibroblasts and deposition of cementum and calcifications

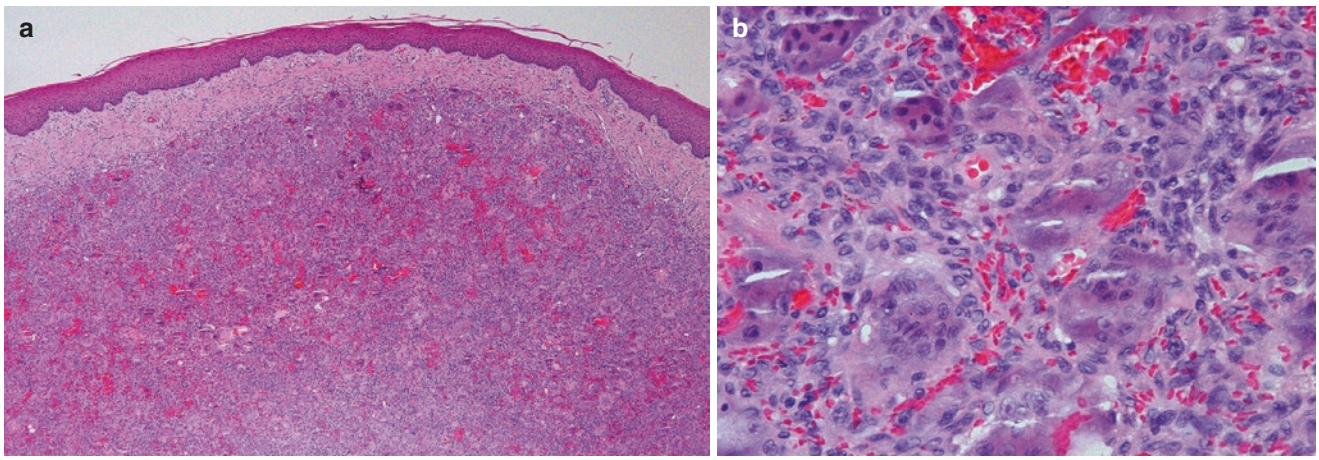


**Fig. 1.12** Peripheral giant cell granuloma. (**a**) Hypercellular, sessile lesion composed of (**b**) plump, monotonous spindle cells and multinucleated giant cells in a vascular stroma

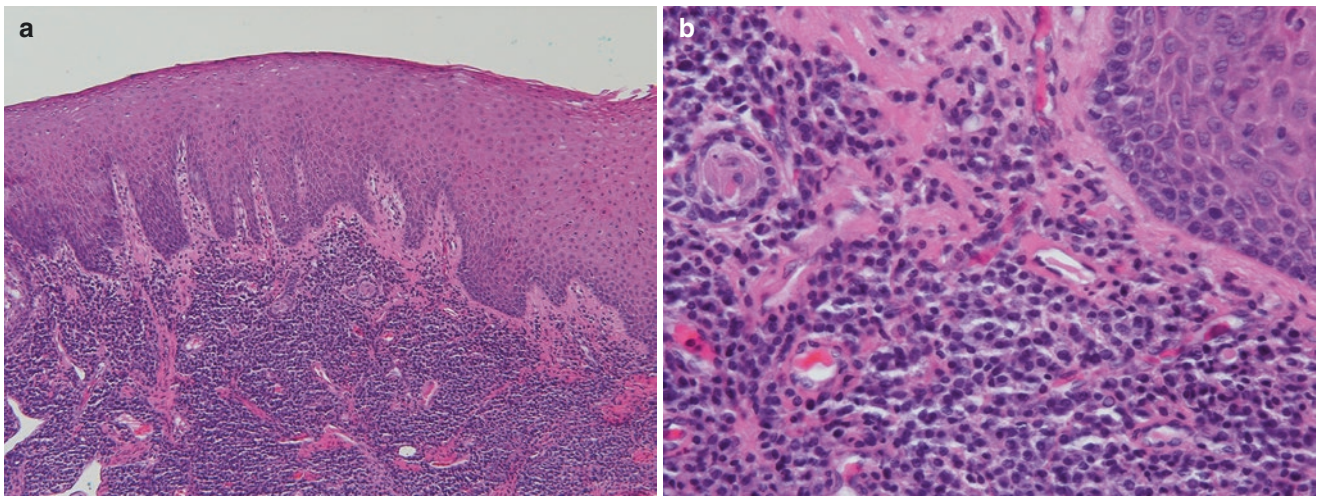


**Fig. 1.13** Plasma cell gingivitis. (**a**) Slightly hyperplastic epithelium with sheets of inflammatory cells that do not efface the normal lamina propria architecture. (**b**) The inflammatory cell infiltrate is composed of mature, reactive plasma cells with no atypical features

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<br>Medullary thyroid carcinoma in childhood | Oral papillomas, neuromas<br>Facial trichilemmomas | Intraoral neurofibromas (NF) | Multiple intraoral, facial, ungal fibromas<br>Enamel pitting of the teeth<br>Desmoplastic fibromas of the jaws |
| Other lesions | Pheochromocytomas<br>Marfanoid habitus<br>Intestinal ganglioneuromatosis | Dysplastic gangliocytoma of cerebellum<br>Macrocephaly<br>Mucocutaneous and GI hamartomas<br>Multiple trichilemmomas<br>High risk for thyroid, breast, endometrial tumors | Plexiform neurofibroma<br>Café au lait macules<br>Multiple neurofibromas<br>Lisch nodules of the iris<br>Optic gliomas<br>Osseous dysplasia | Cutaneous hypomelanotic macules<br>Fibrous plaques of the forehead or scalp<br>Retinal hamartomas<br>Lymphangioleiomyomatosis of the lungs<br>Renal angiomyolipomas<br>Cardiac rhabdomyoma<br>Cortical dysplasias<br>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<br>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.<br>Associated with neurofibromatosis type 2 (vestibular schwannomas) | Encapsulated proliferation of spindled Schwann cells with hypo- and hypercellular areas<br>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<br>Loose, variably myxomatous stroma with wavy collagen<br>Plexiform variant has tangled bundles of tumor cells, each representing a nerve that is distended by tumor cells | S100+, focal<br>SOX10+, var<br>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<br>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-

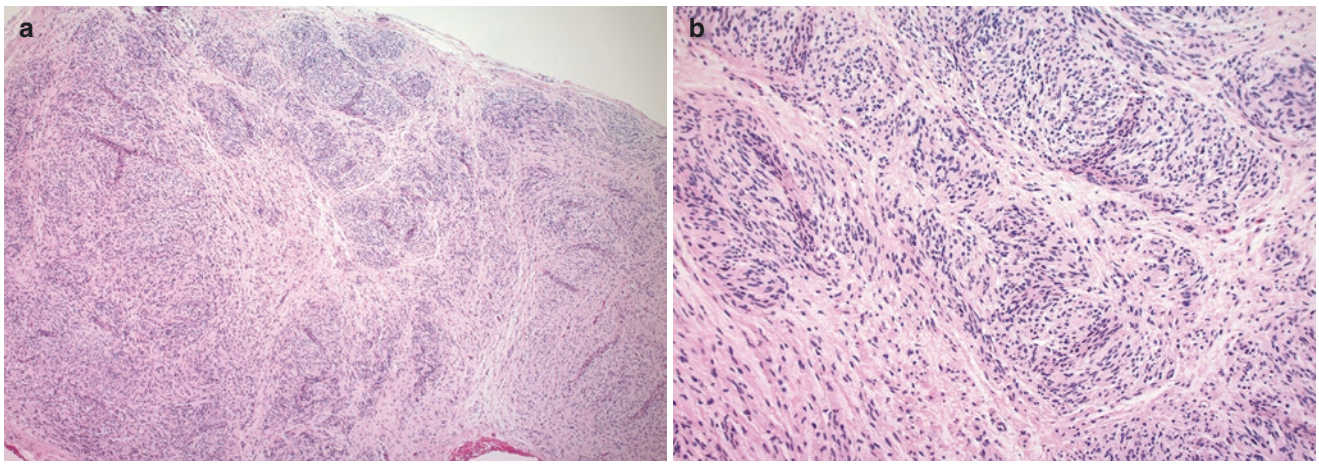


**Fig. 1.14** Palisaded encapsulated neuroma. (**a**) A well-circumscribed spindle cell proliferation arranged in a vaguely lobular pattern with areas of tissue clefting. (**b**) Higher magnification shows short, plump, spindled cells with vague palisading and indistinct cell borders

**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)<br>F > M | Birth to 20 (mean 23)<br>M > F | Adult type: 60–70,<br>M:F=3:1 | Birth to 60 |
| Oral site | Lower lip, palate | Buccal mucosa, tongue | Solitary<br>FOM, tongue, palate | Solitary or multiple<br>Tongue, cheek, palate |
| Morphology | Well-circumscribed, variably encapsulated spindle cell proliferation<br>Bland nuclei are elongated and "cigar-shaped" with blunt ends<br>Prominent vascular spaces<br>Fascicles of spindled cells course between thick-walled vessels | Unencapsulated, circumscribed spindle cell proliferation with a biphasic pattern<br>Lighter zones contain short fascicles or whorls of myofibroblastic cells with glassy, blue-hued stroma<br>Darker zones have increased cellularity with larger nuclei<br>Slit-like blood vessels may be seen<br>±infiltrative border<br>Mitoses may be frequent | Sheets of polygonal cells with abundant, pink, granular cytoplasm<br>Cross striations in cytoplasm<br>"Jackstraw-like" intracytoplasmic, rod-shaped crystals<br>±"Spider" cells with vacuolated cytoplasm<br>Bland, small vesicular nuclei | Myxoid type: spindle cells with short, bland, oval nuclei<br>Occasional striated, muscle cells<br>Myxoid stroma<br>Intermediate type: spindled areas and areas with differentiated muscle cells<br>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.

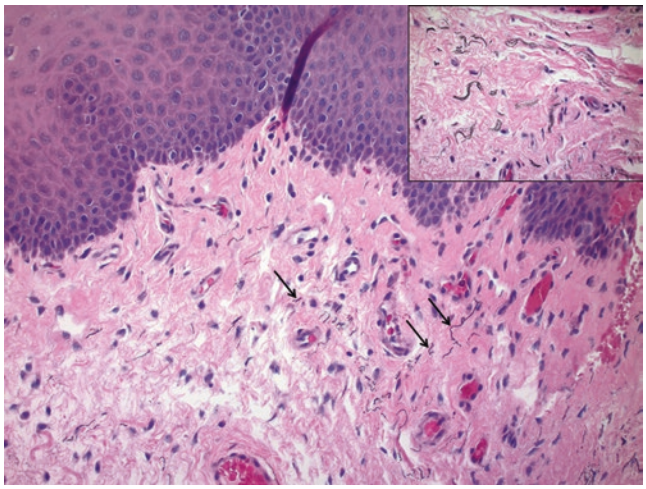

**Fig. 1.15** Amalgam tattoo. Normal-appearing squamous epithelium with coarse, black granules (arrows, inset) deposited in the collagen of the lamina propria. The absence of a tissue reaction is typical

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

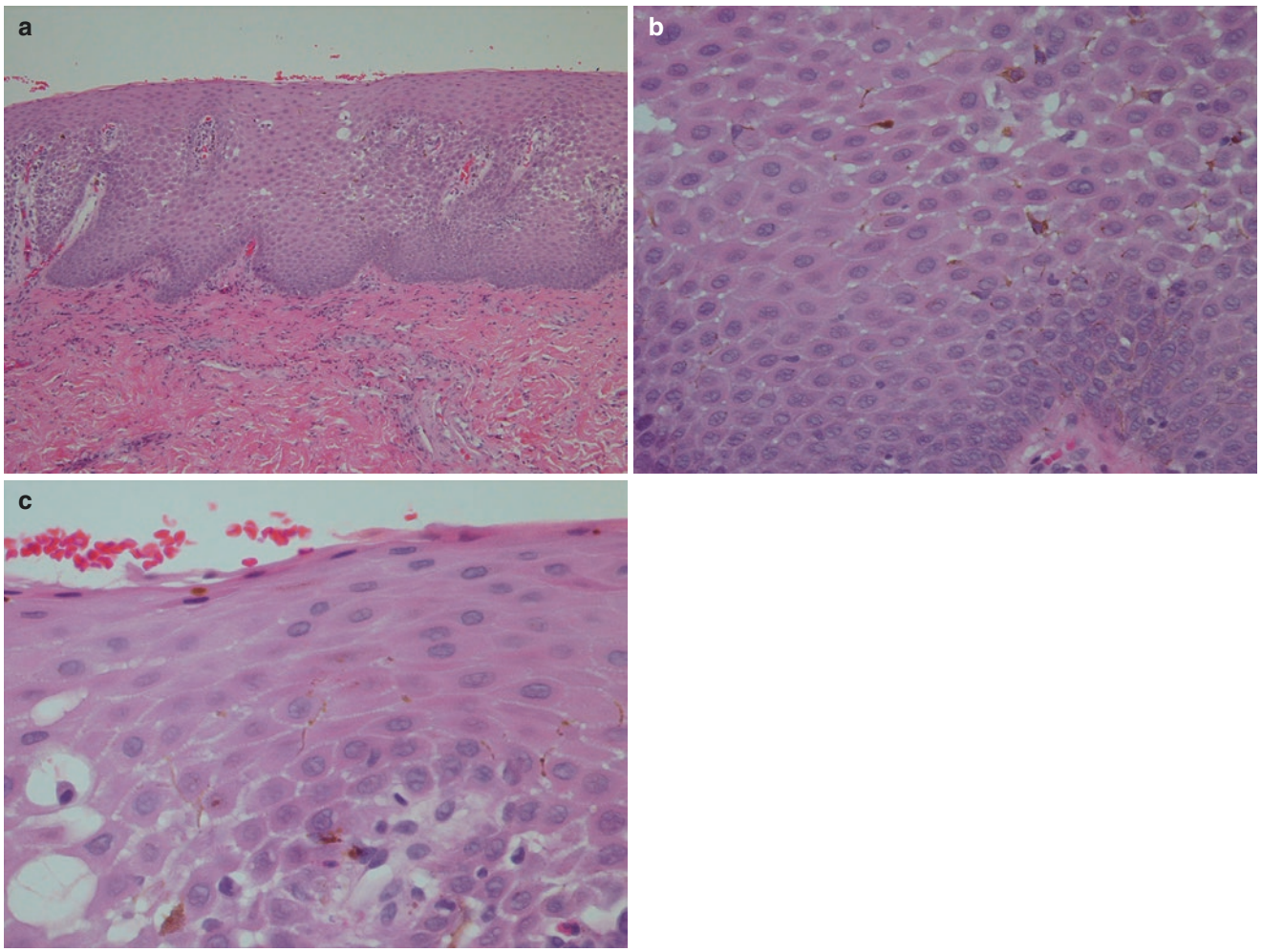


**Fig. 1.16** Oral melanoacanthoma. (**a**) The surface epithelium appears slightly acanthotic and (**b**) contains multiple dendritic melanocytes with bland nuclear features. Focal acantholysis is present, and occasional eosinophils (not shown) can be seen

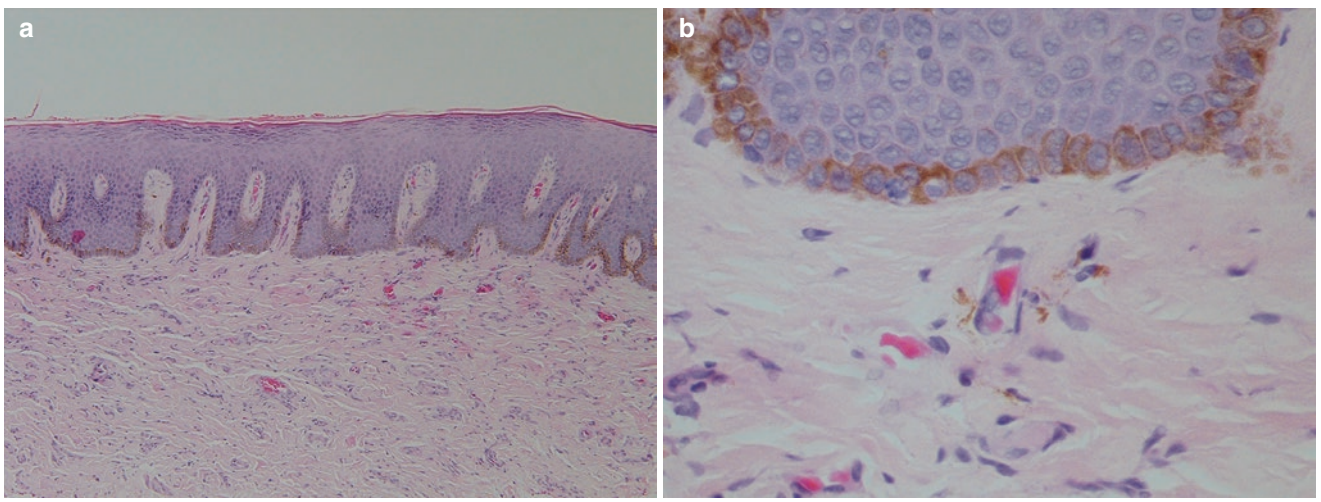


**Fig. 1.17** Melanotic macule. (**a**) The mucosa exhibits increased accumulation of melanin, restricted to the basal keratinocytes. (**b**) Melanocytic hyperplasia and atypia are absent, but melanin incontinence in the lamina propria can be seen (center)

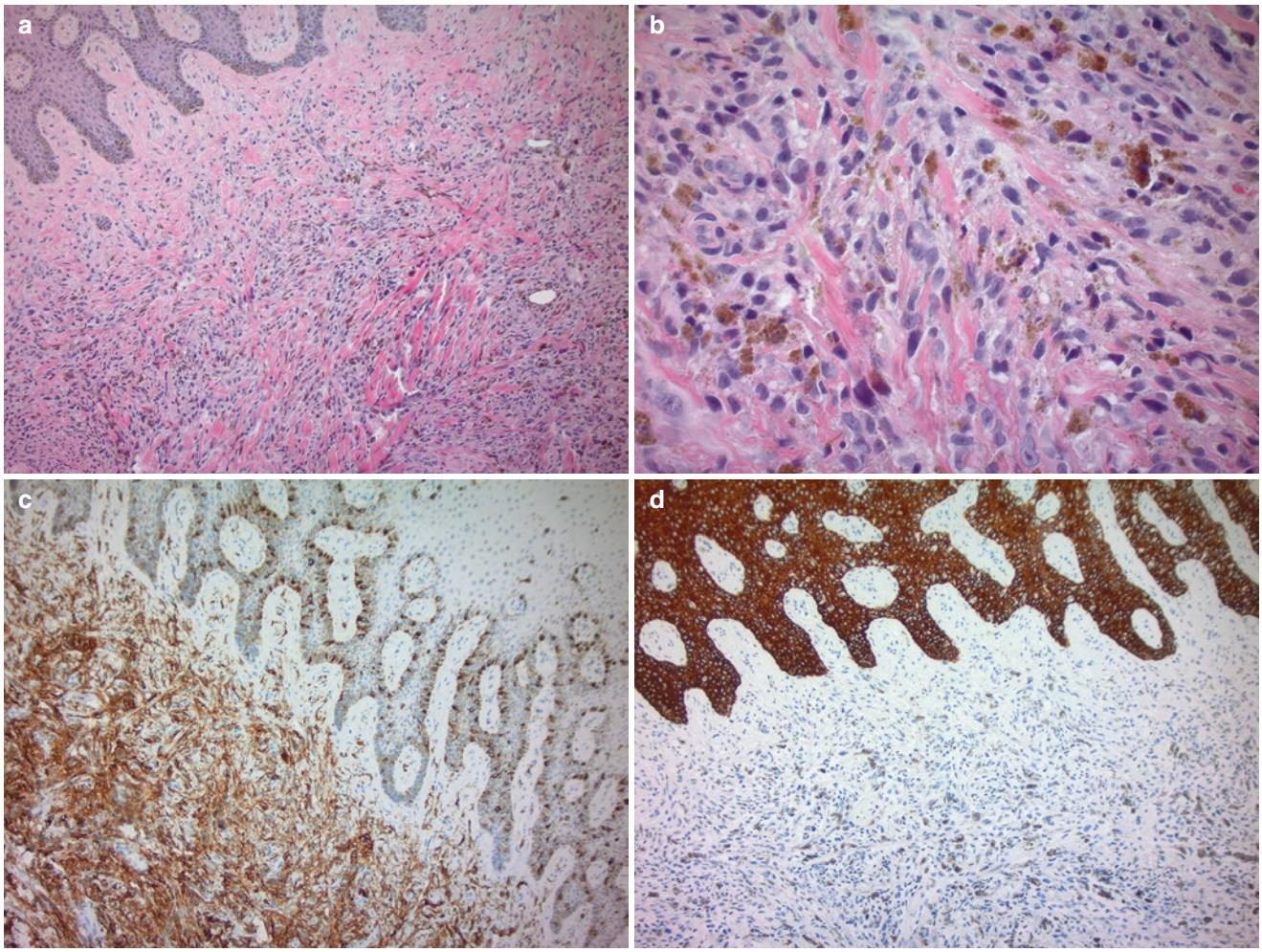


**Fig. 1.18** Melanoma of hard palate. (**a**) Atypical pigmented cells infiltrate the lamina propria, overlying squamous epithelium has a pigmented basal layer. (**b**) Higher magnification shows spindled and epithelioid cells with amphophilic cytoplasm, fine and coarse intracytoplasmic pigment, pleomorphic 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?*

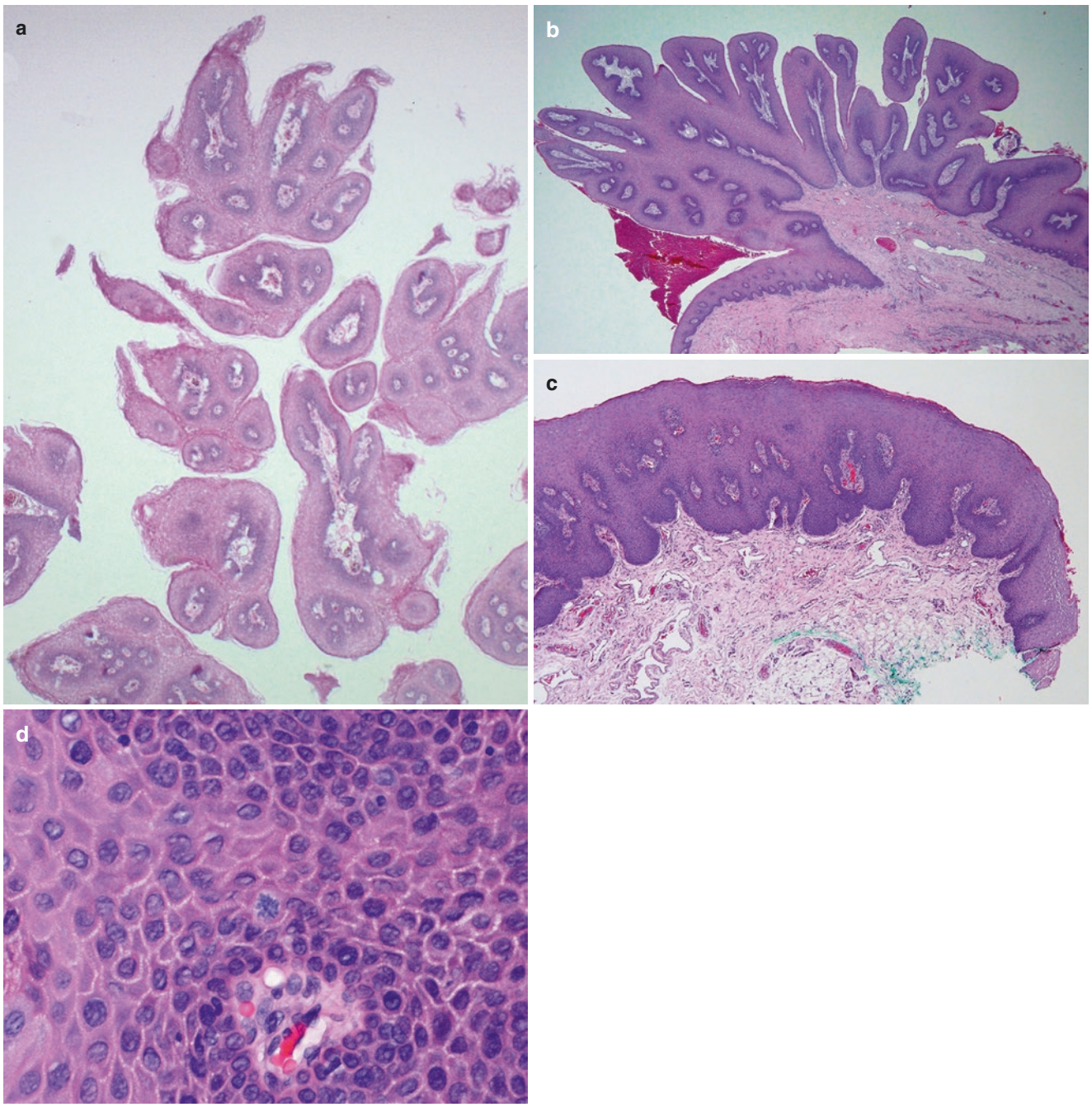


**Fig. 1.19** Benign HPV-associated lesions. (**a**) Squamous papilloma with delicate, pointed hyperkeratotic papillary projections. (**b**) Condyloma acuminatum with a more sessile base and blunt papillary projections. (**c**) Multifocal epithelial hyperplasia showing papule-type lesions with acanthosis 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<br>Sexually transmitted | Children (unsanitary conditions)<br>Adults (immunocompromised) | Any |
| Clinical | Solitary<br>Small, <1 cm<br>Sessile or pedunculated | Usually multiple, confluent<br>Large 1–2 cm<br>Sessile or pedunculated with a cauliflower-like surface | Multiple<br>0.5–1 cm<br>Broad, sessile papules with a pebbly surface | Solitary<br>Sessile or pedunculated |
| Koilocytes | Uncommon | Common, always present | Common | Common |
| Papillae | Delicate, rounded papillae, extend from a narrow base<br>Edematous fibrovascular cores | Large, blunt papillae on a broad base | Papillae not prominent<br>Bulbous rete ridges<br>Acanthotic | Pointed, elongated papillae<br>Extensive hyperkeratosis |
| Characteristic histologic features | Papillary projections extend from narrow base | Minimal keratin<br>Basal cell hyperplasia | Hyperplasia with parakeratosis<br>Mitosoid bodies: karyorrhectic and apoptotic cells with coarse chromatin | Coarse keratohyaline granules in prominent granular cell layer<br>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<br>Related to trauma or irritation |
| Oral site | Gingiva, alveolar | Hard palate | Anterior maxillary gingiva |
| Clinical | Solitary, mucosa-colored, yellow, white, or gray verrucous lesion<br>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)**<br>Distinct orange parakeratin accumulates between papillae.<br>Papillae are filled with large, foamy macrophages<br>Often colonized by *Candida* | Hyperkeratotic papillary epithelial hyperplasia<br>Variably loose to dense lamina propria with moderate to severe chronic inflammation<br>Absence of dysplasia<br>Often colonized by *Candida* species | Nonkeratinizing, hyperplastic epithelium with a papillary architecture<br>Prominent spongiosis and edema with neutrophilic transmigration<br>Lamina propria with acute chronic inflammation |

only 5–9% of oral cavity squamous cell carcinomas are associated with high-risk HPV.

- There is no evidence of benign HPV-associated oral lesions progressing to malignancy.
- The correlation between clinical outcomes and the presence of HR-HPV in oral cavity SCC is not well proven.
- Given the need for more definitive data, HPV testing for benign and malignant oral cavity lesions is not currently indicated.

References: [73, 74]

20. *Which benign lesions are commonly associated with pseudoepitheliomatous hyperplasia?*

Pseudoepitheliomatous hyperplasia (PEH) is an exuberant, reactive, proliferation of squamous epithelium that is usually cytologically bland. Etiologies include fungal infection, underlying tumors or chronic irritation.

- A granular cell tumor (GCT) is the prototypic tumor associated with PEH (Fig. 1.21). The most common site of granular cell tumors is the dorsal tongue.
  - GCT demonstrates sheets, cords, or nests of polygonal cells with abundant, eosinophilic, granular cytoplasm. The nucleus is small, normochromatic, and often eccentric.
  - PEH may show atypia and an irregular proliferation of epithelial nests at its deep border. This can be mistaken for squamous cell carcinoma. However, PEH is usually devoid of atypia, and the nests should not extend beyond the deep border of the granular cell tumor.
  - Tumor cells stain strongly and diffusely for S100 and SOX10.
- Oral candida infection should be considered in the absence of a GCT. It is another common cause of PEH.
  - Microorganisms should be seen in the deep epithelium to exclude surface colonization.

References: [54, 75]

21. *What is the differential diagnosis of leukoplakic lesions of the oral cavity?*

Leukoplakia is a white lesion involving the oral mucosa. It is a purely descriptive, clinical term which gives no indication of etiology or pathogenesis. There are many pathologic conditions that can present as a leukoplakia. Some of the most frequently encountered lesions that clinically may be described as "leukoplakia" are outlined in Table 1.17.

- Most leukoplakic lesions show hyper-, ortho-, or parakeratosis of the surface epithelium, which conveys an opaque, white discoloration to the mucosa.
- Biopsy is typically done to exclude dysplasia or carcinoma.
- The prevalence of dysplasia ranges from 16% to 39%.
- The rate of malignant transformation is 8–18%.

References: [76–85]

22. *What are the criteria used to diagnose oral epithelial dysplasia and how is it graded?*

Oral epithelial dysplasia (OED) is a premalignant lesion of epithelium which shows architectural and cytologic atypia (Fig. 1.22). It may appear clinically as a leukoplakic or erythematous mucosal lesion. The criteria for OED (Table 1.18), established by the WHO in 2005, uses a set of cytologic and architectural features.

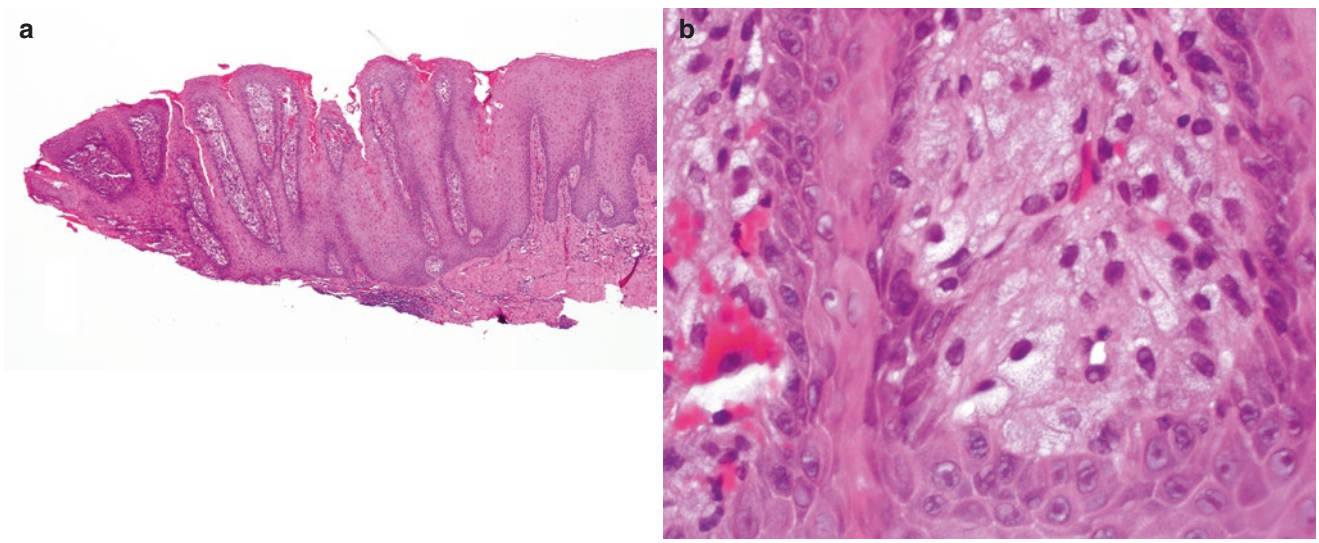


**Fig. 1.20** Verruciform xanthoma. (**a**) Papillary acanthosis with bright, eosinophilic parakeratosis and (**b**) foamy histiocytes between the rete pegs of the surface epithelium

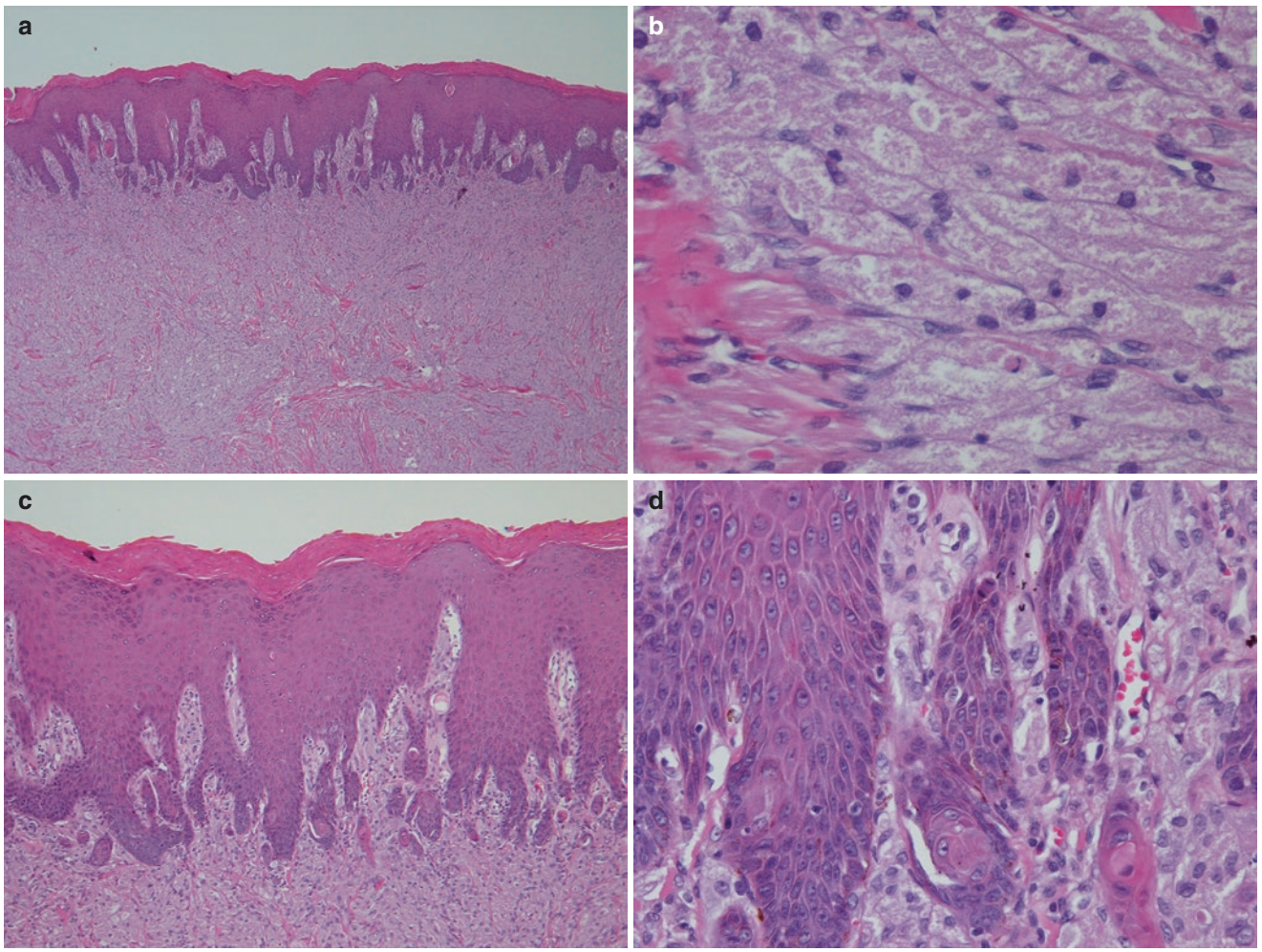


**Fig. 1.21** Granular cell tumor. (**a**) The lamina propria is expanded by an infiltrate of (**b**) pale, eosinophilic cells with small round nuclei and abundant, granular cytoplasm. (**c**) The overlying epithelium shows hyperkeratosis with irregular rete ridges and a downward, orderly proliferation of epithelium diagnostic of pseudoepitheliomatous hyperplasia. (**d**) Higher magnification shows an absence of cellular atypia and abnormal mitoses

**Table 1.17** Leukoplakic lesions of the oral cavity

| | Frictional keratoses | Oral epithelial dysplasia | Proliferative verrucous leukoplakia | Tobacco pouch keratosis | Oral hairy leukoplakia |
|---|---|---|---|---|---|
| Oral site | Buccal, lateral tongue, lower lip, alveolar ridge | Any oral site Tongue, FOM, gingiva | Gingiva, alveolar ridge, palate Multifocal | Mandibular vestibule | Lateral tongue |
| Etiology | Mechanical, thermal, or chemical irritation/ trauma | Alcohol and smoking related | Unknown Progressive, recurrent lesions over years F:M=4:1 | Chemical irritation secondary to smokeless tobacco | EBV reactivation due to immunosuppression |
| Dysplasia/ malignant potential? | None/No | Present/Yes | Present in late stage/ Yes | Not uncommonly/ Yes | None/No |

**Table 1.17** (continued)

| | Frictional keratoses | Oral epithelial dysplasia | Proliferative verrucous leukoplakia | Tobacco pouch keratosis | Oral hairy leukoplakia |
|---|---|---|---|---|---|
| Morphology | Reactive PK with clefting of keratotic layer, acanthosis<br>No inflammation<br>± Bacterial or fungal colonization<br>HK, acanthosis, wedged hypergranulosis, papillary on alveolar mucosa | Cytological and architectural atypia with acanthosis or parakeratosis | HK, OK flat verrucous lesion progresses to exophytic lesion<br>Hypergranulosis<br>±Lichenoid inflammation | Edematous surface keratinocytes with degeneration, karyorrhectic debris, and PK columns<br>Amyloid-like, altered collagen in LP | White, painless plaque/linear lesion, PK, HK, acanthosis<br>Underlying, pale, balloon keratinocytes<br>Superficial keratinocytes with Cowdry viral inclusions (ground-glass nuclei with peripherally condensed chromatin)<br>EBER+ |

*FOM* floor of mouth, *PK* parakeratosis, *HK* hyperkeratosis, *OK* orthokeratosis, *LP* lamina propria, *EBER* Epstein Barr-encoded RNA

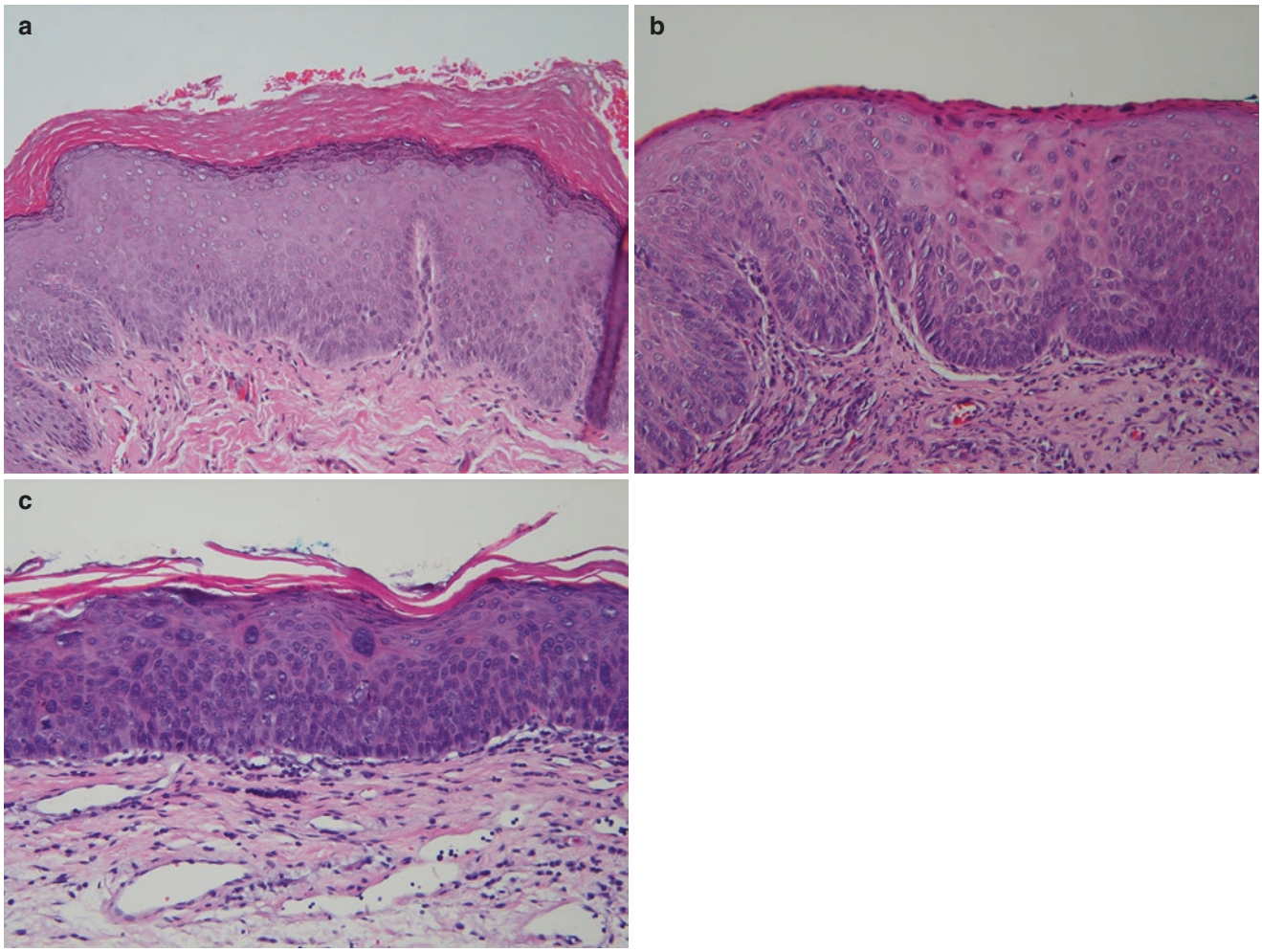


**Fig. 1.22** Oral epithelial dysplasia (OED). (**a**) Mild OED shows atypia limited to the lower third of the epithelium, enlarged nuclei and focal loss of polarity with disordered stratification. (**b**) Moderate OED shows atypia involving at least half of the epithelium. (**c**) Severe OED shows full thickness atypia

- Grading of oral dysplasia traditionally encompasses a three-tiered system based on the amount of epithelium involved by the atypical changes.
- Corresponding rates of malignant transformation increase with the degree of dysplasia.
- Application of these criteria in a 3-tiered system had high inter- and intraobserver variability. As a result, a two-tiered system is advocated by some authors (Table 1.19) with a proposed point system applied based on the number of features present.
  - This binary system has improved observer variability and shows better correlation with disease progression to carcinoma. However, it will require additional validation.

References: [86–89]

23. *What are the clinical and histologic characteristics of oral cavity squamous cell carcinoma and which features are related to prognosis?*

Oral squamous cell carcinoma (SCC) may affect any site in the oral cavity that is lined by stratified squamous epithelium.

- Patients are typically males in the fifth to seventh decades.
- The lip and oral tongue are the most frequent sites, followed by the floor of mouth.
- Smoking is an important risk factor for the development of oral SCC and shows a dose-dependent effect. Alcohol imparts a synergistic effect.
- Additional risk factors vary by site:
  - Lip: sun exposure.
  - Buccal vestibule, floor of mouth: smokeless tobacco, betel quid.
- Oral SCC shows morphologic features similar to those seen at other head and neck sites (Fig. 1.23):
  - Nests and cords of polygonal cells with moderate to abundant, eosinophilic cytoplasm, distinct cell borders.
  - Round, irregular nuclei with coarse chromatin or hyperchromasia.

**Table 1.18** Morphologic criteria for the diagnosis of oral epithelial dysplasia

| Architectural | Cytologic |
|---|---|
| Loss of polarity of basal cells<br>Disordered epithelial stratification<br>Drop-shaped, irregular rete ridges<br>Increased mitotic activity<br>Keratin pearls in rete ridges<br>Superficially located mitoses<br>Premature keratinization of individual cells | Abnormal variation in nuclear size<br>Abnormal variation in nuclear shape<br>Increased nuclear size<br>Nuclear hyperchromasia<br>Abnormal variation in cell size<br>Abnormal variation in cell shape<br>Increased nuclear to cytoplasmic ratio<br>Atypical mitoses<br>Increased size and number of nucleoli |

Based on criteria from [89]

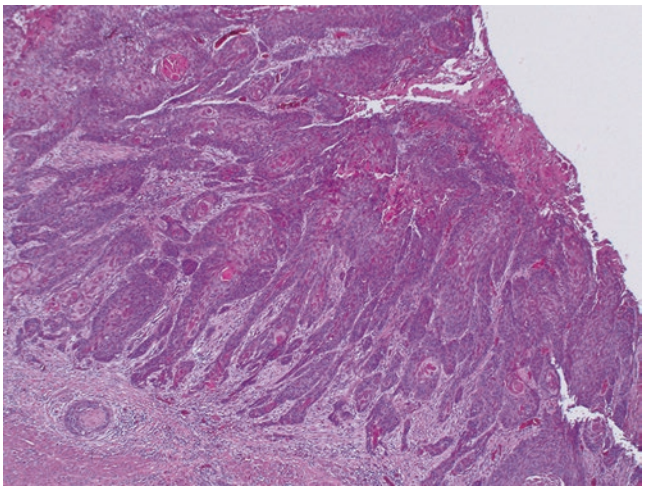

**Fig. 1.23** Conventional squamous cell carcinoma. Irregular nests and strands of tumor cells infiltrate the lamina propria. Surface keratinization and deep keratin pearls are present. Perineural invasion is seen in the lower left corner

**Table 1.19** Comparison of oral epithelial dysplasia grading systems

| Rates of malignant transformation | Criteria for 3-tier system | 3-tier system | Binary system | Criteria for binary system[a] |
|---|---|---|---|---|
| 6% | Atypia confined to lower third of epithelium | Mild | Low-grade dysplasia | Less than 4 architectural<br>and<br>Less than 5 cytologic features of OED |
| 18% | Atypia up to middle third of epithelium | Moderate | | |
| 39% | Atypia up to upper third of epithelium | Severe | High-grade dysplasia | 4+ architectural<br>and<br>5+ cytologic features of OED |
| n/a | Full thickness atypia | Carcinoma in situ | | |

[a]Based on criteria from [89]

**Table 1.20** Variants of oral squamous cell carcinoma

| | Basaloid SCC | Carcinoma cuniculatum | Papillary SCC | Verrucous carcinoma | Spindle cell carcinoma |
|---|---|---|---|---|---|
| Oral sites | FOM > tongue | Lower gingiva | Alveolar ridge/gingiva | Tongue > alveolar ridge | Tongue > FOM |
| Most common H/N site | Oropharynx | Oral cavity | Larynx | Oral cavity | Larynx |
| Gross findings | Endophytic, ulcerated tumor mass | More flat, cobblestone-like surface | Papillomatous, cauliflower-like growth | Warty appearance, abundant HK | Exophytic, polypoid mass, usually ulcerated |
| Morphology | Nests of basaloid cells with abrupt keratinization and necrosis<br>Nuclear pleomorphism and palisading<br>±Hyalinized BM material | Bland cytologic features<br>Large, branching crypts and nests filled with laminated keratin<br>Bone invasion is common | Largely exophytic, papillary tumor<br>Frankly malignant, pleomorphic cells line delicate to slightly bulbous papillae<br>Minimal or no keratinization<br>Frequent mitoses<br>Pushing borders with small infiltrative nests at base | Hyper-, orthokeratotic, with "church spire" keratin projections<br>Minimal to no atypia, rare, basal mitoses<br>Broad pushing border of invasion<br>Moderate chronic inflammation | Spindled proliferation in fascicular or storiform pattern<br>Usually high grade<br>Infiltrative growth<br>May show dysplasia or conv SCC in areas<br>No keratinization<br>Necrosis, frequent mitoses |
| Differential diagnosis | Salivary gland carcinoma, neuroendocrine carcinoma | Verrucous carcinoma | Squamous papilloma, verrucous carcinoma | Verrucous hyperplasia, condyloma, papillary carcinoma | Sarcoma, benign mesenchymal tumor, melanoma |
| Prognosis compared to conv SCC | Worse* | nd | Better | Better | Worse |

*FOM* floor of mouth, *H/N* head and neck, *HK* hyperkeratosis, *conv SCC conventional SCC*, *nd* no data (too few cases)
*This pertains to HPV-negative basaloid squamous cell carcinoma

  - Dyskeratosis and keratin pearl formation can be seen in deep portions of the epithelium.
  - Associated dysplasia or in situ carcinoma and stromal desmoplasia may be present.
- Oral SCC is locally aggressive and demonstrates early nodal disease. Poor prognostic factors include:
  - Depth of invasion greater than 4 mm.
  - Perineural, lymphovascular, and bone invasion.
  - Extranodal extension of lymph node metastases.
  - Two or more LN metastases.
  - Low-level nodal involvement (levels IV or V).
  - Satellite foci of tumor greater than 1 mm away from main tumor mass (WPOI 5: worst pattern of invasion 5).

References: [86, 90]

24. *What are the subtypes of oral squamous cell carcinoma and their significance?*

The oral cavity is one of the most common sites for head and neck squamous cell carcinomas. Not surprisingly, it is also one of the more common sites for the different variants of SCC as well (Table 1.20).

- Most of these variants are relatively rare. Their correlation with prognosis appears to be more closely related to tumor site rather than histologic type.
- Verrucous and papillary carcinomas are notable for their improved prognosis over conventional SCC.
  - As a result of the better prognosis, strict criteria should be applied when diagnosing either of these variants.
    - Verrucous carcinomas are very well-differentiated and characterized by bland cytology, demonstrating essentially no atypia and a pushing border. Areas of small nest infiltration should be absent or minimal.
    - Papillary carcinomas are exophytic with well-developed papillary projections which demonstrate upward growth that extends beyond the surrounding uninvolved epithelium. It has a largely pushing border with scattered, infiltrative nests at the base. The lack of surface keratinization is a strict criteria that has been inconsistently applied to reports in the literature.

- Awareness of the different variants is important for the prognostic value and to distinguish them from their histologic mimics.

References: [91–100]

25. *How does squamous odontogenic tumor differ from squamous cell carcinoma?*

Squamous odontogenic tumor (SOT) is a benign neoplasm of odontogenic origin that most frequently arises in the medullary cavity of the jaws but occasionally presents as a peripheral/extraosseous lesion.

- Radiographs show a radiolucent defect with well-delineated margins.
- The tumor is composed of small islands and nests of bland squamous epithelium with occasional but not prominent keratinization. The tumor islands are haphazardly arranged in a fibrous stroma and may impart a jigsaw puzzle appearance (Fig. 1.24).
- There is no connection with the surface epithelium except in cases in which the cortical bone is broken or when the lesion arises in the gingiva (peripheral squamous odontogenic tumor).
- Differential diagnostic considerations include:
  - Squamous cell carcinoma – lacks the bland tumor cytology of SOT.
  - Acanthomatous ameloblastoma – stellate reticulum, cystic change, and nuclear palisading at the periphery of tumor nodules are not seen in SOT.

Reference: [101]

26. *What are the common fibrous and fibroblastic lesions of the oral cavity?*

Mesenchymal lesions of the oral cavity include those derived from neural, muscular, adipose, and fibrous tissue. Most of the common tumors in the former categories have already been discussed. This current section will address a few miscellaneous entities found in the oral cavity (Table 1.21).

References: [102–111]

27. *What are the common salivary gland tumors of the oral cavity?*

Salivary gland neoplasms arise from the numerous minor salivary glands found throughout the oral cavity. These tumors, along with their intraoral distribution and frequency, are discussed in greater detail in Chap. 5. A few important facts about intraoral salivary gland tumors include:

- The oral cavity is the second most frequent site of salivary gland neoplasms after the parotid gland.
- The palate is the most common intraoral location for salivary gland tumors.
- Pleomorphic adenoma is the most common benign intraoral salivary gland neoplasm.
- Mucoepidermoid carcinoma is the most common malignant intraoral salivary gland neoplasm.

References: [112]

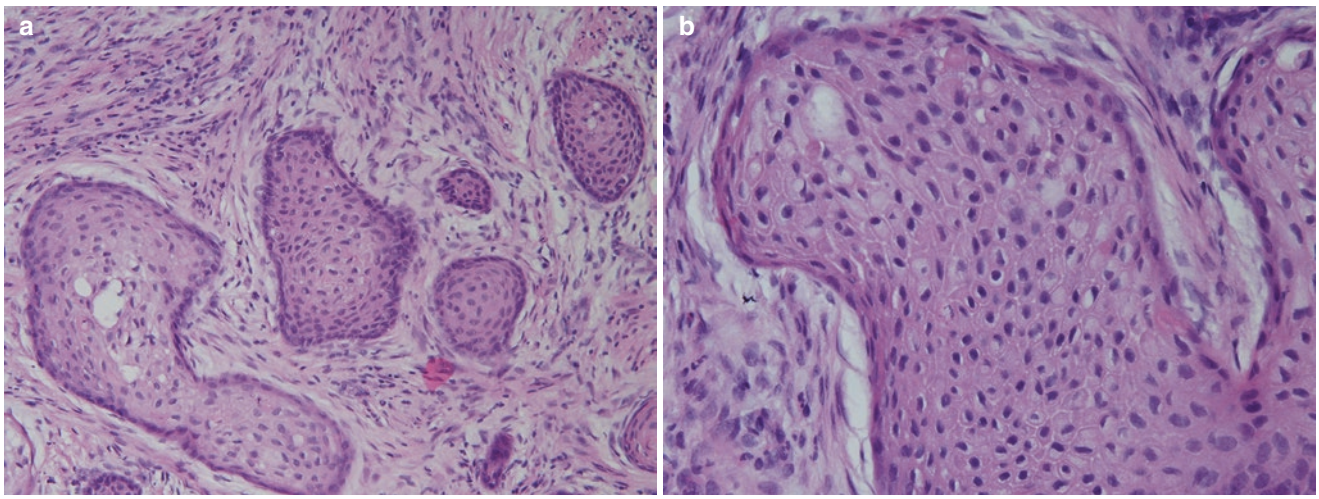


**Fig. 1.24** Squamous odontogenic tumor. (**a**) Islands of bland, squamous epithelium supported by a fibrous stroma. (**b**) The neoplastic cells lack atypia, cystic change or peripheral palisading seen in ameloblastoma or squamous cell carcinoma

**Table 1.21** Fibroblastic and myofibroblastic lesions of the oral cavity

| | Nodular fasciitis | Aggressive fibromatosis | Irritation fibroma | Giant cell fibroma | Solitary fibrous tumor | Low-grade myofibroblastic sarcoma |
|---|---|---|---|---|---|---|
| Gender (age in years) | F:M=2:1, (mean 35) | M=F, (mean 1) | Wide age range | M=F, young, <20 | M=F, 5th–6th decade | M:F=3:2, (median 42) |
| Oral site | Buccal > > upper lip > tongue, gingiva | Tongue | Buccal, lower lip, lateral tongue or tip, gingiva | Gingiva > tongue, palate, cheek | Buccal > > lip, maxilla, tongue | Tongue > >palate |
| Clinical | Rapidly growing, painless mass, intact mucosa<br>Rare history of trauma | Painless, ulcerated mass<br>Slow or rapid growth, bone erosion/ invasion | Caused by trauma or irritation<br>Polypoid nodule or papule | Sessile or pedunculated mass with papillary surface | Slow-growing, painless, intact mucosa | Painful, slow-growing mass, ulcerated mucosa, no inflammation |
| Circumscription | Well-circumscribed, minor infiltration | Infiltrative | Well-circumscribed, unencapsulated | Well-circumscribed, unencapsulated | Circumscribed | Circumscribed, but infiltrative |
| Cellularity | High | Low | Low | Low | Moderate | High |
| Morphology | Uniform spindle cells with plump, oval nuclei, fine vesicular chromatin, inconspicuous nuclei<br>Cells are haphazardly arranged in short fascicles with a myxoid stroma<br>Areas of hypocellularity, inflammation and extravasated RBCs are present | Broad, sweeping fascicles of spindle cells in a dense, collagenous stroma<br>Cells are bland and uniform with small, oval nuclei and indistinct borders | Polypoid, dense fibrous proliferation with overlying PK or HK<br>Scattered, fibroblasts, may be small and spindled or large and stellate<br>±Ulceration, ±inflammation<br>None to minimal atypia (Fig. 1.25) | Pointed, elongated rete ridges, ±papillary epithelium dense, collagenous lamina propria with stellate-shaped fibroblasts<br>Some are multinucleated with vesicular to hyperchromatic nuclei and surrounding retraction artifact<br>±Chronic inflammation, melanin (Fig. 1.26) | Small, short, uniform spindle cells in a haphazard pattern<br>Variably cellular in a collagenous stroma<br>±Branching vasculature<br>±Hyalinized vessels | Spindle cell proliferation arranged in whorled, or herringbone pattern<br>Pale, cytoplasm with indistinct borders<br>Nuclei have tapered ends and fine chromatin, minimal atypia<br>Checkerboard pattern of tumor cells separating muscle fibers<br>Rare necrosis |
| Mitoses | Frequent | Rare | None | None | Low, <4/10 hpf | Low mitoses, average 2/10 hpf |
| Recurrences | None | 25% recur | None | Rare | None | Yes |
| IHC | Vimentin+, var SMA+, CD34–, desmin–, CD99–, BCL2– | (n)ß-catenin+, vimentin+, var SMA+ | CD34+, CD99+, var fXIIIa+ | var SMA+ | str CD34+, CD99+, BCL2+, STAT6+ | Desmin+, MSA+, var SMA+, wk CD34+, CD99– |

*var* variable, *n* nuclear, *wk* weak, *str* strong, *hpf* high power field

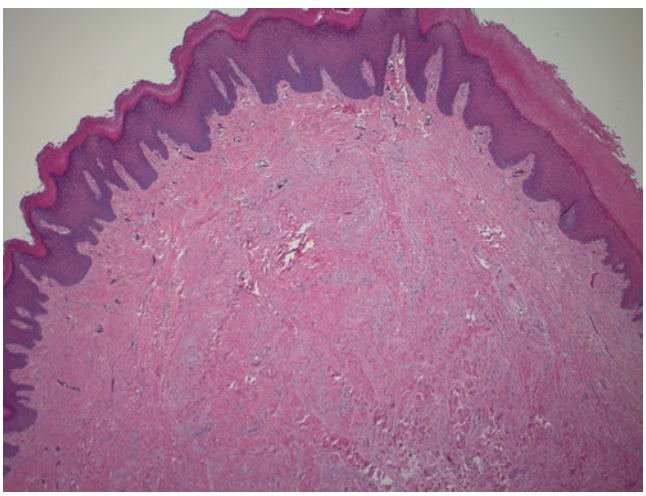

**Fig. 1.25** Irritation fibroma. Polypoid mucosal lesion composed of dense, collagenous stroma

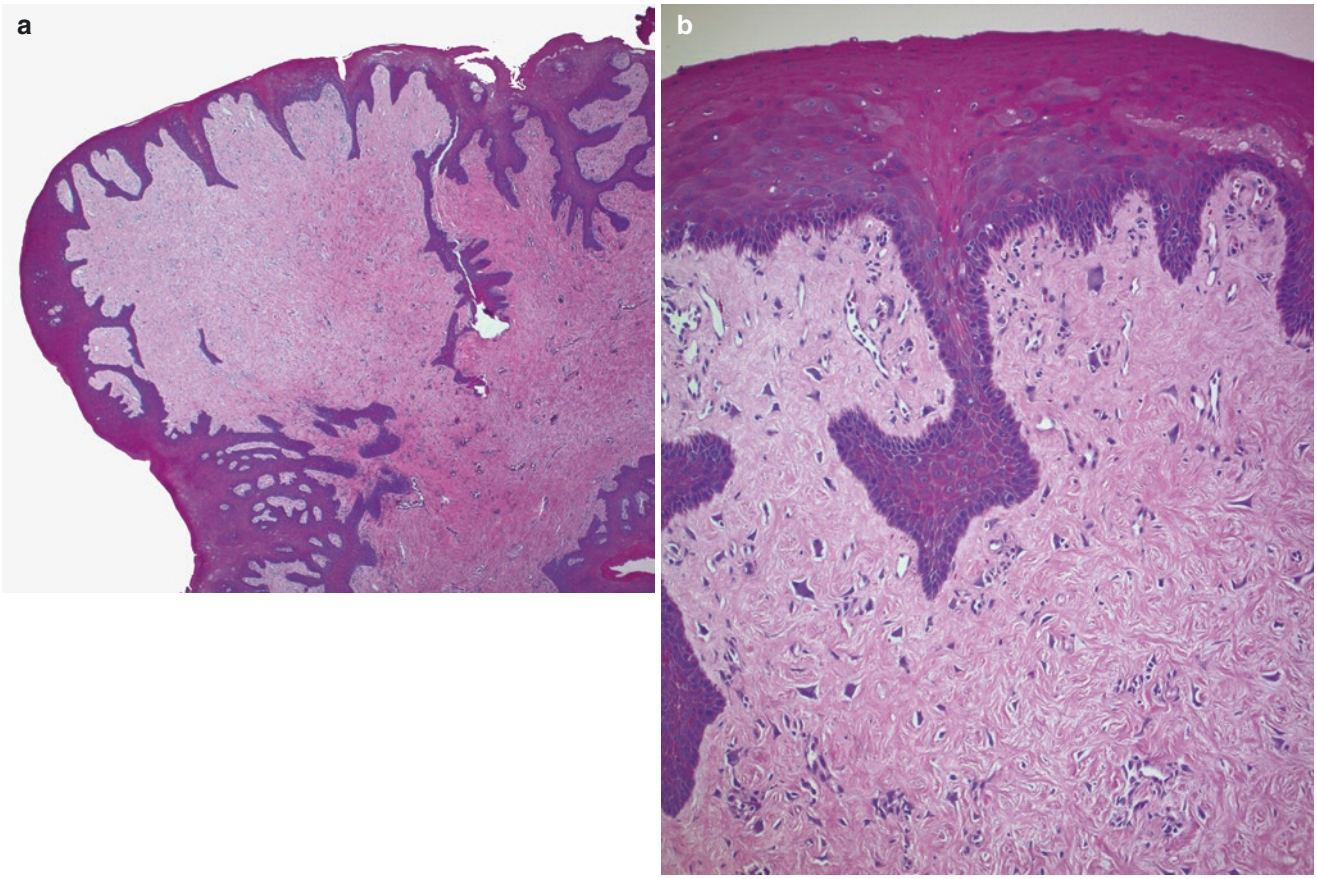


**Fig. 1.26** Giant cell fibroma. (**a**) Polypoid mucosal lesion with unremarkable epithelium and a densely collagenous lamina propria. (**b**) Scattered giant spindled and stellate cells with surrounding retraction artifact are present throughout the lesion and between rete ridges

28. *What are the characteristics of metastases to the oral cavity?*

    Metastatic tumors to the oral cavity are rare, comprising 1–2% of all neoplastic lesions at this site.
    - 25% of oral cavity metastases represent unknown primary tumors.
    - 25% of oral cavity metastases represent the first sign of metastatic disease and are a harbinger of advanced, late-stage disease.
      – Average interval from diagnosis of metastases to death is 5–6 months.
    - The most common oral site of metastasis is the gingiva.
    - The most common primary tumor is lung followed by breast. Kidney, liver, and colorectal carcinomas are among the five most frequent sites, but frequency varies by study.

    References: [113–119]
29. *Which hematolymphoid lesions show a predilection for the oral cavity?*

    Hematopoietic tumors of the oral cavity are rare.
    - Lymphoma is the second most common malignant tumor of the oral cavity; non-Hodgkin lymphoma comprises <4% of all malignancies at this site.
      – Primary lymphomas in this location account for less than 2% of all extranodal lymphomas. Diffuse large B-cell lymphoma is the most common subtype.
    - A few rare hematolymphoid tumors have a particular predilection for the oral cavity and are highlighted in Table 1.22.

    References: [32, 86, 120–127]

## Case Presentations

### Case 1

#### Learning Objectives

1. To recognize the histopathologic features of acantholysis
2. To become familiar with the differential diagnosis of acantholytic disorders
3. To recognize if the biopsy specimen is appropriate for direct immunofluorescent studies

**Table 1.22** Hematolymphoid lesions with predilection for the oral cavity

| | CD30-positive T-cell lymphoproliferative disorder | EBV-positive mucocutaneous ulcer | Plasmablastic lymphoma | Extramedullary myeloid sarcoma |
|---|---|---|---|---|
| Patient (age in years) | M > F (median 60) | F > M (median 70–80) | HIV+males, HIV–females | M > F (median 55) |
| Oral site | Tongue | Tongue > > cheek, palate | Gingiva, palate | Gingiva |
| Clinical | Ulcerated mass | Drug-induced IS: methotrexate, cyclosporin A, azathioprine<br>Age-related IS, elderly<br>Indurated ulcers, sharp edges | HIV-associated and post-transplant<br>Oral mass | May precede systemic disease |
| Morphology | Sheets of atypical lymphoid cells<br>Large atypical, pleomorphic lymphocytes with abundant cytoplasm<br>Mixed inflammatory background | Ulcerated mucosa with mixed inflammatory infiltrate containing scattered large, pleomorphic lymphoid cells with a moderate amount of cytoplasm round nuclei, prominent nucleoli<br>Angioinvasion and necrosis are present | High-grade lymphoma composed of medium to large sized immunoblast-type cells and plasmablasts<br>Cells have a round nuclei, clumped chromatin with peripheral margination and prominent nucleoli | Sheet of myeloid blasts with scant to moderate amounts of cytoplasm, round nuclei with fine chromatin and conspicuous nucleoli |
| IHC | CD30+, CD4 > > CD8+, EBV– | EBV+, CD30+, MUM1+, CD20+, CD10+, PAX5+, CD79a+ | EBV+, var CD45±, var CD56+, var EMA+, var CD30+, CD20–, CD19– | CD34+, CD33+, CD117+ |

*IS* immunosuppression, *var* variable

**Case History**

A 64-year-old male presented with painful oral ulcers and erosions that were increasing in extent and severity over the last 3 months. No other body site was involved, and the patient was otherwise in good general health. He had been taking a daily multivitamin for at least 9 years, but no other medications. An incisional biopsy of one of the lesions was submitted in formalin for routine H&E staining; and a biopsy of peri-lesional mucosa was submitted in Michel's transport media and subsequently submitted for direct immunofluorescence studies.

**Gross Findings**

The biopsy was a 5-mm wedge submitted in formalin; the peri-lesional biopsy was a 5-mm wedge of mucosa submitted in Michel's transport media.

**Histologic Findings** (Fig. 1.27)

- Epithelial acantholysis with underlying non-specific inflammation.
- The basal cell keratinocytes are still attached to the basement membrane.
- Acantholytic cells are suspended inside intraepithelial clefts.

**Differential Diagnosis**

- Pemphigus vulgaris
- Paraneoplastic pemphigus
- Warty dyskeratoma and focal acantholytic dyskeratosis
- Other acantholytic disorders (Darier's disease, Hailey-Hailey, fixation artifact)

**IHC and Other Ancillary Studies**

- The specimen submitted in Michel's transport media was submitted for direct immunofluorescence studies using IgG, IgA, IgM, C3, and fibrinogen antibodies. The tissue was reactive to IgG on all the desmosomes in the epithelium showing a "chicken wire" or "fish net" pattern.

**Final Diagnosis** *Pemphigus vulgaris*

**Take-Home Messages**

1. Acantholytic disorders in the oral mucosa are often found in patients with systemic diseases. Occasionally, patients present with oral involvement only. Some of these patients will progress to systemic disease, and others will remain with localized disease.
2. It is critical to know if the patient has a single lesion (warty dyskeratoma), multiple lesions in a single anatomic location (focal acantholytic dyskeratosis, localized pemphigus), multifocal disease (pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus), or a concomitant malignancy (paraneoplastic pemphigus).

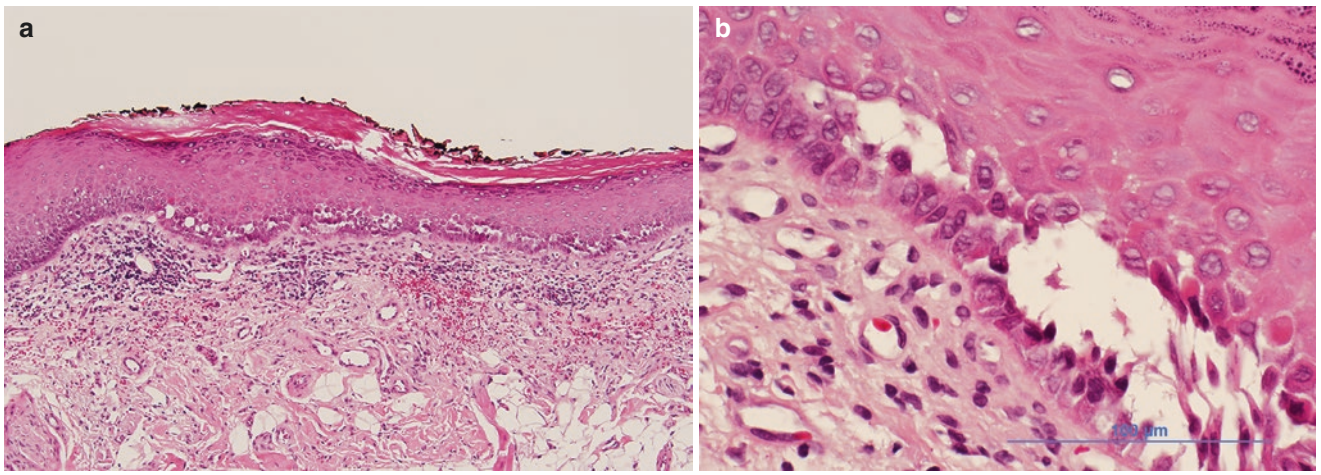


**Fig. 1.27** Case 1 (**a**) The mucosa shows acantholysis with a suprabasal cleft and sparse inflammatory infiltrate in the lamina propria. (**b**) Higher magnification shows dyshesive cells and dyskeratotic cells floating in the cleft

3. It is important that the tissue submitted for direct immunofluorescent studies includes intact epithelium in order to evaluate the mucosa's desmosomes and hemidesmosomes in an unaltered state.

References: [30, 128–131]

## Case 2

### Learning Objectives

1. To become familiar with the histologic features of the tumor
2. To understand the clinical behavior of the tumor despite the histology
3. To be familiar with other lesions associated with the tumor

### Case History

A 77-year-old male presented clinically with a 3-cm papillary, verrucous exophytic lesion on the left buccal mucosa and mandibular vestibule. The patient had a 20-year history of smokeless tobacco use, placed in the same general location.

### Gross Findings

An incisional biopsy specimen of the lesion was submitted. It consisted of an 8 × 5 × 4-mm wedge specimen of oral mucosa with a verrucous surface architecture.

### Histologic Findings (Fig. 1.28)

- The architecture of the lesion is predominantly exophytic, with a verrucous hyperkeratotic surface and a minor endophytic component.
- There is acanthosis and basal cell hyperplasia but no significant cellular atypia or anaplasia.
- Occasional dyskeratotic cells are seen, and in some lesions, there are keratin "plugs" and pearls.
- The basal cell layer assumes a teardrop shape and extends into the lamina propria with broad, pushing margins and no evidence of single cell invasion or thin invasive rete pegs.
- There is a reactive lymphoplasmacytic infiltrate that migrates to the advancing tumor edge.

### Differential Diagnosis

- Verrucous carcinoma
- Carcinoma cuniculatum
- Verrucous hyperplasia
- Condyloma acuminatum
- Verruca vulgaris
- Squamous papilloma
- White sponge nevus
- Hereditary benign intraepithelial dyskeratosis

### IHC and Other Ancillary Studies

- In general, special stains are not required nor useful for this diagnosis.
- Verrucous carcinoma does not exhibit transcriptionally active human papillomavirus. If HPV is identified in the tissue, it is considered a "passenger," but not an etiologic entity.

**Final Diagnosis** *Verrucous carcinoma*

### Take-Home Messages

1. Verrucous carcinoma should be diagnosed after examination of the entire lesion since its architecture is critical. If

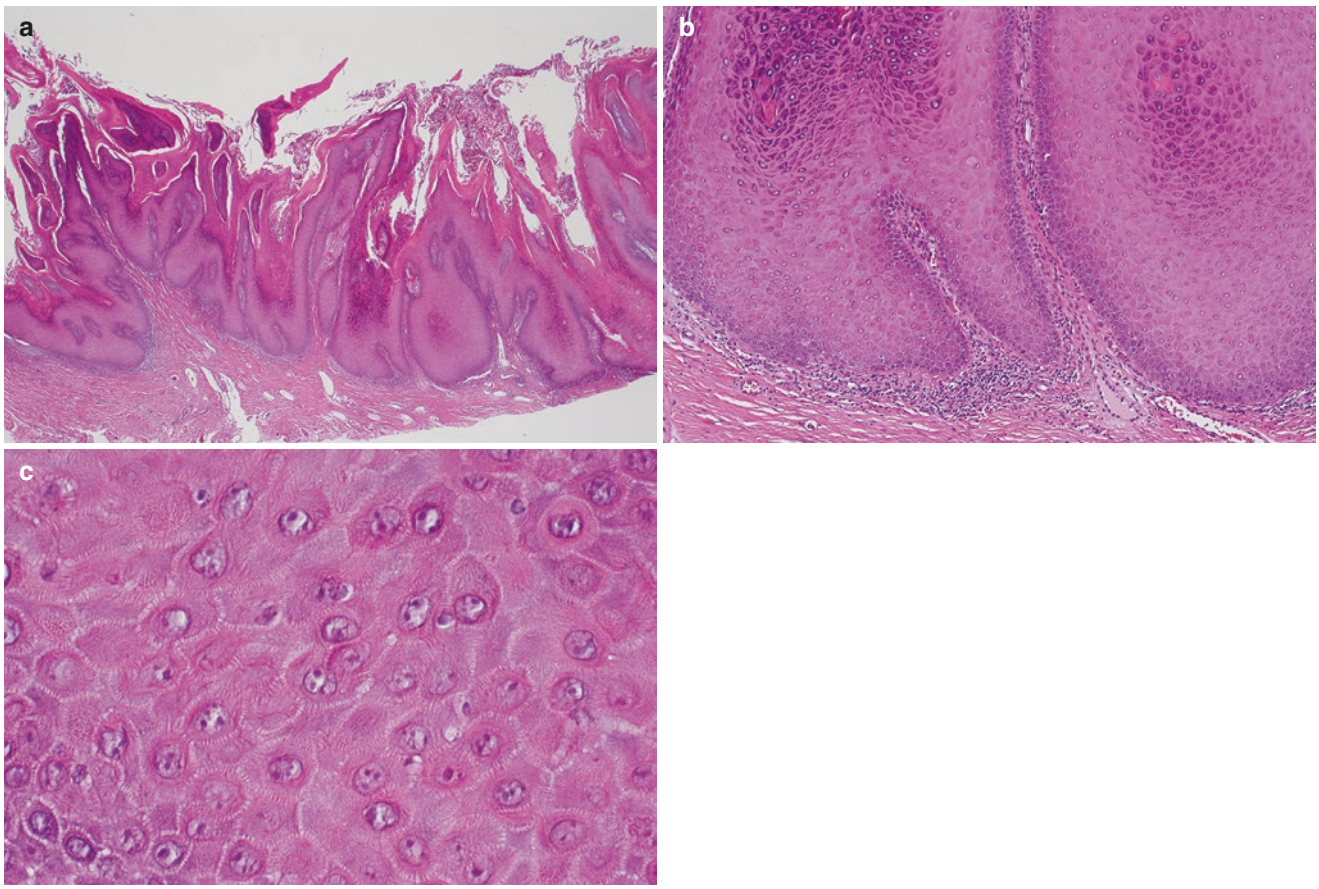


**Fig. 1.28** Case 2. (**a**) Papillary lesion with a significant exophytic component and pointy hyperkeratotic spikes and bulbous rete ridges creating a downward pushing border. (**b**) The interface between the epithelium and the connective tissues has a lichenoid inflammatory infiltrate. (**c**) The epithelium is characteristically bland with minimal to absent atypia

there is any significant atypia, an alternate diagnosis should be considered.
2. Verrucous carcinoma may occasionally undergo high-grade transformation into conventional or spindle cell (sarcomatoid) squamous cell carcinoma in focal areas.
3. Verrucous carcinoma is not driven by HPV infection.
4. Verrucous carcinoma may be associated with proliferative verrucous leukoplakia (PVL). Patients with PVL present with clinically multifocal or persistent lesions that often recur after excision. The early histologic diagnoses range from hyperkeratosis to varying degrees of epithelial dysplasia. There is a high incidence of progression to squamous cell carcinoma.
5. Superficial bony erosion can be seen.

References: [83, 97, 100, 132, 133]

## Case 3

### Learning Objectives

1. To become familiar with intraoral salivary gland tumors
2. To generate the differential diagnosis for intraoral salivary gland tumors
3. To properly utilize ancillary techniques to diagnosis intraoral salivary gland tumors

### Case History

A 77-year-old male presented with a 13-year history of a slowly enlarging mass on the posterior-lateral hard palate. The mass was described as firm and not bony. The surface was not ulcerated, and the patient did not complain of neurosensory disorders or pain.

### Gross Findings

A mucosal wedge incisional biopsy specimen measuring 1 × 1 × 0.8 cm was submitted. The surface mucosa was intact.

### Histologic Findings (Fig. 1.29)

- The tumor is a subepithelial proliferation of salivary epithelium without a capsule and evidence of infiltration into adjacent minor salivary gland lobules and adipose tissue in a whorled pattern.
- The periphery of the tumor shows single cells infiltrating in a tangential-centrifugal orientation.
- Peripheral nerve fibers are encompassed by tumor strands in a targetoid arrangement.
- The tumor cells exhibit a lobular architecture with focal duct formation.
- The chromatin is evenly dispersed within the ovoid, regular nuclei.
- No significant mitotic activity or necrosis is present.
- The nuclei lack angulated edges or hyperchromasia.
- Mucus cells are only occasionally seen and are not an integral part of the tumor.

### Differential Diagnosis

- Adenoid cystic carcinoma
- Cribriform adenocarcinoma of minor salivary glands
- Acinic cell adenocarcinoma
- Polymorphous adenocarcinoma
- Pleomorphic adenoma
- Canalicular adenoma

### IHC and Other Ancillary Studies

- Glial fibrillary acidic protein (GFAP) antibody is usually only focally and weakly positive in the luminal epithelial cells, as opposed to strong and diffuse in pleomorphic adenoma.
- Plasmacytoid myoepithelial cells are rare or absent in polymorphous adenocarcinoma and often abundant in pleomorphic adenoma.
- The Ki-67 proliferation index is low in polymorphous adenocarcinoma and high in adenoid cystic carcinoma. The latter also exhibits hyperchromatic, angulated nuclei as opposed to ovoid and bland nuclei in the former.
- Immunohistochemical markers show a mixture of ductal and myoepithelial cells in different proportions.

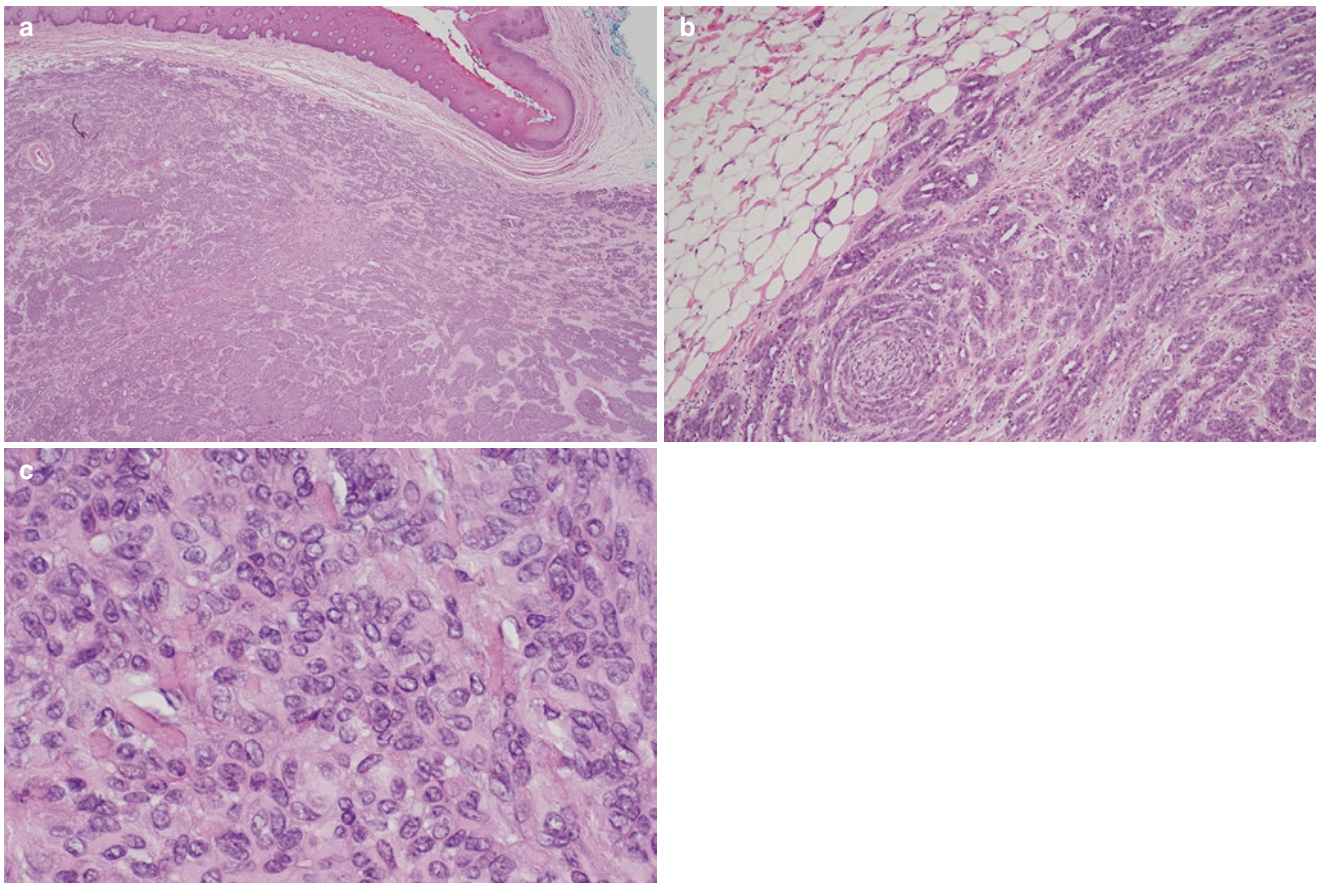


**Fig. 1.29** Case 3. (**a**) An unencapsulated subepithelial tumor with a lobular architecture and smaller nests and tubules at the tumor periphery. (**b**) A small tubular proliferation forms concentric whorls around a nerve. (**c**) Higher magnification shows monotonous, bland tumor cells with oval nuclei, fine, pale chromatin, and inconspicuous nucleoli

**Final Diagnosis** *Polymorphous adenocarcinoma*

**Take-Home Messages**

1. Previously known as polymorphous low-grade adenocarcinoma, the "low-grade" designation has been removed to allow the pathologist to assign a subjective grade. No definitive criteria have been established to grade these tumors yet.
2. It is a non-encapsulated and infiltrative neoplasm that is commonly encountered on the palate and usually is indolent in behavior despite abundant perineural invasion.
3. Immunohistochemistry is of limited use in differentiating it from other tumors, but GFAP and Ki-67 may help in difficult cases. See Chap. 5 for further details.

References: [134–139]

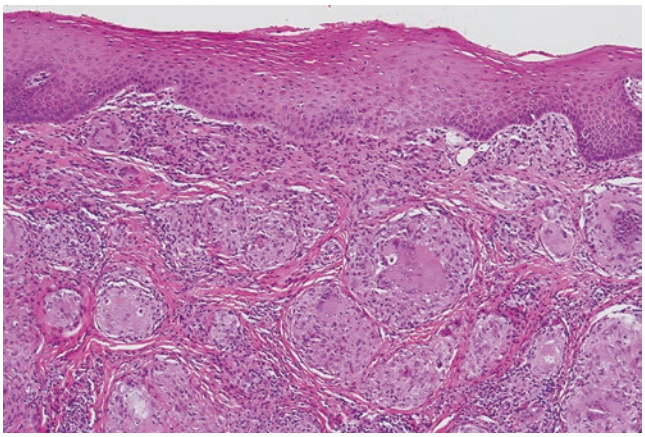

**Fig. 1.30** Case 4. Non-necrotizing granulomas in squamous mucosa with no evidence of foreign bodies or microorganisms

## Case 4

**Learning Objectives**

1. To become familiar with the differential diagnosis of oral lesions with granulomatous inflammation when identified in the oral mucosa
2. To know what special stains are required for all cases of granulomatous disease in the oral cavity
3. To be able to correlate the patient's medical history with the histopathologic findings in order to potentially discover oral manifestations of systemic granulomatous diseases

**Case History**

A 48-year-old African-American male presented with enlargement of his mandibular gingiva adjacent to his left premolar teeth. He denied any history of trauma to the area or recent exposure to new medications or substances. The enlargement had been developing slowly over 5 months. His medical history was unremarkable, and he was not on any medications. He did not use tobacco products and only drank alcohol occasionally and in moderation.

**Gross Findings**

The specimen consisted of a 4-mm punch biopsy of oral mucosa in the area of the lesion. It was bisected and entirely submitted.

**Histologic Findings** (Fig. 1.30)

- The surface epithelium has acanthosis and hyperkeratosis with a slightly pebbly surface architecture.
- Non-necrotizing granulomatous inflammation is present in the lamina propria.

**Differential Diagnosis**

- Granulomatous foreign body reaction
- Orofacial granulomatosis
- Oral manifestation of systemic granulomatous inflammation

**IHC and Other Ancillary Studies**

- Examination of the tissue under polarized light did not show evidence of crystalline foreign body material.
- Special stains for microorganisms are negative (PAS, GMS, AFB).

**Final Diagnosis** *Orofacial granulomatosis*

**Take-Home Messages**

1. Granulomatous diseases in oral biopsies are common and always require evaluation for possible foreign bodies and microorganisms.
2. Granulomatous inflammation in oral biopsies may be an oral manifestation of systemic disease such as Crohn's disease, sarcoidosis, and granulomatosis with polyangiitis. Alternatively, it may be the first manifestation of these diseases.
3. Granulomatous inflammation can be associated with overlying pseudoepitheliomatous hyperplasia of the surface epithelium which may mimic squamous cell carcinoma.
4. The diagnosis of orofacial granulomatosis and related diseases is reached as a diagnosis of exclusion after ruling out all other local and systemic conditions.

References: [140–143]

## Case 5

### Learning Objectives

1. To identify the histological features of giant cell lesions
2. To become familiar with the differential diagnosis of these lesions
3. To understand the clinicopathologic correlation necessary to establish the etiology of a giant cell lesion

### Case History

A 36-year-old Caucasian female presented with a 1.3-cm dome-shaped mass on the marginal gingiva between her upper right premolars. The lesion had been developing over the last 3–4 months and occasionally bled and was mildly painful upon manipulation. She also noted that one of the associated teeth became loose. She had a crown on the other premolar tooth, which was in poor condition and needed to be replaced years ago. The mass was excised down to the periosteum, and the defect was repaired with an autologous gingival graft.

### Gross Findings

The specimen consisted of a 15-mm dome-shaped tan-brown soft tissue mass with a smooth, focally ulcerated surface. It was bisected longitudinally and entirely submitted.

### Histologic Findings (Fig. 1.31)

- The bulk of the specimen is a core of connective tissue with a biphasic population of mesenchymal cells. The cells are a mixture of spindle-shaped single cells admixed with multinucleated syncytial cells resembling osteoclasts.
- Some of the single cells are mitotically active, but no atypia is present.
- The stroma is highly vascularized and contains scattered hemosiderin deposits.
- No evidence of foreign body or bone formation is seen.

### Differential Diagnosis

- Giant cell foreign body reaction
- Central giant cell granuloma with soft tissue extension producing a gingival mass

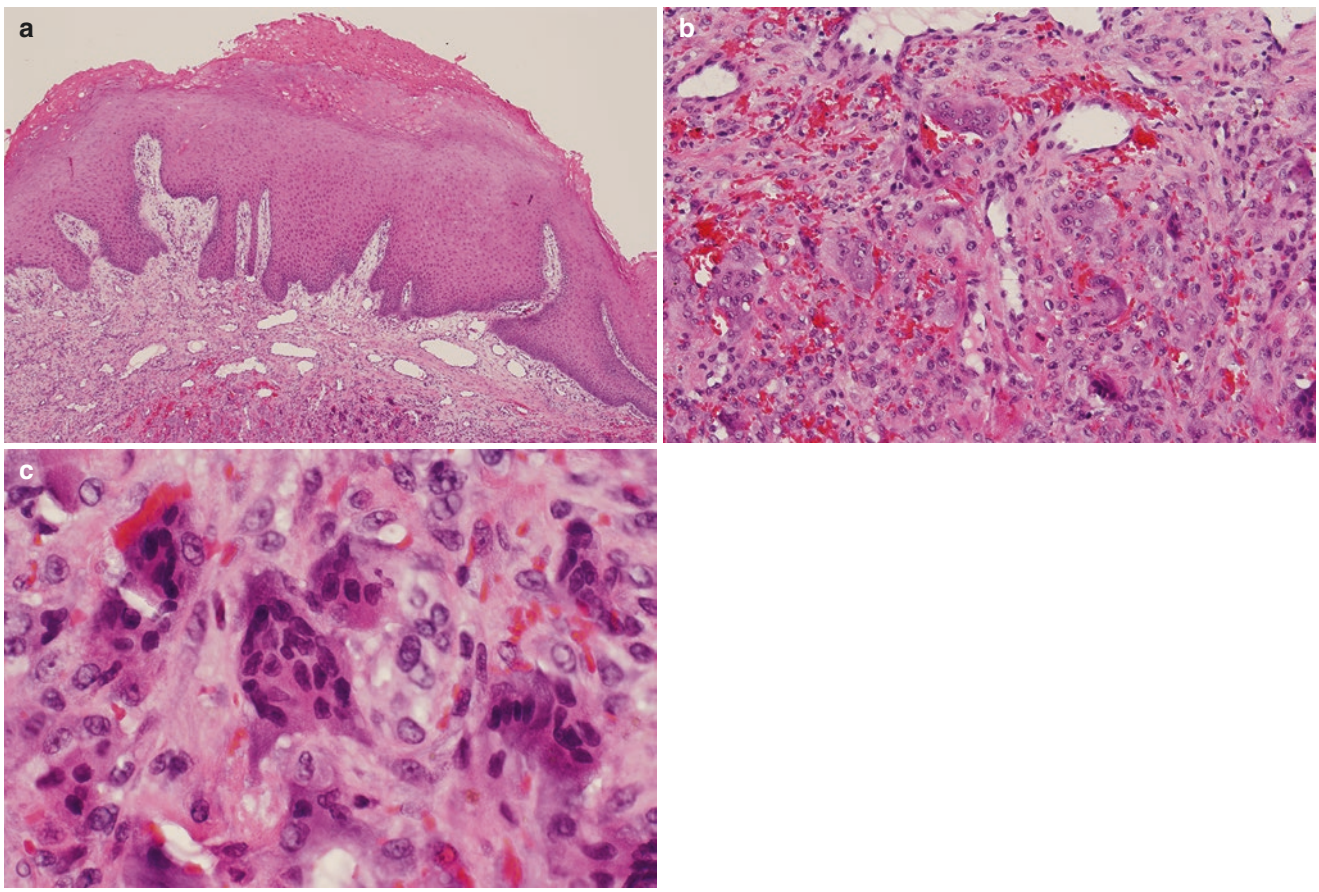


**Fig. 1.31** Case 5. (**a**–**c**) The mass exhibits a smooth surface often ulcerated. The stroma supports a proliferation of osteoclast-type multinucleated giant cells which do not form granulomata nor undergo necrosis. There is no evidence of microorganisms or foreign bodies

- A brown tumor of hyperparathyroidism presenting as an extraosseous mass
- Oral manifestation of granulomatous disease
- Peripheral ossifying fibroma
- Pyogenic granuloma
- Peripheral giant cell granuloma

**IHC and Other Ancillary Studies**

- The osteoclastic multinucleated giant cells have an identical immunoprofile as regular osteoclasts.
- Laboratory evaluation for hyperparathyroidism is necessary if the lesion is large, recurrent, or if it has a central component.

**Final Diagnosis** *Peripheral giant cell granuloma*

**Take-Home Messages**

1. Gingival masses must be removed completely, and a radiograph of the adjacent bone is mandatory to rule out a primary (central) bony lesion with cortical perforation and soft tissue involvement.
2. Hybrid lesions are seen, combining peripheral giant cell granuloma and peripheral ossifying fibroma. The most prominent component should be the diagnosis, with a note regarding the hybrid nature and describing the minor component (e.g., peripheral ossifying fibroma hybrid with peripheral giant cell granuloma)
3. Peripheral odontogenic tumors and mesenchymal neoplasms can stimulate an osteoclastic response, and, therefore, the entire specimen must be evaluated.
4. If there is lesion at the margin of the specimen, it needs to be reported in order to assure radiographic correlation to rule out a central tumor and to alert the surgeon about a higher incidence of recurrence.
5. Occasionally, a brown tumor of secondary hyperparathyroidism may present clinically as a peripheral gingival mass or as a jaw lesion with perforation of the cortical plate and subsequent gingival mass formation.

References: [144, 145]

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# Oropharynx, Nasopharynx, and Waldeyer Ring

2

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## Frequently Asked Questions

1. What are the anatomic borders and contents of the nasopharynx and oropharynx?
2. What are the contents of the Waldeyer ring and the unique characteristics of the tonsillar epithelium?
3. Which viruses are most commonly associated with tumors of the pharynx?
4. Which benign squamous tumor can be seen in the oropharynx?
5. What is the epidemiology and risk factors for human papillomavirus infection, and what is its relationship with oropharyngeal carcinoma?
6. What are the unique clinicopathologic characteristics of HPV-associated oropharyngeal squamous cell carcinoma?
7. What are the differences between HPV-associated and non-HPV-associated oropharyngeal squamous cell carcinomas?
8. What is the preferred method for establishing HPV status in an oropharyngeal squamous cell carcinoma?
9. When is HPV-specific molecular-based testing necessary?
10. What is the most common malignancy of the nasopharynx and what are its epidemiologic characteristics?
11. What are the different subtypes of nasopharyngeal carcinoma?
12. What entities are in the differential diagnosis of nonkeratinizing nasopharyngeal carcinoma?
13. What are the most common adenocarcinomas of the pharynx?
14. What are the important, recent changes to the staging of pharyngeal carcinomas?
15. What are the clinical and pathologic characteristics of juvenile (nasopharyngeal) angiofibroma?
16. What is the differential diagnosis of juvenile angiofibroma and which immunohistochemical stains are helpful in the diagnosis?
17. What are the common hematolymphoid tumors of the pharynx?
18. What are the primary tumors that can metastasize to the oropharynx?

1. *What are the anatomic borders and contents of the nasopharynx and oropharynx?*

The nasopharynx (NP) is an anatomic space situated behind the nasal cavity with anatomic boundaries defined as follows:

- Superior border (roof) – the base of skull and part of sphenoid bone
- Inferior border – soft palate and uvula
- Posterior border – the first cervical vertebra (anterior arch)
- Anterior border – the posterior choanae
- Lateral border – the submucosal cartilaginous elevations (torus tubarius) that form the pharyngeal openings of the Eustachian tube

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- It is lined by nonkeratinizing squamous epithelium in the lower portions and respiratory epithelium in the roof and choanae.
- On its superolateral aspect, there is lymphoid tissue covered by a respiratory mucosa, known as the pharyngeal tonsils or adenoids.
- Numerous seromucinous glands and associated ducts are present throughout the lamina propria of the NP. Table 2.1 lists the contents of the NP.
- The Eustachian tube openings are located on the posterior wall of the NP, just anterior to a shallow depression called the fossa of Rosenmüller.

The oropharynx (OP) lies just inferior to the nasopharynx and is in direct continuity with it. It is lined by nonkeratinizing squamous epithelium with numerous seromucinous glands throughout the lamina propria. The contents of the OP are listed in Table 2.1.

**Table 2.1** Contents of the nasopharynx and oropharynx

| Nasopharynx | Oropharynx |
|---|---|
| Adenoids | Base of the tongue |
| Rathke pouch | Vallecula |
| Orifice of Eustachian tubes | Soft palate |
| Fossa of Rosenmüller | Uvula |
| | Palatine tonsils |
| | Anterior and posterior tonsillar pillars |
| | Tonsillar fossa |
| | Posterior oropharyngeal wall |

The anatomic boundaries of the OP are defined as follows:

- Superior border – a horizontal plane extending posteriorly from the soft palate.
- Inferior border – the superior surface of the hyoid bone and vallecula.
- Posterior border – the posterior pharyngeal wall in this area lies in front of the second and third cervical vertebrae.
- Anterior border –formed by the circumvallate papillae, which divide the base of the tongue from the anterior two-thirds of the tongue. The oropharynx is in continuity with the oral cavity through the oropharyngeal isthmus.
- Lateral border – the lateral pharyngeal wall is formed by the palatopharyngeal arches.

References: [1–3]

2. *What are the contents of the Waldeyer ring and the unique characteristics of the tonsillar epithelium?*

The Waldeyer ring is formed by abundant lymphoid tissue found throughout the pharynx and includes the palatine tonsils, the lingual tonsil (base of the tongue), and the adenoids.

- The epithelial lining of the tonsils and base of tongue is a specialized, stratified squamous epithelium that invaginates into the underlying lymphoid tissue to form crypts.
  - This epithelium is characterized by a discontinuous basement membrane with infiltration of lymphocytes and plasma cells imparting a reticulated appearance (Fig. 2.1).

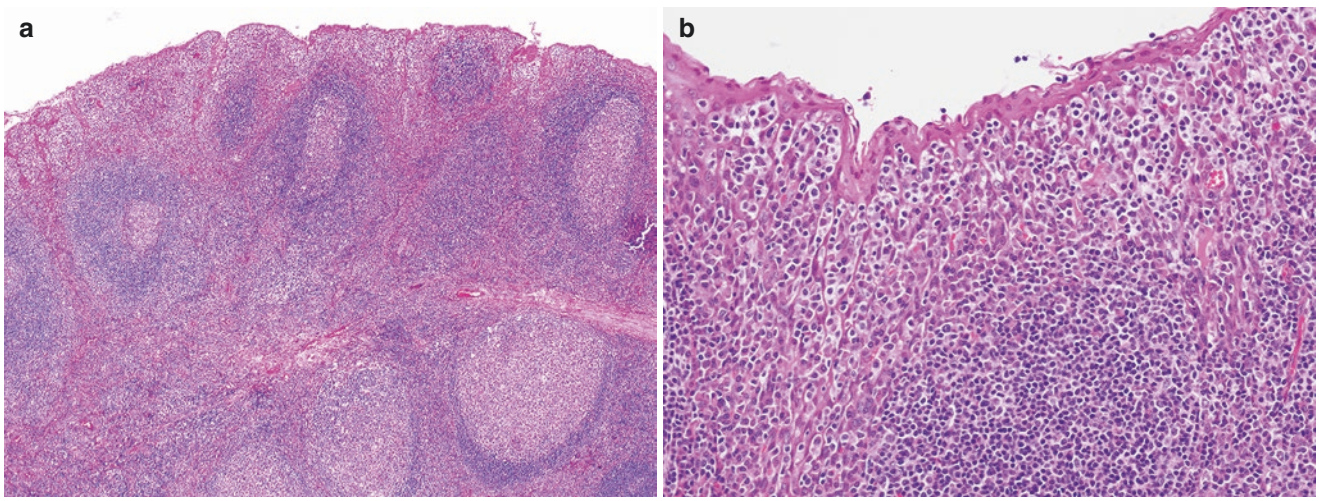


**Fig. 2.1** Normal tonsil. (**a**) Predominantly lymphoid stroma with follicles and germinal center formation covered by (**b**) a nonkeratinizing, stratified squamous epithelium. Note the obscured, discontinuous basement membrane and dense infiltration of lymphocytes and plasma cells in this reticulated epithelium

- The discontinuous basement membrane of this specialized, reticulated epithelium raises doubt about the diagnosis of in situ carcinoma in this region.
- The close association of the reticulated epithelium, intraepithelial lymphocytes, and dendritic cells facilitates direct transport of various viral antigens to the underlying lymphoid tissue.
  - For this reason, crypt epithelium is the presumed site of origin of human papillomavirus (HPV)-related carcinomas at this site.
  - p16 immunoreactivity can be seen in normal crypt epithelium; though staining is generally patchy and weak (Fig. 2.2).
- The adenoids are predominantly lined by a respiratory epithelium.

References: [4, 5]

3. *Which viruses are most commonly associated with tumors of the pharynx?*

Human papillomavirus (HPV) and Epstein-Barr virus (EBV) are the most important viruses affecting tumorigenesis in the pharynx. Table 2.2 lists the nonneoplastic and neoplastic lesions associated with both of these viruses.

- HPV is known to have at least 40 different genotypes that can infect skin and mucosa.
  - The high-risk (HR) genotypes are associated with high-grade dysplasias and carcinomas of the urogenital and upper aerodigestive tracts.
  - Some of the common HR-HPV genotypes include 16, 18, 31, and 32.
  - Low-grade dysplasias and various types of warts are associated with the low-risk genotypes.
  - The common low-risk genotypes include 2, 4, 6, and 11.

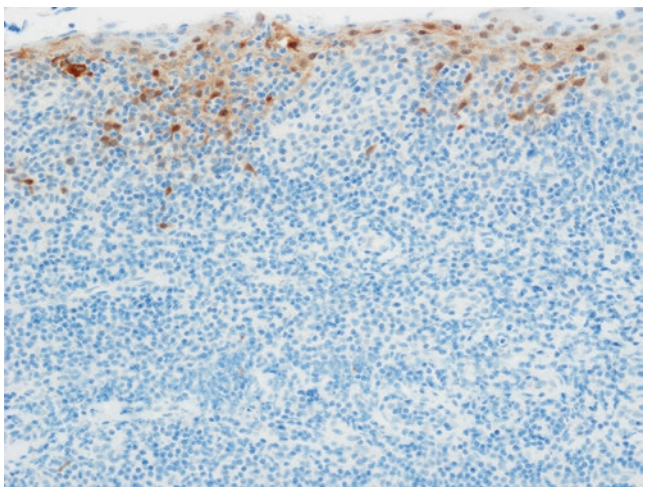

**Fig. 2.2** Normal tonsil. p16 immunostaining can be seen in the nonneoplastic tonsillar epithelium. It is usually weak and patchy and generally does not involve the entire thickness of the epithelium (i.e., no block positivity)

**Table 2.2** Common viral-associated conditions of the oropharynx and nasopharynx

| Virus | Nonneoplastic and benign lesions | Malignant lesions |
|---|---|---|
| HPV | Condyloma acuminatum<br>Squamous papilloma | Oropharyngeal squamous cell carcinoma<br>Small cell neuroendocrine carcinoma<br>Other variants of squamous cell carcinoma<br>Adenosquamous carcinoma |
| EBV | Infectious mononucleosis<br>Chronic active EBV infection | Nasopharyngeal carcinoma<br>Lymphoepithelial carcinoma<br>NK/T-cell lymphoma, nasal type<br>Post-transplant lymphoproliferative disorders<br>Burkitt, Hodgkin, and plasmablastic lymphomas<br>Diffuse large B-cell lymphoma<br>Lymphomatoid granulomatosis |

*HPV* human papillomavirus, *EBV* Epstein-Barr virus, *NK* Natural killer

- EBV primarily infects B-cells. The intimate interaction between the pharyngeal epithelium and the B-cells found in the lymphoid stroma offers some explanation for the pathogenesis of EBV-associated carcinomas.

References: [6–9]

4. *Which benign squamous tumor can be seen in the oropharynx?*

Squamous papilloma is a benign, hyperplastic proliferation of squamous epithelium with a papillary growth pattern (Fig. 2.3). Patients commonly present in the third to fifth decade of life with a solitary, exophytic, painless mass.

- Squamous papillomas comprise delicate, branching papillae with fibrovascular cores that are lined by bland, stratified squamous epithelium.
- Superficial koilocytic changes may be seen, and surface epithelium can show hyperkeratosis or parakeratosis.
- The most common sites in the oropharynx are the tonsils, palate, and uvula.
- HPV subtypes 6 and 11 are associated with squamous papillomas.

References: [6, 7, 10]

5. *What are the epidemiology and risk factors for human papillomavirus infection, and what is its relationship with oropharyngeal carcinoma?*

Squamous cell carcinoma of the oropharynx occurs most commonly in the base of the tongue and palatine tonsils. It is a disease of middle-aged to older, white males. The overall incidence of oropharyngeal squamous cell carcinomas (OPSCC) has increased in the

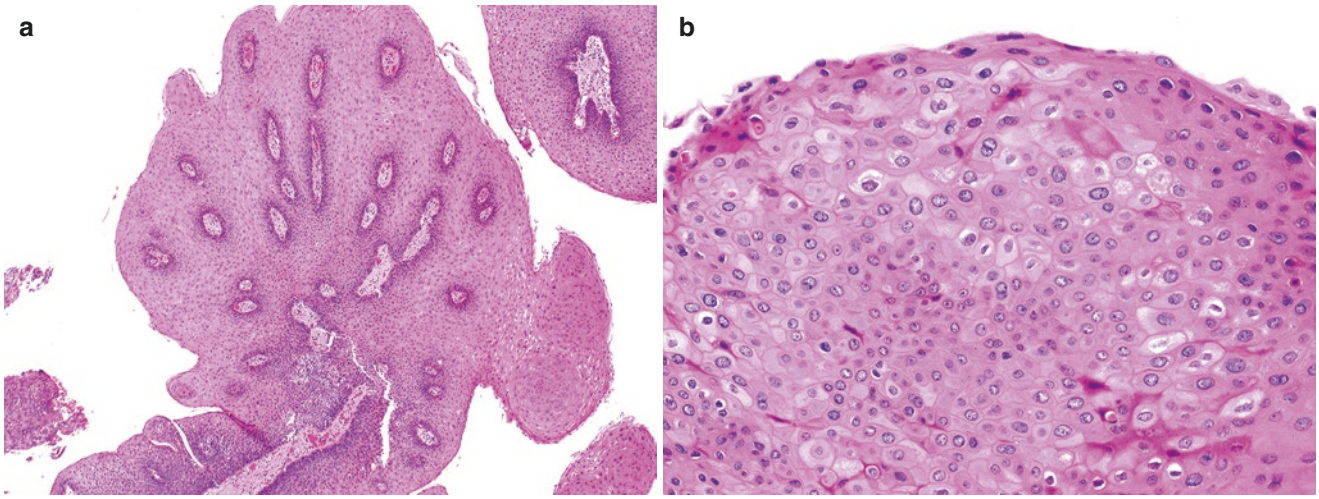


**Fig. 2.3** Squamous papilloma. (**a**) An exophytic, hyperplastic squamous proliferation with bulbous papillae and underlying fibrovascular cores. (**b**) Higher magnification shows viral-associated changes such as koilocytic change with perinuclear clearing, irregular nuclei, hyperchromasia, and binucleation

last 30 years due to the rise in HPV-associated OPSCC. Currently, HPV-OPSCC accounts for as much as 80% of oropharyngeal carcinomas in the United States.

- HPV infection is a sexually transmitted disease, and the prevalence of oral HPV infection in the US population is estimated at 7%.
- HPV type 16 is the most common genotype found in the oral cavity
  - The prevalence of oral HPV16 is approximately 1% in US populations.
  - HPV16 comprises 28% of all oral HPV types and is more common in men.
  - HPV16 accounts for up to 90% of HPV-OPSCC.
- Risk factors associated with oral HPV infection are related to sexual behavior and include:
  - Increased number of sexual partners
  - High numbers of oral and vaginal sexual partners
  - Young age at first sexual experience
  - History of genital warts
- The amount of time from infection to carcinoma is on the order of several years to a decade. Not all patients with oral HPV infection will progress to disease. Other potentiating factors may play a role in disease progression.
  - Tobacco use remains a risk factor for the development of HPV-OPSCC.
  - The prevalence of oral HPV16 and its persistence are directly related to the amount of tobacco exposure.
  - Patients with HPV-OPSCC who smoke have a worse prognosis compared to nonsmokers.

References: [6, 11–16]

6. *What are the unique clinicopathologic characteristics of HPV-associated oropharyngeal squamous cell carcinoma?*

HPV-associated OPSCC is currently recognized as a discrete entity with distinct epidemiologic, clinical, and pathologic characteristics.

- HPV-OPSCC patients are more likely to be white with little or no tobacco exposure.
- The most common clinical presentation is that of a neck mass.
- Cervical lymph nodes (LN) in levels 2 and 3 (upper and mid jugular nodal groups) are the likely sites of metastases.
  - LN metastases are typically cystic and may be bulky, regardless of primary tumor size.
- HPV-OPSCC are commonly nonkeratinizing carcinomas comprising basaloid cells arranged in lobules and large nests with pushing borders, embedded in a lymphoid stroma (Fig. 2.4).
  - The neoplastic cells are round to oval with hyperchromatic nuclei, scant cytoplasm and inconspicuous nucleoli, brisk mitotic activity, and apoptosis.
  - Tumor-infiltrating lymphocytes permeate the malignant epithelium, and necrosis is often present.
  - Desmoplasia and keratinization are usually minimal or absent.
  - Epithelial dysplasia is not a common feature.
- HPV-OPSCC can show a morphologic spectrum and includes variants such as papillary (Fig. 2.5), basaloid (Fig. 2.6), lymphoepithelioma-like, sarcomatoid, and adenosquamous carcinomas.

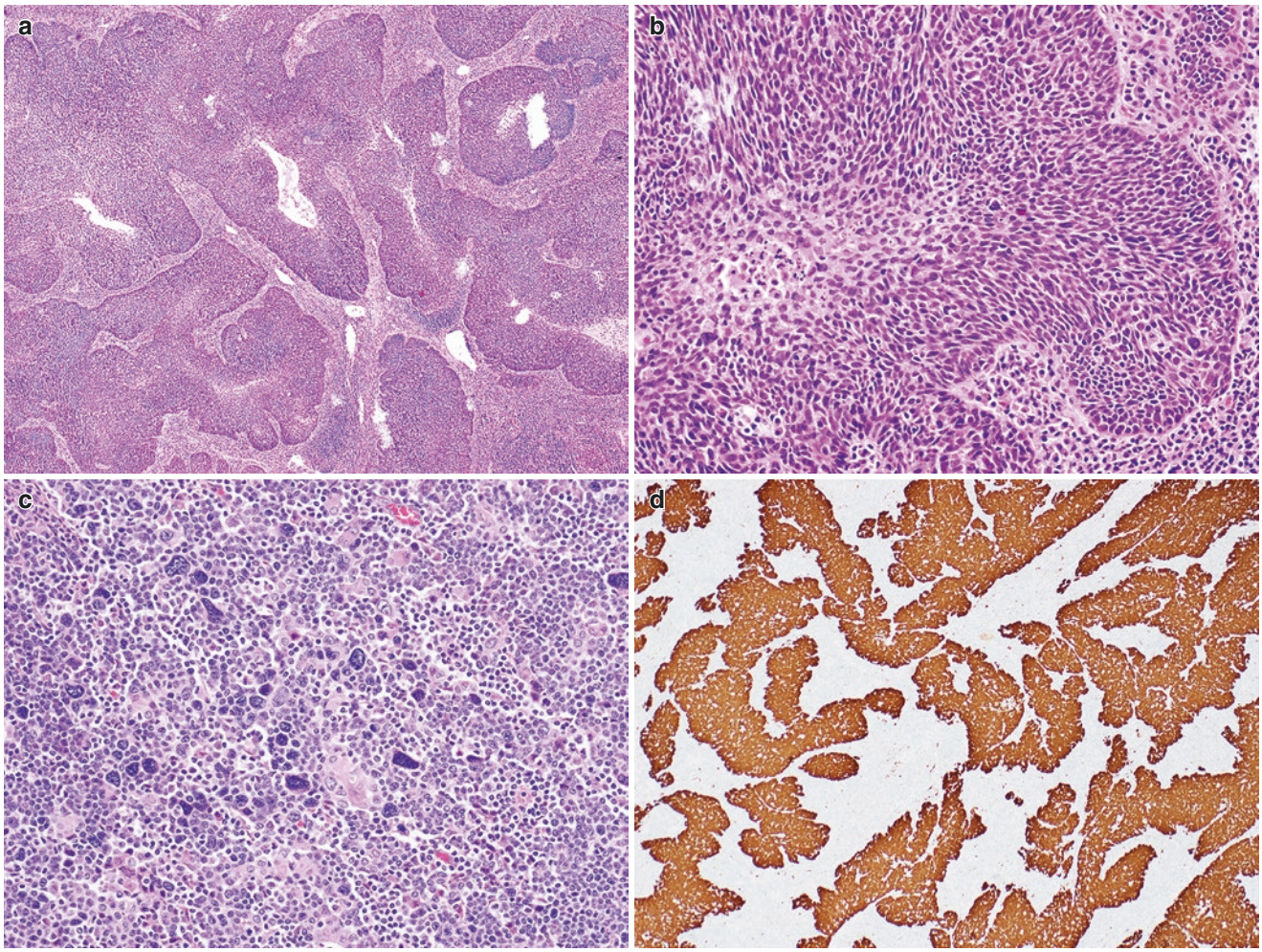


**Fig. 2.4** HPV-associated, nonkeratinizing squamous cell carcinoma of the oropharynx. (**a**) Ribbons and lobules of basaloid tumor cells with a pushing border and lymphoid stroma. (**b**) The neoplastic cells have a high N:C ratio, nuclear hyperchromasia, and inconspicuous nucleoli. Frequent mitoses and apoptotic bodies are noted. (**c**) Occasionally tumor cells may show marked pleomorphism with multinucleation. (**d**) p16 stain shows strong, diffuse block positivity in the tumor cells

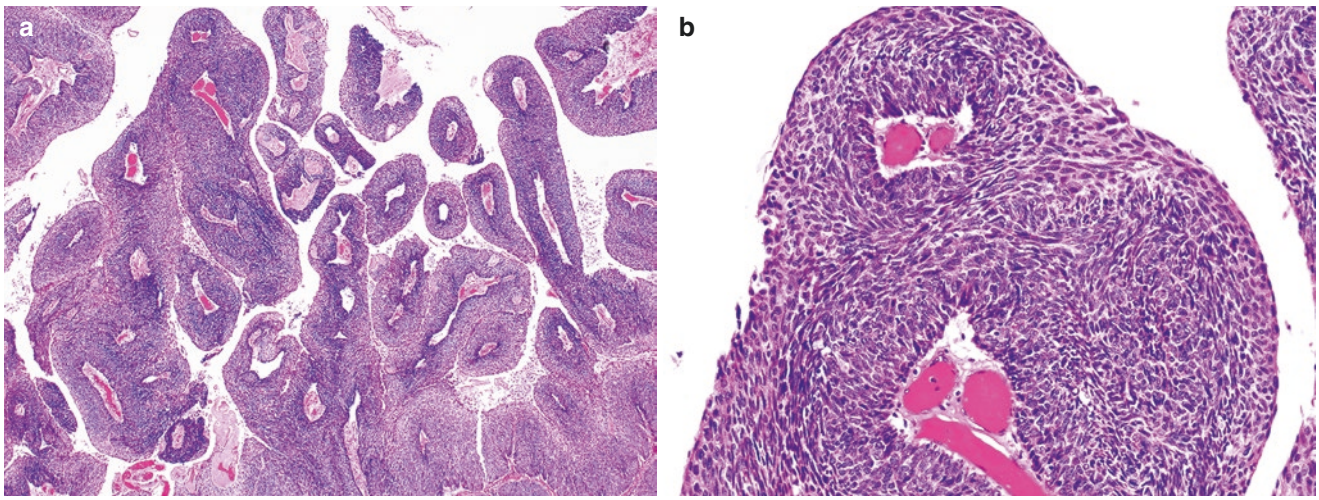


**Fig. 2.5** HPV-associated nonkeratinizing squamous cell carcinoma, papillary variant. (**a**) Proliferation of elongated, slender, papillary fronds with fibrovascular cores. (**b**) The papillae are lined by atypical basaloid cells with a high N:C ratio and coarse chromatin

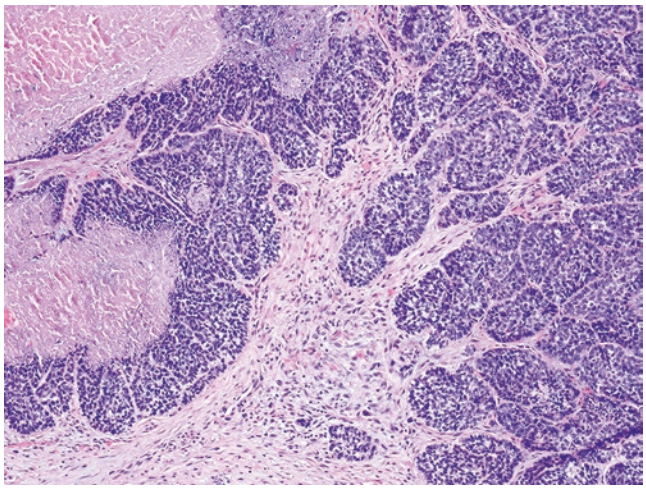

**Fig. 2.6** HPV-associated nonkeratinizing oropharyngeal squamous cell carcinoma, basaloid variant. Tumor nests are arranged in a jigsaw puzzle pattern with peripheral, nuclear palisading and comedo-type necrosis (left)

- Rarely, the tumor can show a hybrid morphology with features of both conventional, keratinizing, and nonkeratinizing squamous cell carcinoma
- Regardless of its morphology, HPV-OPSCC has better clinical outcomes than its HPV-negative counterpart:
  - HPV-OPSCC has a reduced risk of death and treatment failure of 28% and 49%, respectively.
  - Grading of HPV-OPSCC is not recommended, as many may be graded as poorly differentiated, but such a high grade belies the indolent behavior of these tumors.
- HPV-OPSCC can coexist or transform into a small cell variant.
  - The small cell variant comprises small, hyperchromatic nuclei with molding, frequent mitoses, apoptosis, and necrosis.
  - The tumors cells show weak expression of squamous markers (CK5/6, p40, p63) and acquire neuroendocrine markers (synaptophysin, chromogranin, CD56).
  - Unlike other morphologic variants of HPV-OPSCC, the small cell variant has an aggressive clinical behavior including widespread dissemination and poor survival.

References: [4, 11, 17–25]

7. *What are the differences between HPV-associated and non-HPV-associated oropharyngeal squamous cell carcinomas?*

Table 2.3 compares the clinicopathologic features of oropharyngeal SCC associated with and without HPV infection.

References: [5, 12–14, 26]

**Table 2.3** Clinicopathologic features of HPV-associated and non-HPV-associated oropharyngeal squamous cell carcinoma

| Features | HPV-OPSCC | Non-HPV-OPSCC |
|---|---|---|
| Age (median) | 50–56 years | 60–70 years |
| Gender | M:F = 2–3:1 | M:F = 4–5:1 |
| Race | Caucasians > African Americans | Caucasians = African Americans |
| Presenting symptom | Neck mass | Odynophagia |
| Main risk factors | Sexual behavior | Alcohol and tobacco use |
| Dysplasia | Absent | Often present |
| Keratinization | Usually absent | Frequent |
| p16 IHC or HPV in situ hybridization | Positive | Negative |
| Disease extent at presentation | Usually with lymph node metastasis | Any stage |
| Nodal metastasis | Usually cystic | Solid or cystic |
| Therapy | Sensitive to chemoradiation | Usually more resistant to chemoradiation |
| 3-year overall survival | ~80% | ~60% |

*IHC* immunohistochemistry

8. *What is the preferred method for establishing HPV status in an oropharyngeal squamous cell carcinoma?*

Several tests are available to detect the presence of high-risk HPV (HR-HPV) in OPSCC. DNA-based assays establish the presence of HPV genetic material but cannot ascertain whether there is a transcriptionally active form of HPV. Early viral proteins, E6 and E7, interact with the retinoblastoma protein (pRb) and p53, respectively. Increased amounts of both viral proteins are responsible for the tumorigenesis of HPV; their presence confirms transcriptionally active HPV. The E7 protein leads to degradation of pRb resulting in overexpression of p16; this overexpression is an excellent surrogate marker for transcriptionally active HPV.

- p16 immunohistochemistry (IHC) has high sensitivity and specificity for the presence of active HR-HPV.
  - Several large studies report 1–7% of cases will show discordant results between p16 overexpression and all HPV-specific, molecular-based testing methods.
  - Notably, even among HPV-negative cases, p16 overexpression significantly correlates with survival.
- p16 expression correlates strongly with outcomes and provides superior risk stratification when compared to molecular-based, HPV-specific assays. Overexpression of p16 is proven to correlate with:
  1. Overall survival
  2. Disease-free survival
  3. Recurrence-free survival
  4. Disease-specific survival

**Table 2.4** Comparison of HPV detection methods for oropharyngeal SCC

| | RNA methods | | DNA methods | |
|---|---|---|---|---|
| | RT-PCR | mRNA-ISH | DNA PCR | DNA-ISH |
| Sensitivity | High | High | High | Low |
| Specificity | High | High | High | High |
| Advantages | Detects transcriptionally active HPV | Detects transcriptionally active HPV<br>Can view cell morphology<br>Uses FFPE tissue | Sensitive<br>Quantifies viral load<br>Type-specific | Specificity<br>Can view cell morphology |
| Disadvantages | No morphology<br>Requires fresh tissue<br>Complex test | Older methods are technically difficult | No morphology<br>Detects non-clinical infection | Hard to interpret<br>Low sensitivity |

*RT-PCR* reverse transcriptase-polymerase chain reaction, *ISH* in situ hybridization, *FFPE* formalin-fixed, paraffin-embedded

- Positive p16 IHC is defined by the College of American Pathologists (CAP) as diffuse, moderate to strong, nuclear, and cytoplasmic staining in at least 70% of tumor cells (Fig. 2.4d).
  - Partial staining of tumors with p16 is unusual.
- Current National Comprehensive Cancer Network (NCCN) guidelines advocate for the use of p16 IHC alone in the diagnosis and management of OPSCC patients.
- According to CAP 2018 Guidelines, HR-HPV testing is recommended on all newly diagnosed oropharyngeal SCCs. Specific recommendations for HPV-specific molecular testing is addressed in question 9.
  - The CAP recommends routine use of p16 IHC for tissue (i.e., not cytologic) specimens meeting criteria for HR-HPV testing.
  - HR-HPV testing should be performed on cytologic specimens meeting criteria for testing, but a specific methodology is not endorsed by the CAP.
  - The CAP does not recommend repeat HR-HPV testing of recurrent, persistent, or metastatic tumors in which the HPV status of the initial or primary tumor is already known.

References: [5, 27–36]

9. *When is HPV-specific molecular-based testing necessary?*

HR-HPV detection can be performed using a variety of molecular tests (Table 2.4). Even though p16 IHC is the preferred method, it is not specific for the presence of HR-HPV. The use of an HPV-specific, molecular-based assay is particularly helpful in addressing questions related to specificity, such as a tumor site in the case of a large tumor involving multiple anatomic locations. The gold standard assay would directly detect active transcripts (i.e., mRNA) of the viral oncogenes E6 and E7. This includes reverse transcriptase polymerase chain reaction (RT-PCR) and messenger RNA in situ hybridization (mRNA-ISH).

- The CAP provided detailed recommendations for the use of HPV-specific testing in clinical practice (Table 2.5).

**Table 2.5** Summary of CAP recommendations[a] for HR-HPV testing in OPSCC

| | |
|---|---|
| p16 IHC is recommended[a] | Newly diagnosed OPSCC of any histologic subtype<br>Metastatic SCC of unknown primary to cervical LN level 2 or 3<br>Recurrent, persistent, or metastatic OPSCC with unknown *initial* HPV status |
| p16 IHC is *not* recommended | Non-squamous carcinomas of the oropharynx<br>SCC outside of the oropharynx<br>SCC of unknown primary, metastatic to LN *outside* of level 2 or 3<br>Metastatic SCC from a non-oropharyngeal primary |
| p16-positive tumors requiring HPV-specific testing | Tumors involving multiple sites that include the oropharynx<br>SCC of unknown primary, metastatic to an unknown LN level<br>Keratinizing SCC of unknown primary, metastatic to level 2 or 3 LN |

*IHC* immunohistochemistry, *LN* lymph node

[a]p16 use is *recommended* on tissue specimens only. Any method may be used on cytologic specimens, provided it is validated

- Additional indications for HPV-specific testing supported by some authors include:
  1. Negative, weak, or focal p16 IHC of an OPSCC with classic HPV-OPSCC morphology (e.g., basaloid, nonkeratinizing)
  2. p16-positive OPSCC without classic HPV-OPSCC morphology
  3. Metastatic SCC with typical HPV-OPSCC morphology in a neck lymph node with negative or weak p16 staining

References: [32, 36–39]

10. *What is the most common malignancy of the nasopharynx, and what are its epidemiologic characteristics?*

Nasopharyngeal carcinoma (NPC) is the most common epithelial malignancy of the nasopharynx. It shows some evidence of squamous differentiation either by

morphology, immunohistochemistry, or electron microscopy.

- Patients are typically male in the fourth to sixth decades of life.
- NPC is rare in the United States among white patients.
- The incidence of NPC is highest among populations of the Arctic Circle, North Africa, and Southeast Asia.
  - Endemic forms of NPC are usually nonkeratinizing and are strongly associated with Epstein-Barr virus (EBV) infection.
    - 90% of NPCs in Asian populations are nonkeratinizing (NK-NPC) versus 60% in white patients.
  - Additional risks factors include genetic predisposition and ingestion of salted and fermented foods.
    - Familial cases exist, and studies show that NPC is related to increased frequencies of specific HLA alleles (HLA-A2, HLA-B46, HLA-B17) and susceptibility loci on chromosomes 3, 4, and 14.
- Most patients (~50%) present with cervical lymph node metastasis (usually level 2 – jugulodigastric nodes) and advanced local disease.
  - Presenting symptoms include nasal obstruction or discharge, epistaxis, hearing impairment, diplopia, neck mass, and headache.
  - Over two-thirds of the NK-NPCs arise in the fossa of Rosenmüller. Biopsies at this site may yield a positive result, even in the absence of a clinically apparent lesion.

References: [40–45]

11. *What are the different subtypes of nasopharyngeal carcinoma?*

According to the 2017 WHO classification, NPC comprises four subtypes: keratinizing, differentiated nonkeratinizing, undifferentiated nonkeratinizing (Fig. 2.7), and basaloid. The clinicopathologic features of the non-basaloid types are described in Table 2.6.

- The presence of keratinization by light microscopy is an essential feature that distinguishes the EBV-associated forms from the other NPCs.
  - Keratinization may be seen in NK-NPC, but it should be focal or subtle. While keratinizing NPC (K-NPC) shows frank, obvious keratin formation.
  - A large population-based analysis by Ou et al. shows statistically significant differences in 5-year survival rates between the undifferentiated (68.1%) and differentiated (57.6%) NK-NPC. But this difference is less evident in endemic regions and as an independent prognosticator.
- Other uncommon morphologic variants of NK-NPC include spindled, pleomorphic, and papillary types.
- NPC expresses squamous IHC markers including strong, diffuse staining for p63 and p40 (Fig. 2.7d, e).
  - EBV detection by in situ hybridization for EBV-encoded small RNA (EBER) is considered to be the most reliable test (Fig. 2.7f).
  - IHC for latent membrane protein 1 (LMP1) and PCR for EBV, both lack sensitivity, and specificity.
- Basaloid NPC is morphologically identical to basaloid squamous cell carcinoma at other sites. It is very rare and limited to a handful of case reports.
  - Among the reported cases, basaloid NPC is associated with EBV in Asian patients.
  - Tumors are composed of basaloid cells arranged in nests with peripheral palisading.
  - Abrupt squamous differentiation is present with keratinization, dyskeratosis, and keratin pearl formation.
  - Comedo necrosis and stromal hyalinization is common.
- The clinical stage at presentation is the most powerful prognosticator for NPC.
  - Five-year survival rates range from 98% in stage I to as low as 50% in stage IV disease.
  - Ten-year overall survival rates average 35–50% based on stage and treatment modalities.

References: [9, 43, 44, 46–50]

12. *What entities are in the differential diagnosis of nonkeratinizing nasopharyngeal carcinoma?*

The differential diagnosis of nonkeratinizing nasopharyngeal carcinoma includes undifferentiated carcinomas of the head and neck as well as lymphoma, melanoma, and rhabdomyosarcoma. The latter three can be easily distinguished with lineage-specific IHC. Table 2.7 lists entities in the differential diagnosis for NK-NPC and their immunoprofile. A few important points are considered below:

- A subset of NPC is EBV-negative and HPV-positive. These tumors are typically in white males and show a mixture of K-NPC and NK-NPC.
  - Awareness of this entity is important when an EBV-negative NK-NPC is encountered and should be distinguished from an HPV-OPSCC.
  - Small series show no significant differences in outcomes between HPV-positive and HPV-negative NPC.
- Lymphoepithelial carcinoma (LEC) is morphologically identical to undifferentiated NK-NPC but occurs in locations outside of the nasopharynx. LEC of the sinonasal tract and those found in endemic areas are generally EBV-positive.

References: [48, 51–56]

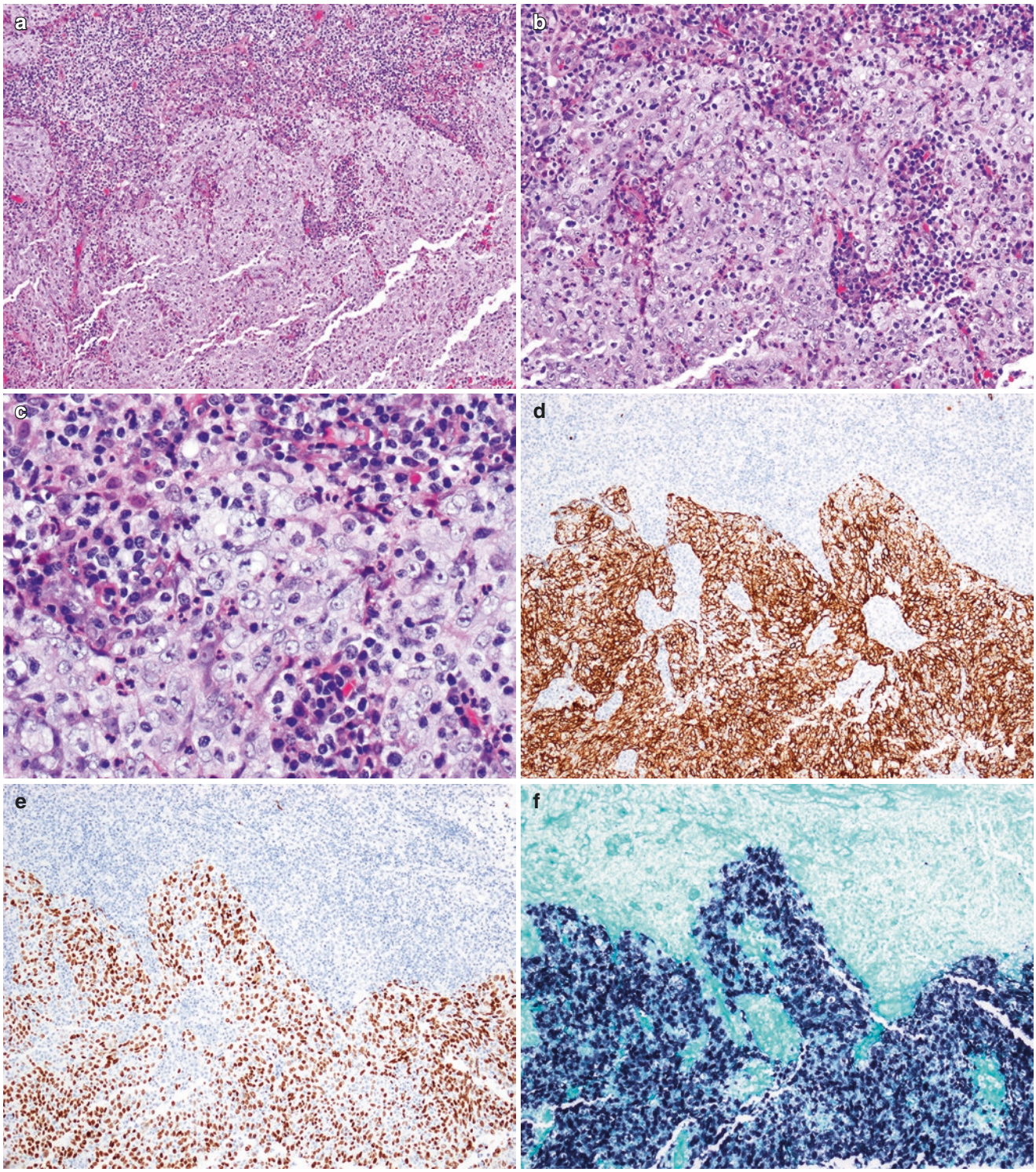


**Fig. 2.7** Nasopharyngeal carcinoma, nonkeratinizing, undifferentiated. (**a**) Large sheets of tumor cells in a dense lymphoid stroma. (**b**) The tumor cells have indistinct cell borders imparting a syncytial pattern. Numerous mitoses and apoptotic bodies are noted. (**c**) The tumor cells have a high nuclear: cytoplasmic ratio and contain amphophilic cytoplasm, round to irregular vesicular nuclei, and prominent nucleoli. The neoplastic cells are (**d**) diffusely positive for CK5/6 and (**e**) nuclear p40. (**f**) EBV-encoded small RNA (EBER) in situ hybridization is positive in tumor nuclei

**Table 2.6** Clinicopathologic features of nasopharyngeal carcinoma subtypes

| Features | Keratinizing NPC | Nonkeratinizing NPC, differentiated | Nonkeratinizing NPC, undifferentiated |
|---|---|---|---|
| Percentage of all NPC | ~25% | ~15% | ~60% |
| EBV association | Weak in non-endemic areas | Strong (~100%) | Strong (~100%) |
| Risk factors | Smoking<br>Alcohol intake | Ethnic: Inuit, Asian, N. African<br>Genetic: HLA antigens, chr. 3, 4, 14<br>Environmental: salted fish | |
| Disease at presentation | Locally advanced (75%) | LN metastases (70%) | LN metastases (70%) |
| Keratinization | Yes | Minimal to absent | Minimal to absent |
| Desmoplasia | Yes | No | No |
| Morphology | Conventional SCC<br>Polygonal cells, abundant eosinophilic cytoplasm<br>Intercellular bridges | Uniform cells, a moderate amount of cytoplasm<br>Round to oval, vesicular nuclei<br>Conspicuous nucleoli<br>Irregular nests, sheets in a pavement pattern<br>Sharp distinction from lymphoplasmacytic infiltrate | Large cells, scant eosinophilic cytoplasm<br>Round nuclei, even to vesicular chromatin, prominent nucleoli<br>Syncytial nests, sheets of dyshesive cells merge with dense lymphoplasmacytic infiltrate |
| Treatment response | Generally less radiosensitive | Radiosensitive | Radiosensitive |

*Chr* chromosome, *LN* lymph node

**Table 2.7** Immunoprofile of tumors in the differential diagnosis of nonkeratinizing-nasopharyngeal carcinoma

| | Nasopharyngeal carcinoma | Oropharyngeal SCC | Sinonasal undifferentiated carcinoma | Lymphoepithelial carcinoma | NUT midline carcinoma | NK/T-cell lymphoma |
|---|---|---|---|---|---|---|
| panCK | + | + | + | + | + | – |
| p63 | + | + | –/focal | + | + | – |
| CK5/6 | + | + | – | + | nd | – |
| p16 | –[a] | + | Rare+ | – | –[a] | – |
| EBV | + | – | – | + | – | + |
| Lymphoid markers | – | – | – | – | – | + |
| Other | Rare EBV-/HPV+ cases | | Focal NE marker+ | | NUT Mab C52+ | |

*CK* cytokeratin, *nd* no data, *Mab* monoclonal antibody, *NE* neuroendocrine
[a]Rare positive cases

13. *What are the most common adenocarcinomas of the pharynx?*

Pharyngeal adenocarcinomas are generally divided into surface epithelial carcinomas and salivary gland (SG) carcinomas.

- Adenocarcinomas of the OP are predominantly of SG origin and account for 3% of all carcinomas at that site.
  - Goel et al. reviewed population-based data for OP salivary gland tumors over a 25-year period (Table 2.8).
  - Histologic features of the salivary gland tumors are similar to those at major salivary gland sites. A detailed discussion of salivary gland tumors can be found in Chapter 5.
- Adenocarcinomas of the NP account for less than 1% of all NP carcinomas; the majority of these are also of SG origin. Adenoid cystic carcinoma is the most common subtype at this location. A much rarer adenocarcinoma of the NP is the nasopharyngeal papillary adenocarcinoma (NPPA).
  - NPPA is a low-grade tumor that occurs at any age and demonstrates no gender preference.
  - Tumors are composed of delicate, branching papillae lined by a single layer of cuboidal to columnar cells with hyalinized fibrovascular cores.

**Table 2.8** Characteristics of salivary gland carcinomas in the oropharynx

| Frequency of MSG carcinomas by site | | Frequency of MSG carcinomas by type | |
|---|---|---|---|
| Soft palate | 39.2% | Mucoepidermoid carcinoma | 32% |
| Base of tongue | 38.6% | Adenocarcinoma, NOS | 25.9% |
| Tonsil | 16.3% | Adenoid cystic carcinoma | 23.3% |

*MSG* minor salivary gland

- Cells have a moderate amount of eosinophilic cytoplasm. The nuclei are round to oval with fine chromatin and irregular membranes. The features are similar to papillary thyroid carcinoma.
- NPPA expresses CK7, EMA, and CK19 with some cases staining for TTF-1 and CK5/6.
- NPPA cells are negative for Pax-8 and thyroglobulin.
- In contrast to minor SG carcinomas at this location, NPPA has an excellent prognosis with no reports of recurrences or metastases.

References: [52, 57–62]

14. *What are the significant, recent changes to the staging of pharyngeal carcinomas?*

In the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual (2018), a different staging system for pharyngeal carcinomas was established. It largely centers around differences in tumor site, viral pathogenesis, and nodal status.

- HPV-negative OPSCC and hypopharyngeal carcinomas remain under the same staging system given their similar risk factors and tumor biology
- HPV-positive OPSCC is staged separately from HPV-negative OPSCC and hypopharyngeal carcinomas. Table 2.9 lists the differences in the pathologic staging of these two carcinomas.
- Changes to NPC staging include:
  - pT0 staging is added for cases with EBV-positive cervical LN metastases and no known primary; the pTX designation remains.
  - Size, lowest nodal level, and laterality of the metastasis are required for nodal staging.

References: [1, 2, 63–66]

15. *What are the clinical and pathologic characteristics of juvenile (nasopharyngeal) angiofibroma?*

Nasopharyngeal angiofibroma is a locally aggressive, fibrovascular tumor which is seen almost exclusively in young males, typically less than 20 years old. Current World Health Organization (WHO) nomenclature refers to these tumors as juvenile angiofibromas (JAF).

**Table 2.9** Differences in pathologic staging of oropharyngeal squamous cell carcinoma

| HPV-positive OPSCC | HPV-negative OPSCC |
|---|---|
| pT0 staging is added for cases with cervical LN metastases and no known primary; pTX is eliminated<br>The presence of ENE is no longer considered for nodal staging<br>pN3 is eliminated – high numbers of metastatic lymph nodes is a key prognosticator, rather than the size of metastatic focus, laterality or ENE | pTX – the unknown primary tumor designation remains<br>pTis (in situ carcinoma) is added<br>pN nodal status is upstaged based on increased numbers of metastatic lymph nodes, size of metastatic focus, laterality, and presence of ENE |

*LN* lymph node, *ENE* extranodal extension

- Patients present with epistaxis, nasal obstruction, and a nasopharyngeal mass.
  - JAF may also occur in the posterolateral nasal cavity.
  - Large tumors can invade adjacent sinuses or the middle cranial fossa.
  - Rarely, JAF has been reported in older females.
- JAF is composed of variably sized blood vessels in a fibrocollagenous stroma (Fig. 2.8).
  - The vascular spaces vary in size and thickness.
  - Stromal fibroblasts are bipolar or stellate-shaped with spindled nuclei that may be small and hyperchromatic or plump and vesicular with conspicuous nucleoli.
  - The stroma may vary from edematous to collagenous with a hypervascular periphery and a hypovascular center.
  - Mitotic figures are usually absent, and atypia is absent or minimal.
  - Scattered mast cells and multinucleated stromal giant cells can be seen.
- JAF is a hormone-driven tumor which responds to treatment with androgen antagonists.
- Isolated reports show an association between JAF and familial adenomatosis polyposis.
- Recurrences occur in 5–25% of patients with higher rates noted in incompletely resected tumors.

References: [67–72]

16. *What is the differential diagnosis of juvenile angiofibroma, and which immunohistochemical stains are helpful in the diagnosis?*

The clinicopathologic features of juvenile angiofibroma will usually lead to a straightforward diagnosis. However, large tumors involving more than one site may raise other diagnostic considerations (Table 2.10).

References: [73–79]

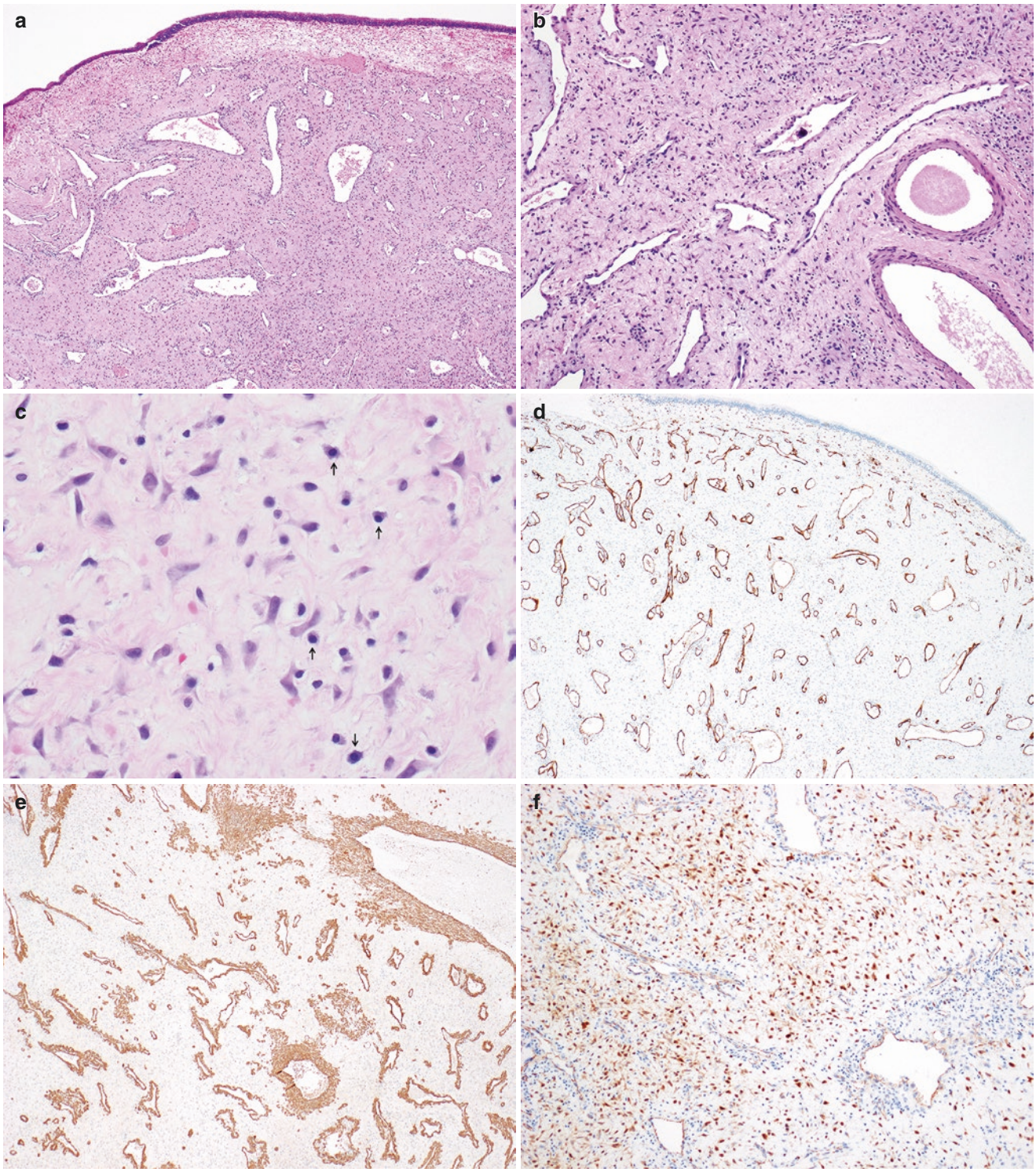


**Fig. 2.8** Juvenile angiofibroma. (**a**) A circumscribed submucosal, spindled tumor with (**b**) variably sized, branching and slit-like vessels lined by bland plump endothelial cells without atypia. (**c**) The cellular stroma comprises spindle to stellate fibroblasts/myofibroblasts and admixed mast cells (arrows) in a loose collagenous to myxoid stroma. The vasculature is more confluent at the tumor edge. (**d**) CD31 and (**e**) SMA highlight endothelial cells of the blood vessels while the stromal cells are negative. (**f**) A beta-catenin stain shows nuclear localization in the stromal cells

**Table 2.10** Entities in the differential diagnosis of nasopharyngeal angiofibroma

| | Juvenile angiofibroma | Solitary fibrous tumor | Glomangiopericytoma (sinonasal HPC) | Aggressive fibromatosis |
|---|---|---|---|---|
| Gender, age (years) | M, teen-aged | F > M, middle-aged | F > M, middle-aged to elderly | M/F, 40–50, children |
| Site | Nasopharynx<br>Posterolateral nasal cavity | Paranasal sinuses<br>Mouth | Nasal cavity<br>Paranasal sinuses | Nasal cavity<br>Paranasal sinuses |
| Morphology | Bland spindle cells focally arranged around vessels<br>Giant cells and multinucleated cells are present | Bland, short, spindle cells randomly arranged | Uniform, oval to short spindle cells<br>Solid, fascicular, or whorled pattern | Uniform, short spindle cells<br>Herringbone, storiform, or broad fascicles infiltrative borders |
| Stroma | Collagenous and hypocellular to edematous and hypercellular | Collagenous hypo- and hypercellular areas | Minimal | Dense, collagenous |
| Vessels | Numerous; small irregular, slit-like or dilated, ±muscular wall | Focally prominent, thick-walled, ±branching | Prominent; branching, "staghorn," without muscular walls | Inconspicuous, compressed |
| Positive IHC | (n)β-catenin, AR, ±SMA | CD34, CD99, Bcl-2, (n)STAT6, vimentin | Vimentin, SMA, fXIIIa, rare CD34, rare S100 | (n)β-catenin, strong vimentin, f. SMA, f. desmin |
| Negative IHC | CD34, desmin, S100 | (n)β-catenin, desmin, SMA, S100, fVIII-RA | bcl-2, CD31, desmin, EMA, fVIII-RA | CD34, S100, STAT6, bcl-2 |

*HPC* hemangiopericytoma, *M* male, *F* female; *(n)* nuclear, *SMA* smooth muscle actin, *f* focal, *RA* related antigen, *AR* androgen receptor

17. *What are the common hematolymphoid tumors of the pharynx?*

Waldeyer ring (WR) is the second most common site for extranodal, non-Hodgkin lymphomas (after the gastrointestinal tract) and it is the most common head and neck location for extranodal lymphomas. It harbors approximately 50% of all such lymphomas in this region. Chapter 10 includes a more detailed discussion of hematolymphoid tumors. Concerning the OP and NP, a few essential points will be mentioned here.

- Diffuse large B-cell lymphoma is by far the most common type of lymphoma in the OP and NP accounting for as much as 80% of the lymphomas.
  - The sites of involvement in order of frequency are palatine tonsil and nasopharynx.
  - Tonsillar lymphoid hyperplasia secondary to EBV infection (mononucleosis) and NK-NPC pose particular differential diagnostic challenges in this area.
  - Other lymphomas in this region include:
    - Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is the second most common type of lymphoma of WR.
    - Peripheral T-cell lymphoma.
    - Burkitt lymphoma – the endemic type has a predilection for the head and neck. It is the most lymphoma of WR in children.
    - Mantle cell lymphoma – head and neck is the most common extranodal site.
- Nasopharyngeal and oropharyngeal extraosseous plasmacytomas account for up to 20% of all head and neck extraosseous plasmacytomas.
- Hodgkin lymphoma is exceedingly rare in this region.

References: [80, 81]

18. *What are the primary tumors that can metastasize to the oropharynx?*

Metastases to the tonsils are extremely rare and mainly involve the base of the tongue and palatine tonsils.

- Metastases to the base of the tongue comprise approximately a third of all tongue metastases.
  - The most common primary sites are the lung, kidney, and skin (melanomas).
- Metastases to the tonsils comprise less than 1% of all tonsillar tumors, with approximately 100 cases reported in the literature.
  - The skin (melanoma), lung, breast, and kidney are the most frequent primary tumor sites.
  - Rare sites such as the gastrointestinal tract, prostate, and thyroid have also been reported.
- A metastasis to the oropharynx portends a fatal outcome with a mean survival of just a few months.

References: [82–86]

## Case Presentations

### Case 1

**Learning Objectives**

1. To become familiar with the clinical presentation and histologic features of pharyngeal tumors
2. To become familiar with the immunohistochemical features of these tumors

**Case History**

A 48-year-old man presents with a slow-growing neck mass he discovered while shaving. He noticed the mass 4 months ago. On clinical examination, a 3.5 cm mass is noted in the left neck at level 2.

**Gross Findings**

A 3.5 cm lymph node is sectioned to reveal a cystic, firm, tan-white mass with central necrosis.

**Histologic Findings** (Fig. 2.9a)

Ribbons and nests of basaloid tumor cells in a lymph node with extensive necrosis

**Differential Diagnosis**

- Metastatic nasopharyngeal carcinoma, nonkeratinizing undifferentiated type
- Metastatic oropharyngeal carcinoma

**IHC and Other Ancillary Studies** (Fig. 2.9b)

- Positive: CKAE1/CKAE3, CK5/CK6, p40, and p16
- Negative: EBV in situ hybridization (EBER)

**Final Diagnosis** *Metastatic non-keratinizing squamous cell carcinoma, HPV-associated, likely from oropharyngeal primary*

**Take-Home Messages**

1. The location of the lymph node and the cystic morphology are characteristic of nonkeratinizing squamous cell carcinoma of oropharyngeal primary.
2. Oropharyngeal squamous cell carcinoma can present primarily as cervical lymph node metastasis, especially at levels 2 and 3. The metastases tend to be bulky and cystic.
3. According to CAP 2018 Guidelines, p16 IHC is recommended for metastatic squamous cell carcinoma of unknown primary to cervical lymph nodes at levels 2 or 3 (see Table 2.5).
4. Positive p16 immunohistochemistry is defined as diffuse, moderate to strong, nuclear, and cytoplasmic staining in at least 70% of tumor cells.
5. If the p16 staining is weak or negative and the tumor shows typical nonkeratinizing morphology, HPV-specific testing such as mRNA-ISH or DNA-ISH should be performed.
6. EBER staining may also be performed to exclude metastasis from a nasopharyngeal primary.

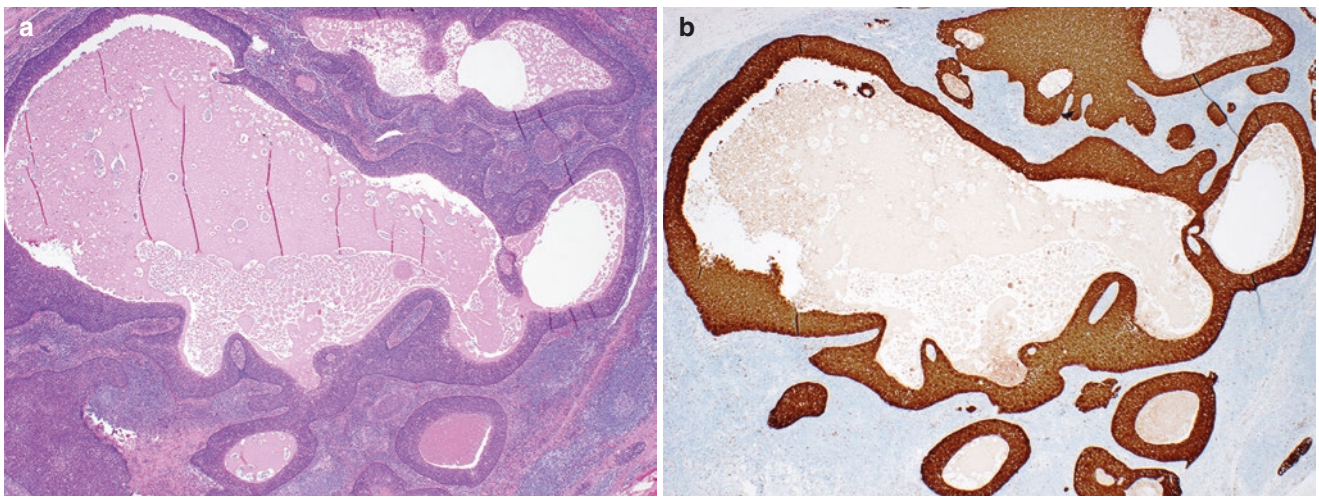


**Fig. 2.9** Case 1. (**a**) Metastatic nonkeratinizing squamous cell carcinoma to a cervical lymph node shows cystic change with central necrosis and ribbons of neoplastic cells. (**b**) p16 IHC shows strong and diffuse, block positivity (both nuclear and cytoplasmic) in the tumor cells

7. HPV-associated OPSCC has better outcomes compared to their HPV-negative counterparts.

References: [27–29, 31–33]

## Case 2

### Learning Objective

1. To determine the indications for molecular testing of high-risk HPV oropharyngeal squamous cell carcinomas

### Case History

A 56-year-old male presents with complaints of a sore throat when swallowing. Physical exam shows asymmetry of the base of the tongue. Palpation of the left tongue base is firm. Biopsies are taken, and radiologic studies are ordered.

### Gross Findings

Firm, tan-white tissue fragments aggregating 1.0 cm

### Histologic Findings (Fig. 2.10a, b)

Sections show a nonkeratinizing squamous cell carcinoma with basaloid morphology making up approximately 30% of the tumor. The basaloid component is nested with abrupt foci of keratinization. The cells have a high N:C ratio with hyperchromatic nuclei showing peripheral palisading. The keratinizing component comprises large, polygonal cells with abundant, eosinophilic cytoplasm, vesicular nuclei, and conspicuous nucleoli.

### Differential Diagnosis

- HPV-associated SCC
- SCC, not associated with HPV

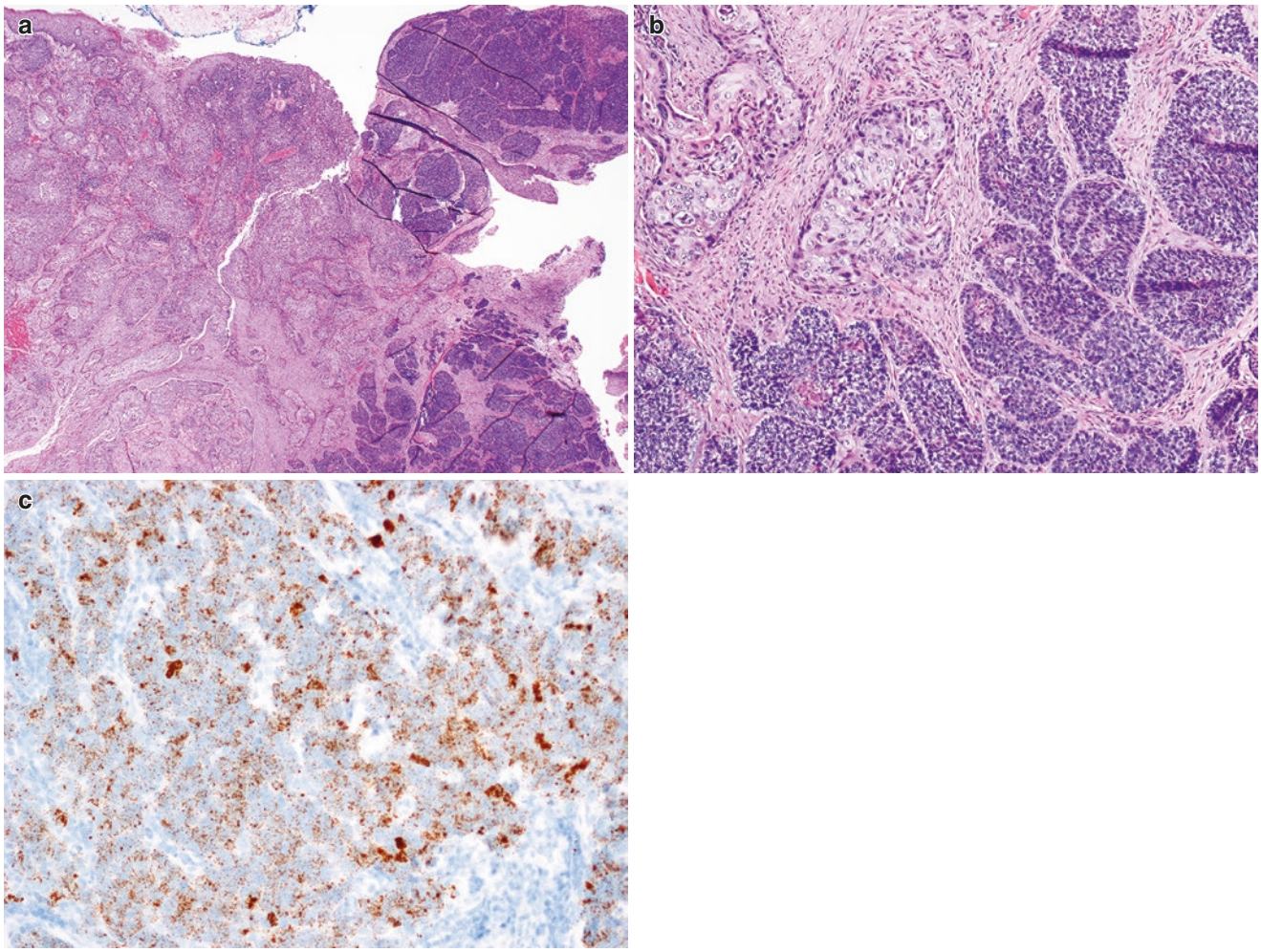


**Fig. 2.10** Case 2. (**a**) Sections show a more eosinophilic keratinizing SCC on the left with a more basophilic, nonkeratinizing basaloid SCC on the right. (**b**) The carcinoma shows a desmoplastic stroma with nests of keratinizing SCC (left) with abrupt transition to a nonkeratinizing component (right). (**c**) The neoplastic cells show diffuse signals for E6 and E7 messenger RNA by in situ hybridization

**IHC and Other Ancillary Studies** (Fig. 2.10c)
- Strong, diffuse p16 staining is noted in the basaloid portions of the tumor, with weaker staining in the keratinizing component (not shown).
- HR-HPV RNA ISH shows diffuse, strong expression in tumor cells in both components.

**Final Diagnosis** *HPV-associated oropharyngeal squamous cell carcinoma, with hybrid morphology*

**Follow-Up** Computed tomography (CT) revealed a left neck mass and negative lung findings.

**Take-Home Messages**
1. The morphology of this tumor is unusual with two different and distinct patterns. The basaloid component was a minor portion of the tumor. Hybrid carcinomas of the oropharynx comprise approximately 15% of all OPSCC. Similar to the NKSCC at this site, the hybrid carcinomas are more likely to be associated with HPV, though not as frequent as the nonkeratinizing type.
2. This clinical scenario, in which a p16-positive tumor has an unusual morphology, is a reasonable indication for HPV-specific molecular testing.

References: [28, 36–38, 87, 88]

## Case 3

**Learning Objective**
1. To become familiar with the differential diagnosis of non-squamous lesions of the oropharynx

**Case History**
A 68-year-old male presents with a sore throat and a globus sensation on swallowing. Physical exam reveals an enlarged left tonsil. Biopsies are taken and reveal a neoplastic process. He is referred to a tertiary care center for further management where a tonsillectomy is performed.

**Gross Findings**
A fleshy, enlarged 2.8 cm tonsil is noted with a tan-white, solid cut surface and focal ulceration.

**Histologic Findings** (Fig. 2.11a, b)
A solid sheet of epithelioid tumor cells arranged in sheets, and trabeculae are present in the submucosa obliterating the normal lymphoid stroma. The severely atypical cells are large and polygonal with a moderate amount of amphophilic cytoplasm, round nuclei, and prominent central nucleoli. Glandular and squamous differentiation are not identified.

**Differential Diagnosis**
- Nonkeratinizing squamous cell carcinoma
- Poorly differentiated carcinoma from an adjacent site
- Poorly differentiated carcinoma of salivary gland origin
- Metastatic carcinoma
- Non-epithelial malignancy: high-grade lymphoma, sarcoma, or melanoma

**IHC and Other Ancillary Studies** (Fig. 2.11c, d)
- Positive: S100 and HMB45
- Negative: pan-cytokeratin

**Final Diagnosis** *Metastatic melanoma to palatine tonsil*

**Follow-Up** The patient chart was reviewed, given the unusual morphology of the tumor. The patient reported a remote history of an eyelid melanoma. Positron emission tomography (PET) scan reveals lung and gallbladder metastases.

**Take-Home Messages**
1. SCC is overwhelming the most common oropharyngeal tumor. The histomorphology of OPSCC is usually not a diagnostic challenge. When a malignancy found at this site does not show classic morphologic features of SCC, the differential diagnosis must be expanded.
2. The oropharynx is adjacent to a handful of anatomic sites, and it may be secondarily involved by a tumor from the nasopharynx or oral cavity (e.g., retromolar trigone, hard palate). Primary tumors at these sites may include squamous cell carcinomas as well as primary minor salivary gland carcinomas (retromolar trigone, palate). Immunohistochemical stains for squamous markers will aid in the diagnosis.
3. Metastases to the tonsils are rare but should also be considered in this case. Skin melanomas are among the more common primary malignancies to metastasize to the tonsil. The negative pan-cytokeratin should prompt the use of additional IHC stains. It is always important to order a pan-cytokeratin in this setting, as more specific keratins may show equivocal staining which can confound the diagnostic picture.

References: [82, 85, 86, 89]

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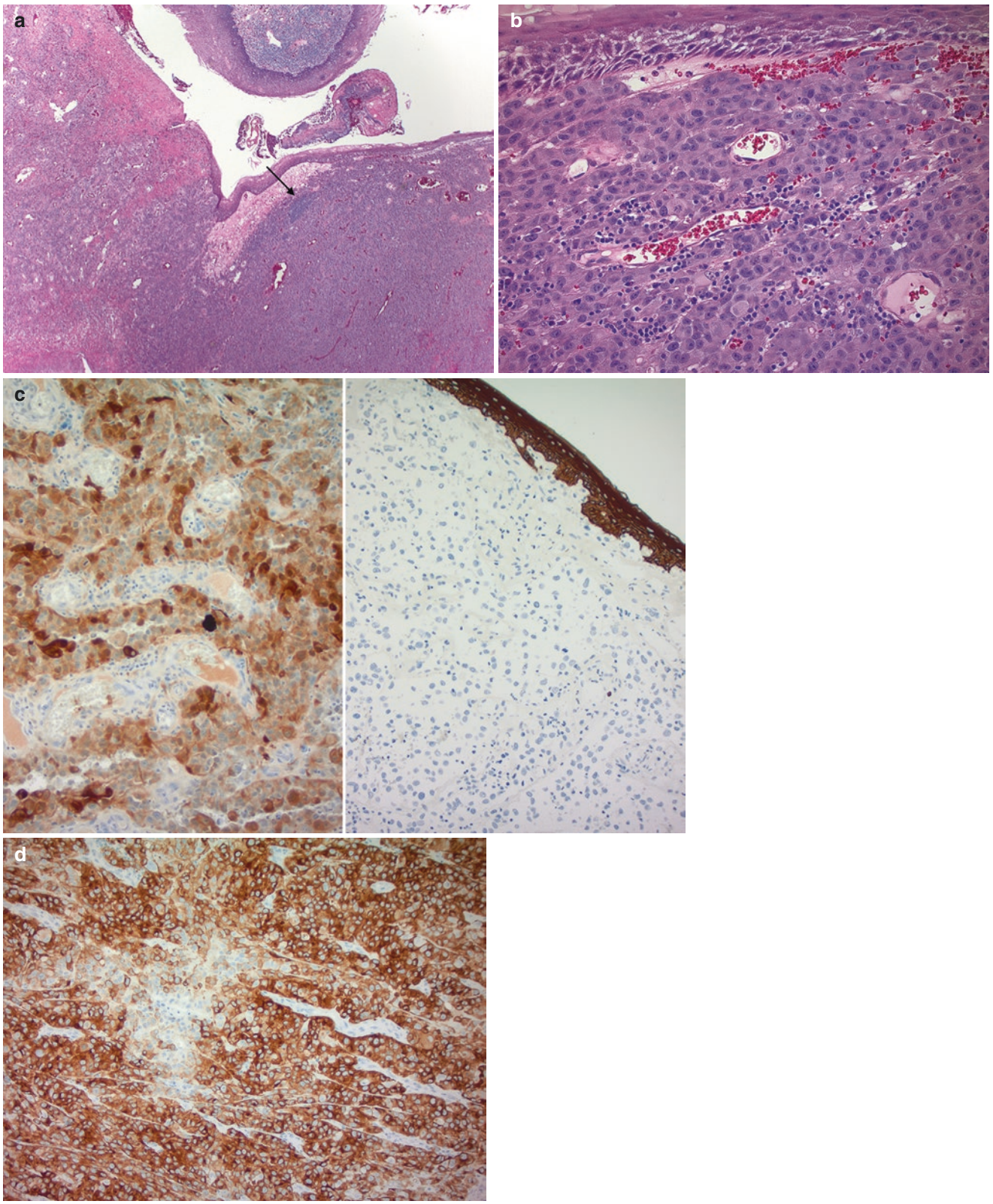


**Fig. 2.11** Case 3. (**a**) Ulcerated tonsil with sheets of large, epithelioid cells replacing the normal lymphoid stroma. A small focus of residual lymphoid tissue (arrow) remains. (**b**) The tumor cells are large, with a moderate amount of cytoplasm, pleomorphic nuclei with prominent nucleoli. (**c**) The tumor cells are positive for S100 (left) and negative for pan-cytokeratin (right). (**d**) A stain for HMB45 is diffusely positive

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# Larynx

3

Xiaoyin "Sara" Jiang

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1. *What are the causes of infectious laryngitis?*

Infectious laryngitis (and pharyngitis and epiglottitis) is caused by a variety of viruses, bacteria, and fungi. The clinical presentation is dependent on the site of inflammation and causal organism.

- Croup typically occurs in the pediatric population, with symptoms of stridor and a "barking" cough:
  - Viruses are generally the culprit, with parainfluenza viruses 1 and 2 and influenza A being the most common. RSV, adenovirus, and enterovirus may cause croup as well.
  - Characteristic radiographic finding is the "steeple sign": a tapered narrowing of the subglottis.
- Acute epiglottitis also mainly affects children:
  - Symptoms include airway obstruction with a "hot potato voice," high fever, and drooling.
  - Rapid progression may be life-threatening. Epiglottic erythema is present on laryngeal examination with a characteristic radiographic "thumb sign" of an enlarged epiglottis.
  - Haemophilus influenzae type B is the most common etiologic agent.
- Pertussis is caused by *Bordetella pertussis*. In children, the classic "whooping cough" is seen with fever, while the presentation in adults may be a prolonged cough.
- Laryngeal tuberculosis may be a consequence of pulmonary tuberculosis or present independently of pulmonary disease:
  - Lesions may be nodular or ulcerated and can mimic carcinoma clinically.
  - Biopsy shows necrotizing granulomata with scattered giant cells, and special stains for acid-fast bacilli may help demonstrate the causative organisms.
- *Treponema pallidum* is the causative agent in syphilis which progresses in three stages:

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  - Primary syphilis is characterized by a painless ulcer at the inoculation site, which may occasionally be the oral cavity.
  - Secondary syphilis may present as systemic systems of fever, headaches, and rash. It occurs weeks to months after the initial infection.
    - Laryngeal hyperemia may be present at this stage along with raised, flat-topped mucosal lesions on the epiglottis.
  - Tertiary syphilis is characterized by gummas, which are granulomatous nodules occurring in various parts of the body. Gummas may heal with scarring. In the larynx, this can lead to the destruction of the laryngeal cartilage and laryngeal stenosis.
    - Biopsy findings depend on the stage of the lesion. A dense lymphoplasmacytic infiltrate may be present at all stages. Granulomatous inflammation may be seen in secondary or tertiary syphilis.
    - Silver stains or immunohistochemical (IHC) stains may be used to demonstrate microorganisms. They tend to be sparse and may be hard to identify.
- Candida is a normal component of oral flora and often causes opportunistic infections in immunocompromised hosts:
  - White plaques or leukoplakia are the characteristic endoscopic findings and biopsy demonstrates pseudohyphae and yeast forms.
  - The organism may be seen on routine hematoxylin and eosin (H&E) stains though special stains for fungus (GMS, Gomori methenamine silver, or PASD, periodic acid-Schiff with diastase) may aid in the identification.
- Blastomycosis is endemic to the Ohio and Mississippi River valleys and the southeastern United States. The causative agent is *Blastomyces dermatitidis*, a fungus that lives in soil. Infection is caused by direct inoculation or through inhalation:
  - Tissue reaction is characterized by a granulomatous response which may involve the larynx.
  - Laryngeal blastomycosis results in a mass lesion that may be erythematous and can mimic carcinoma.
  - Unfortunately, the histology of these lesions may also mimic carcinoma, as Blastomyces induces florid pseudoepitheliomatous hyperplasia with hyperkeratosis.
  - Fungal stains may be used to demonstrate the 8–12 μm broad-based budding yeast forms which have a "double cell wall" appearance.

References: [1, 2]

2. *What are common causes of laryngeal inflammatory disorders?*

Noninfectious laryngeal inflammation has some common causes, including reflux laryngitis, amyloidosis, autoimmune disease, and iatrogenic causes.

- Reflux laryngitis is caused by gastroesophageal reflux which occasionally reaches the level of the larynx.
  - Symptoms include hoarseness, dysphagia, and a globus sensation.
  - Patients with reflux laryngitis may not describe symptoms of heartburn or indigestion.
  - Endoscopically, laryngitis is noted with erythema and edema of the posterior portions of the vocal cords.
  - Vocal cord polyps or nodules may also be present.
- Laryngeal amyloidosis is usually a localized form of amyloidosis not associated with systemic disease.
  - Hoarseness is a common presenting symptom, and immunoglobulin light and heavy chain (AL/AH) amyloid is most common.
  - Patients present with a nodule or a diffusely infiltrating process of the larynx.
  - The false cord is the most common site followed by true cord and ventricle.
  - Biopsy demonstrates amorphous, waxy eosinophilic material which can form a mass and be present in a perivascular distribution.
  - The amyloid shows positive staining with Congo Red (Fig. 3.1) and the classic "apple-green" birefringence under polarized light microscopy.
- Autoimmune disorders: Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Wegener granulomatosis (WG) also known as granulomatosis with polyangiitis, may all show manifestations in the larynx.
  - The nodules of rheumatoid arthritis (RA) may be histologically identical to those in SLE, showing a central area of fibrinoid necrosis in the submucosa, rimmed by palisading histiocytes and chronic inflammatory cells.
  - The classic triad of histologic findings in WG consists of granulomatous inflammation, vasculitis, and necrosis. The vasculitis affects small-to-medium-sized vessels.
    - Despite this classic description, all three features rarely coexist in a given biopsy, and the diagnosis of WG is made by integrating biopsy findings with serologic studies and clinical parameters. A more detailed discussion of WG can be found in Chap. 4.
    - Sarcoidosis is a systemic disease characterized by granulomatous inflammation in a variety of

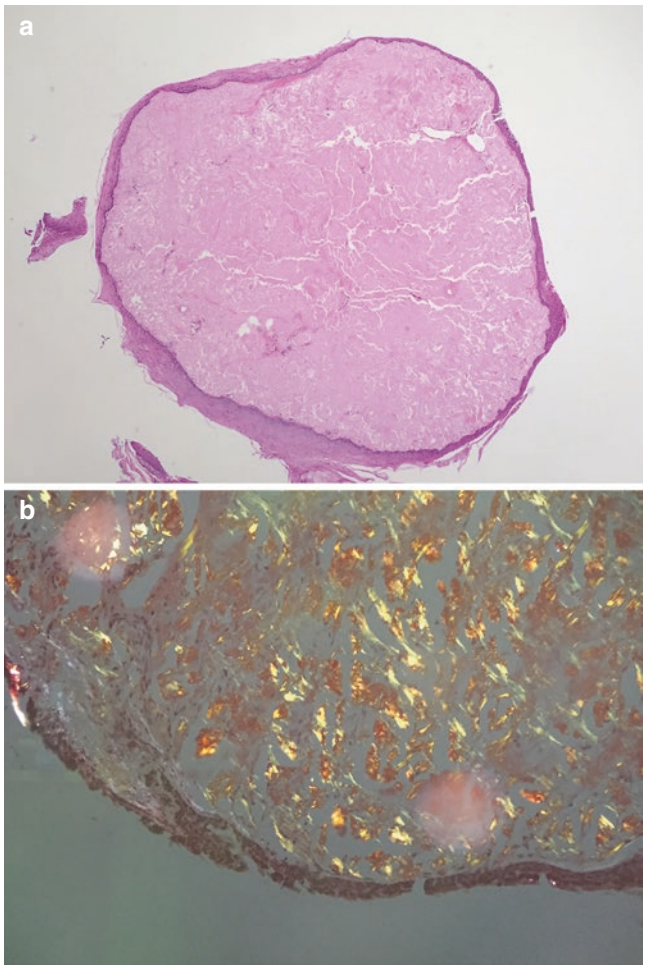


**Fig. 3.1** Laryngeal amyloidoma. (**a**) Low magnification shows replacement of the submucosa by amorphous pink material. (**b**) A Congo Red stain is positive for amyloid and demonstrates "apple-green" birefringence under polarized light microscopy

organs. In the larynx, granulomatous involvement may lead to airway compromise.
  - Histologic examination reveals non-necrotizing, well-formed granulomas, which may be hyalinized. Giant cells with starlike inclusions ("asteroid bodies") may be seen but are not specific for sarcoidosis.
  - Infectious etiologies including mycobacteria and fungal infections should be excluded with acid-fast bacilli (AFB), PASD, and GMS stains.
- Tracheopathia osteoplastica (TPO) is also known as tracheobronchopathia osteochondroplastica or tracheopathia chondro-osteoplastica. TPO is a rare benign disease of uncertain etiology that affects the trachea and bronchial tree.
  - The disease generally affects patients over the age of 50, though it has been reported in younger individuals as well.
  - The disease is characterized by multiple foci of submucosal cartilaginous and osseous nodules that result in a "cobblestone" or "rock-garden" appearance on clinical examination. Multiple nodular projections can be seen in the lumen.
  - Biopsy shows heterotopic cartilage and the bone with intact overlying mucosa.
- Iatrogenic events can cause laryngeal inflammatory changes.
  - Endotracheal intubation may cause mucosal necrosis and ulceration, particularly when prolonged. This contact ulcer may progress to granulation tissue, scar, and even nodule formation in later stages (see question 5 below).
    - Tissue examination shows an ulcerated epithelium with overlying fibrinopurulent exudate and a prominent, underlying vascular proliferation.
    - The presence of reactive stromal atypia may raise concerns for a vascular neoplasm.
  - Laryngeal injections of foreign material such as polytetrafluoroethylene (trade name: Teflon) are used to treat dysphonia and may cause a foreign body giant cell reaction that clinically mimics a neoplasm.
    - Biopsies show multinucleated, foreign body giant cells containing amorphous, clear, refractile material.

References: [1, 3–7]

3. *What are the most common congenital lesions of the larynx?*

Congenital laryngeal lesions are rare, but potentially life-threatening, as they may present in the neonatal period with airway compromise. Lesions include laryngomalacia, congenital vocal fold immobility, cysts, subglottic hemangiomas, subglottic stenosis, and laryngeal atresia. Many of these lesions are diagnosed based on clinical presentation and are not generally biopsied for diagnostic purposes. Occasionally specimens from surgical reconstruction are received, which generally show non-specific fibroinflammatory changes. Cystic lesions will be discussed later, in question 4.

- Congenital subglottic hemangiomas are vascular lesions that may wax and wane in size, causing variable respiratory symptoms, in the first 6 months of life.
  - Symptoms include cough, stridor, dysphagia, and failure to thrive.
  - Endoscopically, hemangiomas may be circumferential or form a mass lesion with a red to blue coloration. A biopsy may not be performed given the classic clinical appearance and the increased risk of bleeding.
  - Histology shows capillaries with plump endothelium, often arranged in a lobular architecture.

References: [8, 9]

**Table 3.1** Pathologic findings of laryngeal cysts

| | Laryngocele | Saccular cysts | Ductal cysts |
|---|---|---|---|
| Lining | Respiratory mucosa | Respiratory, oncocytic, or squamous mucosa | Squamous ±lymphoid tissue or oncocytic |
| Contents | Air, rarely mucus, or inflammation (laryngopyocele) | Mucus | Mucus, keratin |
| Location | Internal (confined to larynx) or internal/external (herniates into anterior neck) | Lateral, anterior | Vallecula, ventricle, vocal fold, aryepiglottic folds, epiglottis |

4. *What is the differential diagnosis for cystic lesions of the larynx?*

Laryngeal cysts are divided into three main categories: laryngocele, saccular cysts, and ductal cysts (Table 3.1).

- Laryngoceles occur when the saccule of the laryngeal ventricle (space between true cord and false cord) is dilated with air. This dilation may be limited to the larynx (internal laryngocele) or extend and bulge through the anterior neck tissues (mixed or internal/external laryngocele).
  - When the laryngocele has an external component, the presenting symptom may be an anterior neck mass.
  - The lining of a laryngocele is respiratory epithelium and may undergo squamous metaplasia. Contents can be air, or if obstructed, mucus or inflammation.
- Saccular cysts result from congenital or acquired dilation of the saccule that becomes filled with mucin. The lining is usually respiratory epithelium but may be oncocytic or squamous.
- Ductal cysts are named for their presumed origin, in blocked minor salivary ducts.
  - The lining of these cysts may be squamous, oncocytic, or tonsillar type.
    - The tonsillar type is lined by squamous mucosa with prominent lymphoid aggregates in the stroma.
    - Cyst contents may be mucinous or comprise keratin debris.
    - Ductal cysts may occur anywhere in the larynx.

References: [10, 11]

5. *What is the difference between laryngeal nodules, polyps, and ulcers?*

Laryngeal nodules, polyps, and ulcers are often related to vocal abuse and are a common cause of hoarseness. Individuals with professions that entail extensive voice use (singers, lecturers, etc.) are often affected, giving rise to the term "singer's nodule." A study has even suggested a correlation between an extroverted personality and the presence of nodules and polyps. Reactive, benign lesions of the larynx show great histologic overlap. While some studies have described subtle differences in histology between nodules and polyps, it is generally accepted that there are no definitive histologic features that differentiate the two. They are distinguished based on clinical features (Table 3.2).

**Table 3.2** Clinicopathologic findings of laryngeal nodules, polyps, and ulcers

| | Ulcer | Nodules | Polyps |
|---|---|---|---|
| Laterality | Bilateral | Bilateral | Unilateral |
| Location | Posterior larynx "kissing ulcers" | Anterior or middle vocal cord | Vocal cord |
| Gross findings | Ulcerated | "Swellings" | Pedunculated |
| Histology | Ulcerated epithelium with associated inflammation and exudate | Subepithelial edema, myxoid or vascular stromal changes<br>Surface hyper- or parakeratosis, ulceration<br>Older lesions may be fibrotic with stromal atypia | |

- Laryngeal nodules present as bilateral, symmetrical subepithelial swellings in the anterior or middle third of the true vocal cord.
  - Patients are generally young to middle-aged.
  - The pathogenesis is related to the repeated collision between the vocal cords, which is greatest in the anterior to middle portions of the cords.
  - Symptoms are hoarseness, voice loss, and vocal fatigue.
- Laryngeal polyps present as unilateral masses, often on the true vocal cord. These lesions tend to be broad-based or pedunculated.
  - A male predominance is documented by some authors.
  - Symptoms include a "breathy" voice, hoarseness, voice loss, and vocal fatigue.
- The histology of nodules and polyps is variable.
  - The lesions may be nodular in architecture, showing subepithelial edema, with acellular proteinaceous (or amyloid-like) material.
  - Granulation tissue-type changes can be seen, and vascularity or myxoid change may be prominent. Atypical stromal cells can be present.
  - Longstanding lesions may show predominantly subepithelial fibrosis or hyalinization. The superficial epithelium may be attenuated, ulcerated, or

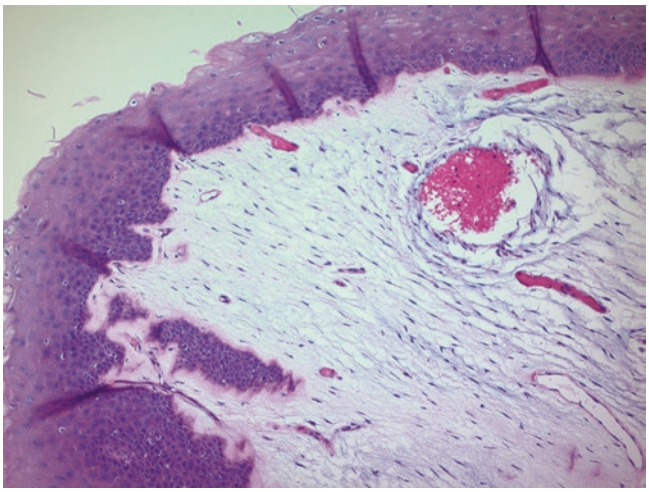

**Fig. 3.2** Vocal cord polyp, with subepithelial edema and myxoid change

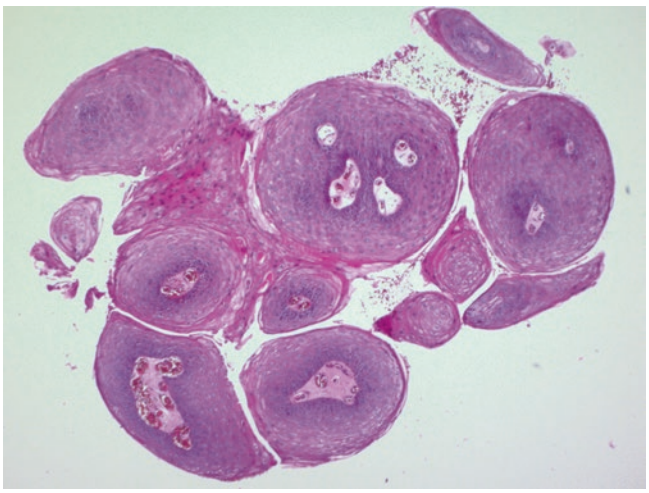

**Fig. 3.4** Laryngeal (squamous) papilloma: fingerlike projections of squamous epithelium cut in cross section with fibrovascular cores. The squamous epithelium shows maturation toward the surface

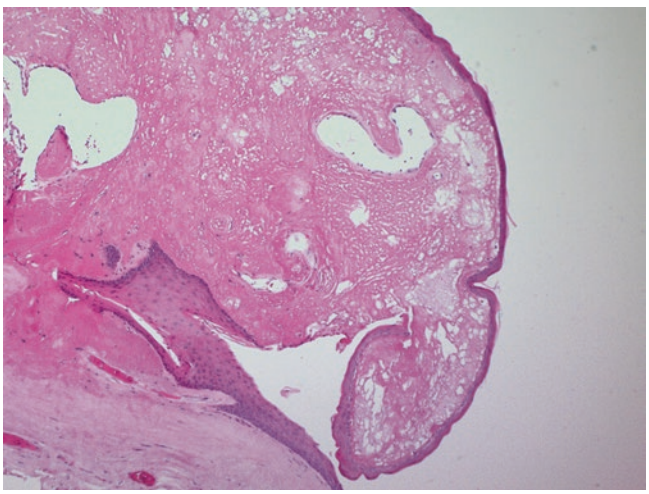

**Fig. 3.3** Vocal cord polyp, with subepithelial fibrinoid change

even undergo epithelial hyperplasia with hyperkeratosis or parakeratosis (Figs. 3.2 and 3.3).

- Laryngeal contact ulcers are also referred to as contact granulomas. In addition to being caused by vocal abuse, these ulcerations may be seen in patients with reflux or a history of endotracheal intubation.
  - The ulcers are generally bilateral, polypoid masses in the posterior larynx. There may be "kissing ulcers" on the contralateral cord.
  - Histologic examination shows surface ulceration and fibrinoid necrosis. Granulation tissue lies deep to the ulceration, with prominent vascularity, and mixed acute and chronic inflammation.
  - Reactive epithelial hyperplasia with reepithelialization at the ulcer edge may show prominent reactive atypia and should not be mistaken for malignancy.

References: [12–15]

6. *What are the risks, associations, and clinical implications of laryngeal papillomas?*

   Squamous papillomas of the larynx are associated with human papillomavirus (HPV). HPV types 6 and 11 are implicated. They present in children (juvenile-onset) and adults with different clinical features.

   - Juvenile-onset papillomatosis or recurrent respiratory papillomatosis (RRP) is typically acquired when newborn patients are infected via transvaginal exposure. This explains the increased risk of developing RRP for infants born to women with genital warts.
     - The clinical progression is of multiple recurrences, with innumerable papillomas throughout the larynx and upper respiratory tract. Aggressive cases may involve the lower respiratory tract.
     - Symptoms include hoarseness, stridor, and airway obstruction.
     - Multiple excisions are generally required to maintain airway patency.
     - The disease may be resolved; however, length of disease involvement is variable and death may occur, particularly if pulmonary involvement occurs.
   - Adult-onset papillomas are usually single papillomas which generally do not progress to RRP and are cured by surgery. If RRP onset is in adulthood, the course is usually less aggressive than juvenile-onset RRP.
   - Histologically, squamous papillomas are pedunculated epithelial tumors with a papillary architecture. The papillae are lined by squamous epithelium with supporting fibrovascular cores in the stroma (Fig. 3.4).

  - The squamous epithelium shows maturation, and superficial koilocytic changes related to HPV may be seen.
    - Koilocytes are squamous cells with a crinkled, hyperchromatic, "raisinoid" nucleus and perinuclear, cytoplasmic clearing (halo).
    - Mitoses may be present but should be limited to the basal portion of the epithelium.
- The complications of RRP are airway compromise, as mentioned. Pulmonary involvement often proves fatal. Malignant transformation is a feared, but uncommon, finding in patients with RRP, with rates ranging from 2% to 20%. Malignant transformation may occur in either juveniles or adults, and with either single or multiple papillomas, and is associated with smoking or exposure to ionizing radiation.

References: [16–19]

7. *What are the principal benign mesenchymal tumors of the larynx?*

The major benign mesenchymal tumors of the larynx include granular cell tumor, hemangioma, inflammatory myofibroblastic tumor, nerve sheath tumors, and rhabdomyoma.

- Granular cell tumor (GCT) is a benign neoplasm believed to be of Schwann cell origin. Half of these occur in the head and neck area. The larynx is an uncommon site, representing only around 2% of GCTs.
  - GCTs of the larynx present as a polypoid tumor, with a white mucosal surface which may mimic papilloma or vocal cord nodule.
  - Histologically, GCTs are composed of nests and cords of syncytial tumor cells with abundant granular cytoplasm and small, sometimes eccentrically placed, nuclei.
    - Pseudoepitheliomatous hyperplasia of the overlying epithelium is characteristic and may be so exuberant as to mimic a squamous cell carcinoma.
    - Careful inspection is needed not to overlook the granular cell tumor, which can be subtle in these cases.
    - The cytoplasmic granules are PAS-positive and diastase-resistant.
    - Tumor cells are positive for S-100 and NSE.
- Hemangiomas of the larynx may be seen in neonates and adults. The neonatal/congenital form is discussed above in question 3. Laryngeal hemangiomas in adults arise from the true vocal cord or other supraglottic sites. Both are characterized by a proliferation of vascular channels lined by bland endothelium (Fig. 3.5).
  - Patients present with hoarseness, and endoscopic examination shows submucosal nodules. The biopsy may lead to significant bleeding.
  - Types of hemangiomas include:
    - Capillary type – small vascular spaces with thin walls
    - Cavernous type – large, thin-walled vascular spaces
- Inflammatory myofibroblastic tumor (IMT) is a lesion of borderline clinical behavior, characterized by mixed inflammatory cells and a proliferation of myofibroblastic cells. Common sites for IMT are in the soft tissue and viscera. It is rare in the head and neck.
  - The most common head and neck site is the larynx. The majority of IMTs are of the true vocal cord.
  - Clinical presentation includes hoarseness and a foreign body sensation.
  - Macroscopically, IMT is a polypoid or nodular lesion with a fleshy consistency.
  - Histology shows a cellular proliferation of myofibroblastic cells, which may be spindled-to-stellate shaped or even epithelioid.
    - The cells are arranged in a storiform or fascicular pattern.
    - Mixed inflammation is present in variable proportions, as are stromal vessels. A zonation effect may be seen.
    - So-called spider cells with long cytoplasmic extensions may be present.
    - Mitoses may be present or even numerous.

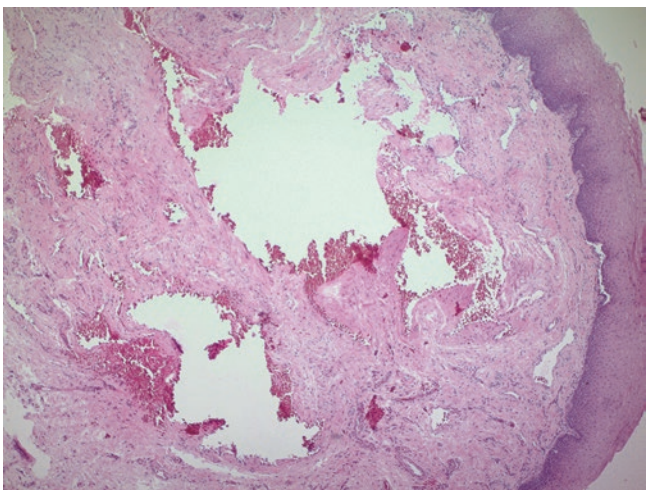

**Fig. 3.5** Hemangioma, cavernous type, with thin-walled vascular spaces in the submucosa

    - Atypical mitoses, necrosis, and marked nuclear pleomorphism are absent.
    - Rearrangement of the anaplastic lymphoma kinase (*ALK*) gene has been demonstrated in these tumors, particularly in younger patients.
    - Tumor cells are positive for vimentin and may be positive for ALK. There is variable expression of desmin, SMA, and CK.
- Peripheral nerve sheath tumors include neurofibromas and schwannomas, both of which may rarely occur in the larynx.
  - A laryngeal neurofibroma may be solitary or associated with neurofibromatosis syndromes types 1 or 2.
  - The histologic features of these lesions in the larynx are identical to those seen elsewhere in the body and are discussed in Chap. 10.
- Rhabdomyoma is a benign skeletal muscle tumor which occurs in cardiac tissue. However, the head and neck is the most common extracardiac site of rhabdomyomas. The larynx and parapharyngeal space are the most common head and neck locations.
  - Rhabdomyomas are divided into the adult and fetal types (Table 3.3), both of which present as soft tissue masses.
  - Adult rhabdomyoma presents in older adults with a median age of 60.
    - Histologically these tumors are composed of polygonal cells with abundant, striated cytoplasm, reminiscent of normal mature skeletal muscle.
    - Nuclei are small and may be centrally or eccentrically located. "Spider cells" with glycogenated cytoplasm are seen.
  - Fetal rhabdomyoma shows a variety of appearances, ranging from a classic (immature) form with bland spindle cells with fetal myotubules in myxoid stroma to an intermediate form which has ganglion-like or spindled rhabdomyoblasts.
  - For both fetal and adult rhabdomyomas, IHC is consistent with skeletal muscle origin. Weak staining for S-100 may be present, posing a potential pitfall with granular cell tumor. GCT should show strong S-100 staining and lack staining for muscle markers.

References: [9, 20–24]

8. *What are the major benign osseous and cartilaginous tumors of the larynx?*

Benign cartilage and bone tumors are rare in the larynx, with some lesions of note being aneurysmal bone cyst (ABC), chondroma, and giant cell tumor (GCT).

- Aneurysmal bone cyst (ABC) commonly occurs in the long bones, vertebrae, or sacrum of young individuals, with the majority found in patients under the age of 20. ABCs in the head and neck region occur in the larynx but are rare. The maxillofacial bones are a more common site and discussed in detail in Chap. 6.
- Chondroma is a rare, benign cartilaginous tumor. In the larynx, chondrosarcomas are more common than chondromas.
  - Chondromas occur most commonly in the cricoid cartilage followed by the thyroid, arytenoid, and epiglottic cartilages.
    - Chondromas consistent of bland, hyaline-type cartilage with low cellularity and usually one cell per lacuna.
  - The distinction between chondroma and a low-grade chondrosarcoma may be impossible on biopsy, as there can be significant morphologic overlap.
    - Imaging features of invasive or destructive growth support the diagnosis of chondrosarcoma.
- Giant cell tumor (GCT) is a benign lesion with the potential for local destruction. In the larynx, they are rare and most commonly involve the thyroid cartilage.
  - Morphologic features show the characteristic, dual population of osteoclast-like giant cells in a

**Table 3.3** Features of head and neck rhabdomyomas

| | Fetal | Adult |
|---|---|---|
| Median age | 4 years | 60 years |
| Site | Larynx, postauricular soft tissue | Oral cavity > pharynx > larynx |
| Histology | Variety of appearances<br>Classic: Bland spindled cells with fetal myotubules in myxoid stroma<br>Intermediate: Ganglion-like or spindled leiomyoma-like rhabdomyoblasts | Polygonal cells with striated cytoplasm<br>Small, eccentric nuclei<br>"Spider cells" |
| Immunohistochemistry | Desmin+, MSA+, myoglobin+, ±weak S-100, ±weak SMA | |

*MSA* muscle-specific actin, *SMA* smooth muscle actin

**Table 3.4** Classification and features of neuroendocrine carcinomas of the larynx

| | Well-differentiated (carcinoid) | Moderately differentiated | Poorly differentiated | |
|---|---|---|---|---|
| | | | Small cell | Large cell |
| Age (decades) | 7–8th | 6–7th | 6–7th | 6th |
| Metastases | In 1/3 of cases | 50% LN metastases, 50% DM | LN metastases at presentation, 90% DM | LN metastases at presentation, DM common |
| Histology | Salt-and-pepper chromatin, nested/ organoid pattern | Salt-and-pepper chromatin, nested/organoid pattern, pleomorphism | Small, dark nuclei, scant cytoplasm, nuclear molding. crush artifact<br>Mitoses, apoptosis | Large cells with eosinophilic cytoplasm, nucleoli, mitoses, necrosis |
| Invasion | No | Yes | Yes | Yes |
| Mitoses | <2/10 hpf | 2–10/10 hpf | >10/10 hpf | >10/10 hpf |
| Necrosis | No | Focal | Yes | Yes |

*DM* distant metastases, *hpf* high-power fields, *LN* lymph node

background of sheets of mononuclear cells with identical nuclei to the giant cells.
- The nuclei are oval with vesicular chromatin and occasional nucleoli; mitotic figures may be seen.

References: [25–28]

9. *How are neuroendocrine neoplasms of the larynx classified and diagnosed?*

The larynx is the most common site in the head and neck for neuroendocrine tumors. Neuroendocrine tumors of the larynx are divided into those of epithelial and paraganglia origin. The tumors of epithelial origin are referred to as neuroendocrine carcinoma (NEC) and subclassified, based on behavior, into a three-tiered system (Table 3.4) endorsed by the 2017 WHO classification. All three tumors show a male predominance and are associated with smoking.

- Well-differentiated NEC (WDNEC) is also referred to as carcinoid tumors or grade 1 NEC. These are uncommon in the larynx. These tumors have an indolent course, with a generally good prognosis, even though metastases occur in about a third of patients.
  - Histologically, these tumors look like carcinoids from other sites, with bland, monomorphous, small epithelial cells arranged in nest, trabeculae, or ribbons. A fibrous stroma may be seen.
    - The cells have moderate amounts of cytoplasm and finely stippled ("salt-and-pepper") chromatin.
    - Pleomorphism is minimal, and mitoses are less than 2/10 high-power fields (hpf). If the Ki-67 index is used, <2–4% of tumor cells should be positive to meet the suggested cutoff for the diagnosis.
    - Necrosis and invasion (perineural, lymphovascular) are absent.
- Moderately differentiated NEC (MDNEC) is also known as atypical carcinoid or grade 2 NEC. These are the most frequently encountered neuroendocrine carcinoma in the larynx.
  - MDNEC is aggressive. Half of the patients will have lymph node metastases and half will have distant metastases. The 5-year survival is only 50%.
  - Histologically, these tumors have a similar growth pattern to WDNEC, with bland neuroendocrine cells in a nested pattern.
    - However, more pleomorphism and occasional nucleoli are present.
    - Mitoses are between 2 and 10/10 hpf. Ki-67 index is >4%.
    - Necrosis and invasion (perineural, lymphovascular) may be present.
    - Mucinous, spindle, and oncocytic change are possible.

Poorly differentiated NECs are classified as either small-cell NEC or large-cell NEC (LCNEC).

- Small-cell NEC is also referred to as grade 3 NEC. These tumors are very aggressive with a poor prognosis; the 5-year survival is 5%. Most patients present with lymph node metastases and 90% with distant metastases.
  - Small-cell NEC has distinctive histology with sheets of small, dark nuclei with finely stippled chromatin and minimal cytoplasm. Tumor cells usually do not exceed 30 μm.
    - Nuclear molding of one cell to another is a characteristic feature.
    - Crush artifact is often seen. Mitoses (>10/10 hpf) and apoptosis are prominent.
    - Nucleoli are inconspicuous.
    - Necrosis and invasion (perineural, lymphovascular) are seen.

- Large-cell NEC is the least common of the neuroendocrine carcinomas in the larynx. These tumors are highly aggressive, and most patients develop distant metastases.
  - The tumor cells are large, with eosinophilic cytoplasm and nested or trabecular architecture.
  - Ribbons and rosettes can be seen and cells are generally larger than 30 μm.
  - Nuclei show salt-and-pepper chromatin, and nucleoli, in contrast to small-cell NEC, may be prominent. Mitoses are >10/10 hpf.
  - Necrosis and invasion (perineural, lymphovascular) are seen.
- IHC shows reactivity with neuroendocrine markers (chromogranin, synaptophysin, CD56). TTF-1 and calcitonin may be positive as well.
- Laryngeal paragangliomas are more often located in the supraglottis than the subglottis. Laryngeal paragangliomas have a female predominance and may be associated with paragangliomas in other sites.
  - Histology demonstrates cells with abundant granular cytoplasm forming the classic "Zellballen" or cell balls, with wispy sustentacular cells surrounding them.
  - Nuclei show "salt-and-pepper" finely stippled neuroendocrine chromatin. As with paragangliomas elsewhere, profound nuclear pleomorphism can be seen.
  - By IHC, the cells are reactive with neuroendocrine markers (chromogranin, synaptophysin, CD56) but negative for pan-cytokeratin. The sustentacular cells will stain with S-100.

References: [29–33]

10. *How is dysplasia graded in the larynx?*

As with many areas of pathology, there have been a number of different systems used to grade dysplasia in the larynx. The 2017 World Health Organization classification proposes a two-tiered system of low- and high-grade dysplasia. This binary system has been shown to improve interobserver agreement. It should be noted that the breakpoint of high- and low-grade dysplasia in the three-tiered system for laryngeal lesions is not the same as the breakpoint for oral epithelial dysplasia. In addition, the WHO 2017 system does allow for the distinction of high-grade dysplasia from carcinoma in situ. A comparison of the breakpoints and criteria for both systems are summarized in Table 3.5.

- Low-grade dysplasia is characterized by hyperplastic squamous epithelium with atypia and increased numbers of basal and parabasal-type cells.
  - The dysplastic cells are prominent in the lower half of the epithelium, with maturation toward the surface.
  - Mitoses are basally located, and there are few, if any, apoptotic or dyskeratotic cells.
- High-grade dysplasia (Fig. 3.6) is characterized by a typically hyperplastic squamous epithelium with atypia, encompassing typically one half or more of the epithelial thickness. High-grade dysplasia may be keratinizing or non-keratinizing.
  - There is abnormal maturation with disordered stratification of nuclei.
  - Nuclear atypia is obvious with size variation, hyperchromasia, and increased nucleoli.
  - Nuclear to cytoplasmic ratios are increased.
  - Dyskeratosis and apoptosis are frequent and present throughout the epithelium.
  - Invasion and stromal changes are not present.

References: [32, 34, 35]

11. *What variants of squamous cell carcinoma are common in the larynx?*

Squamous cell carcinoma (SCC) is the most common malignancy in the larynx and often presents as

**Table 3.5** Comparison of the WHO two- and three-tiered grading systems for laryngeal dysplasia

| Level of atypia | WHO 2005 system | WHO 2017 system |
|---|---|---|
| Lower 1/3 of epithelium | Mild dysplasia | Low-grade dysplasia |
| Middle 1/3 to upper 3/4 | Moderate dysplasia | High-grade dysplasia |
| Full thickness atypia | Severe dysplasia | [a]Carcinoma in situ |
| | Carcinoma in situ | |

[a]The high-grade category may be further divided into high-grade dysplasia and carcinoma in situ

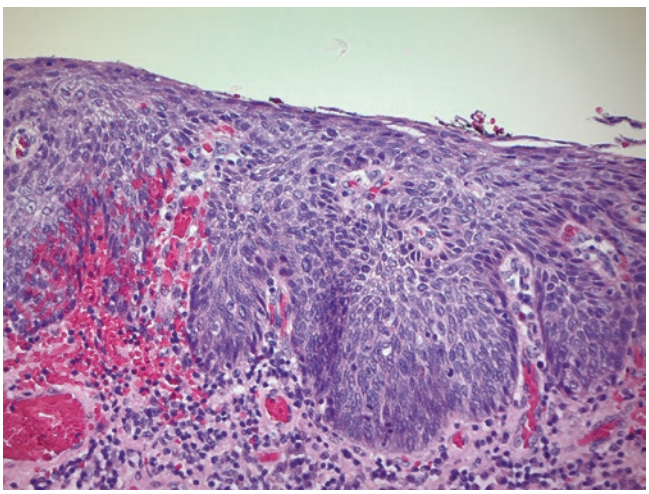

**Fig. 3.6** Squamous epithelium with high-grade dysplasia, showing lack of maturation, and mitotic activity towards the surface

**Table 3.6** Variants of squamous cell carcinoma in the larynx

| | Adenosquamous | Basaloid | Papillary | Spindle cell | Verrucous |
|---|---|---|---|---|---|
| Age (decades) | 6–7th | | | | |
| Gender | Male ≫ female | | | | |
| Risk factors | Alcohol, tobacco | | | | |
| Behavior | Aggressive | Aggressive | Better prognosis than conventional SCC | Aggressive | Locally invasive, no metastases |
| Key histologic features | Glandular and squamous components | Basaloid cells, mitoses and necrosis present | Papillary architecture with invasion into stroma | Spindled, sarcomatoid, may not have clear epithelial component | Very well differentiated, little pleomorphism |

conventional SCC. There are a few variants that should be noted in this area as they pose diagnostic challenges and/or carry differing prognoses. These subtypes are also discussed in Chap. 1. The more common variants of SCC seen in the larynx include adenosquamous carcinoma, basaloid SCC, papillary SCC, spindle cell (sarcomatoid) SCC, and verrucous carcinoma (Table 3.6).

- Adenosquamous carcinoma (Fig. 3.7) is a rare but aggressive variant, characterized by a mix of conventional SCC and adenocarcinoma. There is a male predominance, with an average age in the sixth to seventh decade. The majority of patients present with metastases and the prognosis is poor.
  - While both clear squamous and glandular components are present, they tend to be distinct, but closely apposed, with some areas of mixing.
  - The squamous carcinoma may show a dysplastic or in situ surface component.
  - The adenocarcinoma component can have mucocytes, including mucoepidermoid carcinoma (MEC) in the differential diagnosis.
    - Unlike adenosquamous carcinoma, however, MEC shows close admixtures of squamous and glandular cells and does not show surface dysplasia or in situ changes. The distinction may be challenging. MEC is discussed in greater detail in Chap. 5.
- Basaloid squamous cell carcinoma is characterized by a higher stage at presentation than conventional SCC, with frequent lymph node and distant metastases. Basaloid SCC may be related to alcohol and tobacco. Unlike basaloid SCC in the oropharynx, which are often related to HPV and have a better prognosis, laryngeal basaloid SCC is usually unrelated to HPV and demonstrates more aggressive clinical behavior.
  - The histology of a basaloid SCC consists of a basaloid component arranged in a solid, nested, or cribriform architecture.
    - The tumor cells have a high N:C ratio with scant cytoplasm and crowded, hyperchromatic nuclei (Fig. 3.8).
    - Palisading of tumor cells at the periphery of tumor nests may be seen. Nucleoli are generally absent.
    - Necrosis and mitoses are frequent.
    - Focal squamous differentiation is present in the form of scattered keratin pearls or small squamous nests.
- Papillary SCC is a rare variant of squamous cell carcinoma. Most of the patients with papillary SCC are male; age at presentation averages 60 years old. Like basaloid SCC, many of the patients have a history of exposure to alcohol or smoking.
  - Histologically, papillary SCC shows a papillary architecture with fibrovascular cores lined by highly atypical epithelium. Keratosis may be minimal.
  - Stromal invasion by the atypical epithelium is present, often accompanied by a dense lymphoplasmacytic response.
  - Extensive histologic sampling may be required to identify areas of invasion.
    - If there is no stromal invasion, the lesion should be classified as either papillary SCC in situ or atypical papillary hyperplasia.
- Spindle cell/sarcomatoid SCC is a biphasic tumor with a malignant spindle component as well as a squamous cell carcinoma. Patients are predominantly males in the seventh decade of life. The tumor has been linked to smoking, alcohol, and radiation exposure.
  - Histology demonstrates both a squamous cell carcinoma (either invasive or in situ) and a malignant

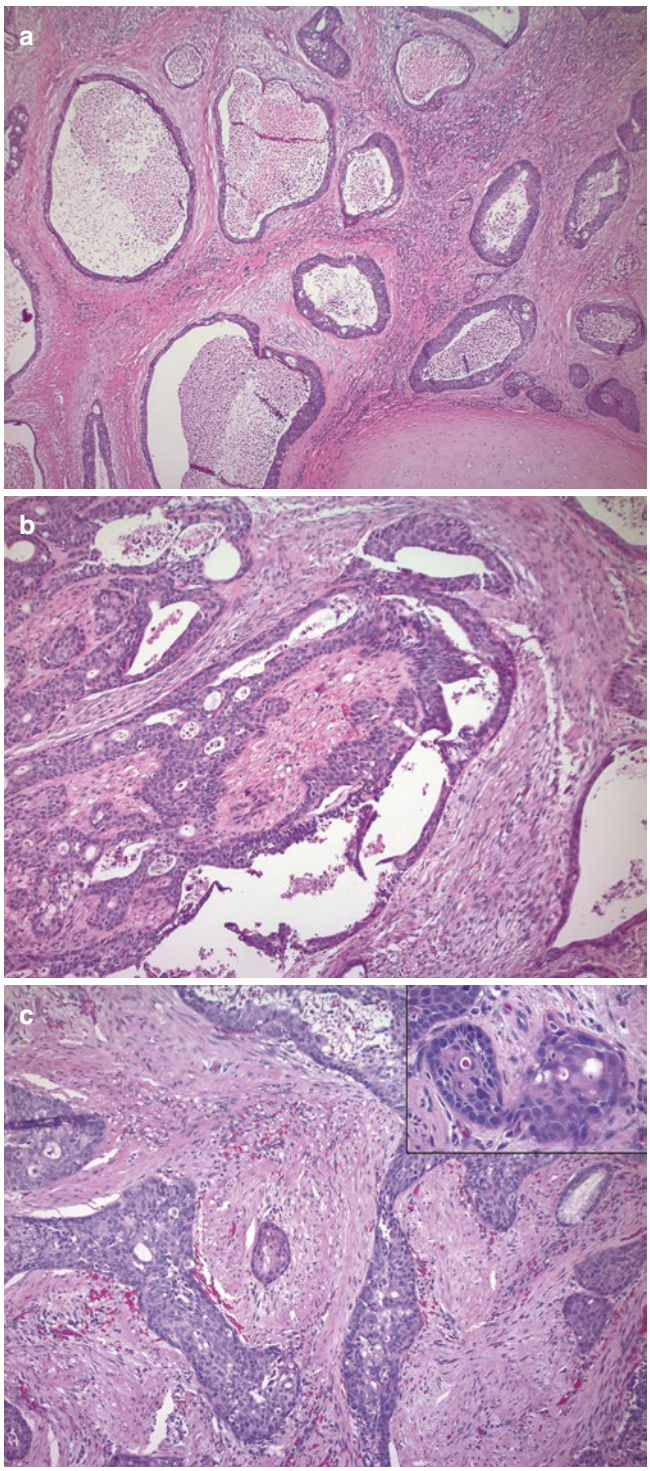


**Fig. 3.7** Adenosquamous carcinoma. (**a**) Infiltrative, haphazard duct-like, glandular proliferation with (**b**) extensive perineural invasion and (**c**) infiltrative, small nests of distinct, squamous cell carcinoma with keratin pearl formation and intercellular bridges (inset)

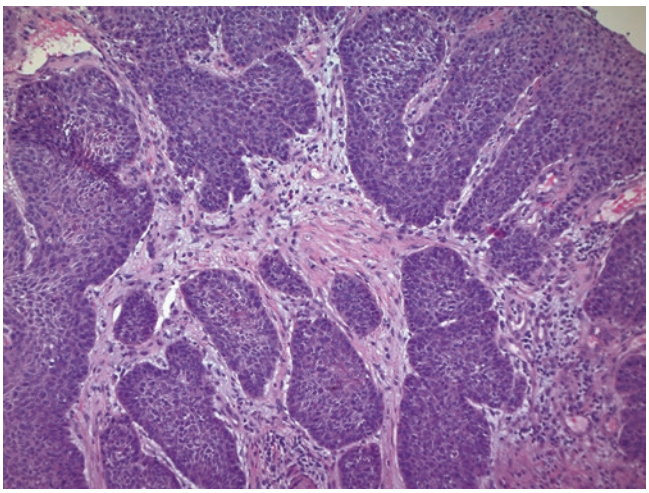

**Fig. 3.8** Basaloid squamous cell carcinoma. Nests of tumor cells with scant cytoplasm and peripheral palisading in a mildly hyalinized stroma

spindle cell component, often infiltrating the submucosa (Fig. 3.9a).

- The spindle cells may merge or transition into the conventional squamous cell carcinoma (Fig. 3.9b). However, some cases only show the spindled component, and a true sarcoma must be excluded.
- Evidence of epithelial differentiation may be assessed using epithelial IHC markers.
  - Up to a third of spindle cell SCCs are negative for epithelial markers. However, this finding does not exclude the diagnosis as sarcomatoid carcinoma is much more common than sarcomas of the larynx.
- Verrucous carcinoma is a well-differentiated form of squamous cell carcinoma. The patients are predominantly men in their 60s and 70s. The clinical course is indolent with local growth, and metastases are generally not seen.
  - Histology shows hyperplastic epithelium with a "warty" appearance which gives the tumor its name. The rete is expanded, with "church-spire" keratosis.
  - Cytology is bland, and the diagnosis may be impossible on superficial biopsies, which may show only the marked hyperkeratosis and parakeratosis.
  - The infiltrating border is broad and pushing, with chronic inflammatory cells surrounding the base (Fig. 3.10).

References: [34, 36–41]

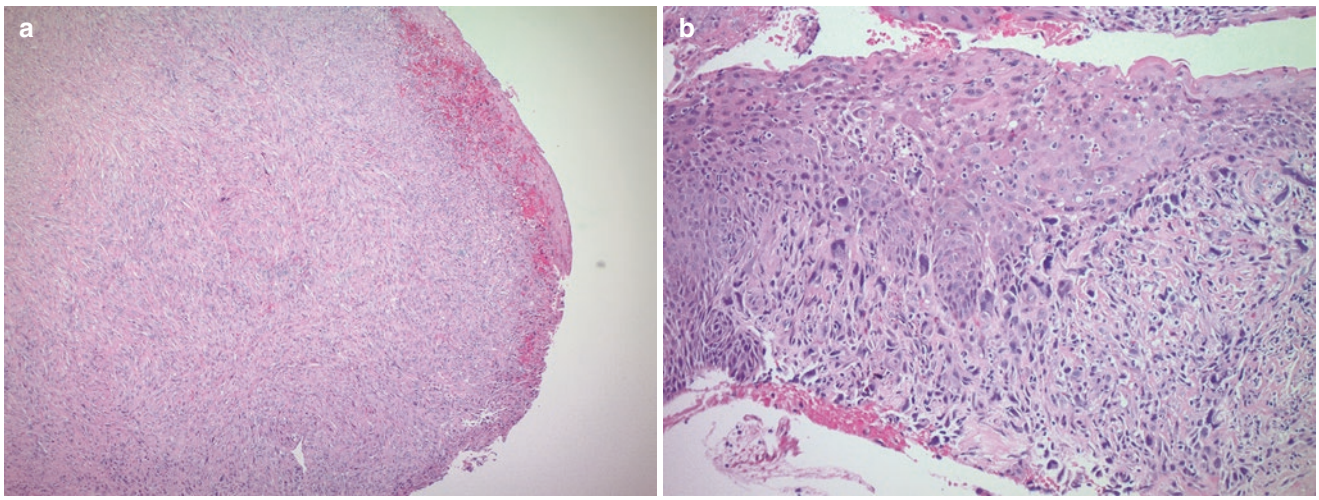


**Fig. 3.9** Sarcomatoid squamous cell carcinoma. (**a**) Low magnification shows a spindled proliferation in the submucosa and an attenuated, overlying squamous epithelium. (**b**) The spindled component merges with the overlying dysplastic squamous epithelium

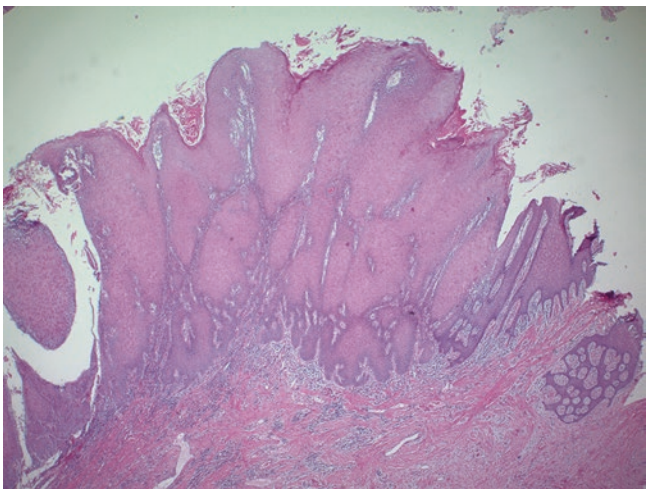

**Fig. 3.10** Verrucous carcinoma. Low magnification shows hyperplastic epithelium with a "warty" appearance, "church-spire" keratosis, and a broad, pushing border at the base and associated chronic inflammatory cells

12. *What malignant surface epithelial tumors, besides squamous cell carcinoma, occur in the larynx?*

    The vast majority of epithelial malignancies in the larynx are SCC and its variants. Lymphoepithelial carcinomas and giant cell carcinoma are some of the other surface epithelial tumors.

    - Lymphoepithelial carcinoma (LEC) in the larynx is extremely rare. There is a male predominance, and the mean age is 60 years. Smoking and alcohol are noted associations.
      - LEC is an aggressive neoplasm which tends to have both lymph node and distant metastases.
      - LEC has an appearance in the larynx often identical to its appearance in other sites, with undifferentiated carcinoma cells admixed with small lymphocytes and plasma cells. In half the cases, there is a component of squamous cell carcinoma.
    - Giant cell carcinoma is also exceedingly rare and is associated with smoking and alcohol use.
      - Histology shows numerous large bizarre giant cells that are often multinucleated. Debris and inflammatory cells may be present in the cytoplasm.
      - In the background, there may be non-giant tumor cells displaying nuclear anaplasia.
      - Giant cell carcinoma may be seen in conjunction with squamous cell carcinoma and may not actually represent a distinct entity.

    References: [42–48]

13. *Which salivary gland tumors are commonly seen in the larynx?*

    Salivary gland tumors of the larynx are uncommon, and malignant salivary tumors are more common than benign salivary tumors at this location.

    - Adenoid cystic carcinoma is the most common salivary gland tumor of the larynx, followed by mucoepidermoid carcinoma, and adenocarcinoma, not otherwise specified (NOS).
      - Case reports and small series have documented other salivary gland carcinomas including carcinoma ex-pleomorphic adenoma, salivary duct carcinoma, acinic cell carcinoma, myoepithelial carcinoma, and epithelial-myoepithelial carcinoma. All of these carcinomas of the larynx show identical histology to those of major salivary gland and are discussed in greater detail in Chap. 5.

    Benign salivary gland tumors seen in the larynx include pleomorphic adenoma and oncocytic papillary cystadenoma.

- Pleomorphic adenoma arises from minor salivary gland and can occur in any part of the larynx. The epiglottis is the most common site. Histology is identical to pleomorphic adenomas elsewhere.
- Oncocytic papillary cystadenoma is an oncocytic laryngeal lesion that can be cystic, as is the case in ductal cysts (question 4).
- Some of these lesions can show areas of papillary proliferation with a Warthin-like lymphoid infiltrate and have been termed oncocytic papillary cystadenomas.
- These lesions may actually be sequelae of duct metaplasia rather than a true neoplasm.

References: [49–54]

14. *What are the most common sarcomas of the larynx, and how are they diagnosed?*
    - Chondrosarcoma is the most common sarcoma of the larynx, comprising up to three-fourths of sarcomas in this region. The incidence is highest in the fifth to eighth decades, and there is a male predominance. Laryngeal chondrosarcomas primarily arise in the hyaline cartilage of the larynx (cricoid and thyroid cartilages). Involvement of the elastic cartilages (epiglottis and arytenoids) is far less common. The hyoid bone is an uncommon site due to its early ossification.
      - Imaging shows an expansile tumor, often containing calcifications, which may be fine or coarse. The distinction between chondroma (see question 8) and a low-grade chondrosarcoma may be impossible on biopsy due to the morphologic overlap.
        - Radiographic features of invasion or destructive growth are often required for the diagnosis of chondrosarcoma.
      - Histologically, the tumors are composed of lobules of disorganized chondrocytes with an invasive and destructive growth pattern (Fig. 3.11). Binucleated and pleomorphic nuclei are present in a hyaline cartilage matrix (Fig. 3.12). Myxoid change may be present.
        - The tumors are variably cellular based on grade. Dedifferentiation may occur but is a rare event.
        - Chondrosarcomas are graded on a three-tiered system. The majority of laryngeal tumors are morphologic grade I (up to 78% in one report).
        - Variants include clear cell, mesenchymal, and periosteal chondrosarcoma.
    - Kaposi sarcoma (KS) is a vascular malignancy with four forms distinguished by clinical features: classic, AIDS-related, endemic, and iatrogenic/transplant-related (Table 3.7).
      - Classic KS only rarely involves the head and neck.

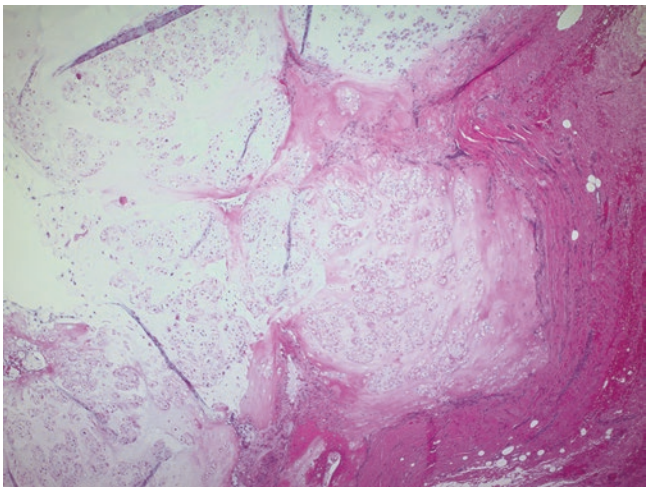

**Fig. 3.11** Chondrosarcoma of the larynx. Lobules of disorganized chondrocytes with an invasive and destructive growth pattern

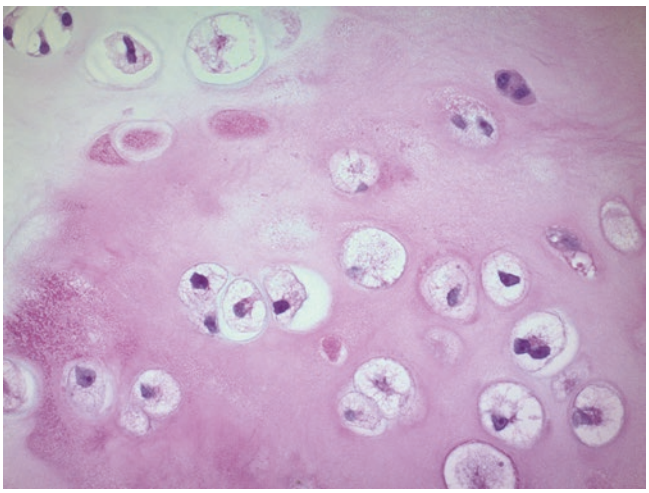

**Fig. 3.12** Chondrosarcoma of the larynx. There are binucleated/pleomorphic nuclei in a matrix of hyaline cartilage

**Table 3.7** Clinical features of Kaposi sarcoma

| | Classic | AIDS-related | Iatrogenic/transplant | Endemic |
|---|---|---|---|---|
| Population | Elderly men, Mediterranean descent | Patients infected with HIV | Transplant patients or patients who are immunosuppressed | Children, men, and women |
| Sites | Extremities, rarely mucosal or genital | Skin of head/neck, upper airway mucosa | Viscera, skin of extremities, mucosa | Extremities, viscera, lymph nodes |
| Clinical course | Indolent | Aggressive | Variable | Variable |

  - AIDS-related KS involves the head and neck about half of the time, with 20% of cases in the mucosa of the upper aerodigestive tract, including the laryngeal mucosa.
  - HHV8 is implicated in all four forms, though the presence of HHV8 is not specific to KS, having been found in other soft tissue lesions such as angiosarcoma and hemangiomas.
    - Histology may be variable depending on the stage of disease and shows plump spindle cells with vascular spaces and mixed inflammatory cells, including lymphocytes and plasma cells. The vascular spaces are slit-like, with extravasated erythrocytes.
    - The tumor cells are positive for HHV8, vimentin, CD31, CD34, D2-40, FLI1, and ERG.
- Synovial sarcoma (SS) is a sarcoma with a wide age range but is most frequent in young patients between 30 and 40 years old. Ten percent of SS involve head and neck sites, including the pharynx and larynx. The tumor is thought to arise from pluripotent mesenchymal cells and explains its frequent occurrence in non-articular sites. SS may be monophasic, biphasic, or undifferentiated.
  - Monophasic SS is composed of fascicles of relatively uniform spindle cells with thin-walled, branching blood vessels. A nodular architecture may predominate or a herringbone pattern similar to fibrosarcoma.
  - The biphasic type includes spindle cells and an additional epithelial component which can show a prominent glandular morphology.
  - The undifferentiated type demonstrates abundant necrosis and mitotic activity.
  - By IHC, the tumors are variably positive for CD99 and TLE1, with patchy EMA, cytokeratins, and BerEP4, particularly in the epithelial elements.
- SS has a characteristic genetic alteration, t(X;18), which creates a fusion gene, either *SYT-SSX1, SYT-SSX2*, or *SYT-SSX4*.
- Osteosarcomas of the larynx are very rare, high-grade neoplasms. Patients present with a polypoid mass of the airway that arises in the soft tissues of the glottis or the laryngeal cartilage.
  - Imaging demonstrates a mass with calcification or ossification. Tumors are composed of spindle and stellate tumor cells with pleomorphism and occasionally osteoclastic giant cells. Osteoid deposition may be present.
  - An important entity in the differential diagnosis is spindle cell SCC, which is much more common in the larynx and may also show osteoid production.
    - Careful inspection for an in situ or dysplastic squamous component, as well as IHC evaluation for cytokeratin expression, is helpful in distinguishing these entities.

References: [55–70]

15. *What are the most common hematolymphoid neoplasms primary to the larynx?*

Hematologic neoplasms of the larynx are rare, comprising less than 1% of all laryngeal neoplasms. The most common laryngeal hematolymphoid neoplasms are extramedullary plasmacytoma and non-Hodgkin lymphoma. Of the non-Hodgkin lymphomas, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is the most common, although there are rare case reports of various other lymphomas, including diffuse large B-cell lymphoma, extranodal NK/T-cell lymphoma, and Burkitt lymphoma.

- The head and neck is the most common site of extramedullary plasmacytomas (EMP) with approximately 80% occurring in this area. Most of these cases are primary disease, with about a fifth of the cases representing secondary involvement by myeloma.
  - The most common locations for head and neck EMPs are the sinonasal tract and Waldeyer's ring, with the larynx comprising only 5% of cases.
  - The prognosis for EMP is better than for myeloma. However patients may develop recurrence, and a small proportion of patients will progress to myeloma.
  - Histology shows sheets of plasma cells which may show immaturity and nuclear pleomorphism, multinucleation, and loss of the perinuclear clearing ("hof") typical of normal plasma cells. Rarely, amyloid may be present.
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma of the larynx is rare. However, the head and neck is the second most common site for MALT lymphoma.
  - Laryngeal MALT lymphoma occurs in the supraglottic area and may present with hoarseness and dysphagia.
  - There is an association with chronic inflammatory conditions (e.g., autoimmune disease) and infection.
  - Histology is identical to MALT lymphomas elsewhere, which show a monotonous population of small lymphocytes, which are described as centrocyte-like, small cleaved follicular cells with abundant cytoplasm.
- The lymphoma cells are positive by IHC for CD20 and CD79a and negative for CD5 and CD10. Flow cytometry may be helpful in establishing light chain restriction.
- Genetic alterations are generally rearrangements involving IgH or IgL chains such as t(14;18) leading to *IGH-MALT1*, trisomy 3, and trisomy 18.

References: [71–75]

16. *What are the most common secondary tumors of the larynx?*

A tumor may involve the larynx secondarily either by direct extension or by metastasis. Direct extension occurs from tumors of the thyroid as well as squamous cell carcinomas and other malignancies from adjacent anatomic locations, such as the base of the tongue. These primary tumors are discussed in detail in their respective chapters. Metastasis to the larynx is a rare event. The most common malignancies to metastasize to the larynx are melanoma and renal cell carcinoma.

- Metastatic melanoma to the larynx, while rare, is more common than primary laryngeal melanoma. These metastases may occur many years after the original primary diagnosis. A good clinical history and thorough physical exam are helpful in distinguishing a primary and secondary melanoma in this area.
  - The histology is variable and detailed in Chap. 4.
  - IHC will be positive for melanoma markers – Melan-A, HMB-45, S-100, and SOX10.
- The diagnosis of metastatic renal cell carcinoma (RCC) in the larynx will generally be preceded by a diagnosis of a primary RCC. Occasionally a laryngeal metastasis from RCC will be the first presentation of an occult primary.
  - IHC for RCC demonstrates expression for Pax-8, RCC-antigen, and CD10.
- Breast, prostate, and lung may metastasize to the larynx, usually in the setting of advanced-stage, widely metastatic disease. Site-specific IHC markers may be required to confirm the site of origin.

References: [76–78]

## Case Presentations

### Case 1

#### Learning Objectives

1. To become familiar with the histologic features of this disease process
2. To generate a differential diagnosis
3. To understand distinct clinical presentations of this disease

#### Case History

A 50-year-old male presents with hoarseness and is found to have a mass on his right true vocal cord.

#### Endoscopic Examination

A 5-mm exophytic lesion is found on the right vocal cord. An excisional biopsy is performed.

#### Histologic Findings

- Fingerlike projections of squamous epithelium with fibrovascular cores (Fig. 3.13).
- Squamous epithelium shows maturation toward the surface (Fig. 3.14). There is basal hyperplasia with koilocytic change in the upper epithelium.

#### Differential Diagnosis

- Squamous papilloma
- Recurrent respiratory papillomatosis
- Verrucous carcinoma
- Papillary squamous cell carcinoma

**Final Diagnosis** *Squamous papilloma*

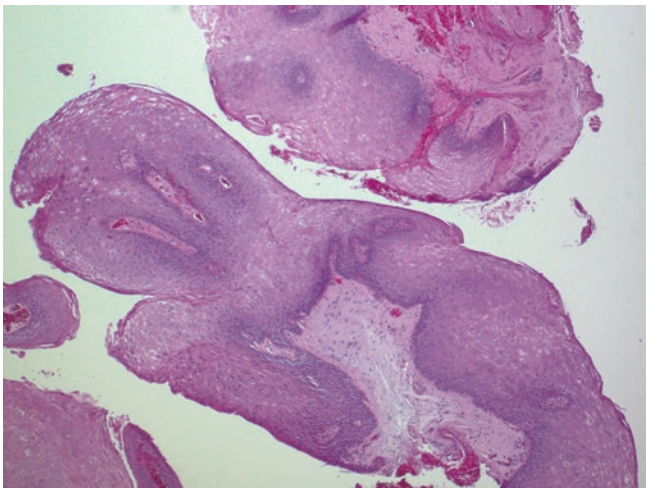

**Fig. 3.13** Case 1: fingerlike projections of squamous epithelium cut in cross section with fibrovascular cores

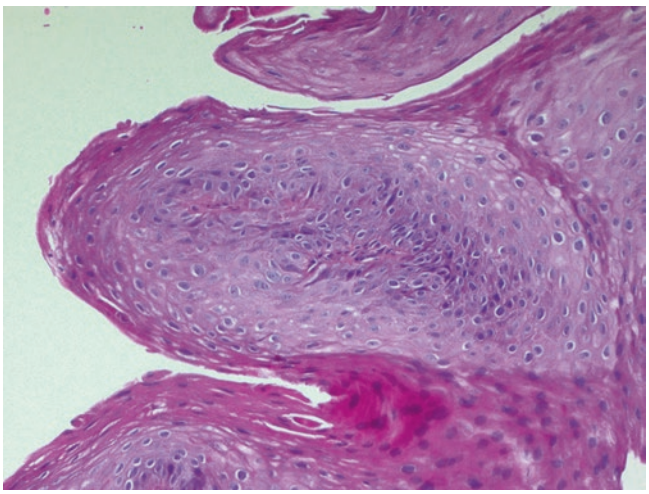

**Fig. 3.14** Case 1: The hyperplastic squamous epithelium shows maturation toward the surface

**Take-Home Messages**

1. Squamous papillomas may occur in both children and adults. When in children, multiple papillomas may be seen with an aggressive clinical course, with recurrence.
2. Most solitary papillomas in adults do not progress to recurrent respiratory papillomatosis and are cured with surgery.
3. Koilocytic change is seen, reflecting the role of HPV. Types 6 and 11 are implicated.
4. In papilloma, while there is basal hyperplasia and may be mild atypia, maturation toward surface epithelium is seen, and mitoses are restricted to the basal area.

References: [16–18]

## Case 2

**Learning Objectives**

1. To become familiar with the histologic features of this neoplasm
2. To become familiar with the immunohistochemical stains used to aid in the diagnosis of this neoplasm
3. To generate a differential diagnosis

**Case History**

A 66-year-old male presents with voice changes. He is found to have a polypoid, ulcerated mass arising in the area of the left vocal cord.

**Gross Findings (Not Pictured)**

A polypoid mass with a firm, fibrotic cut surface is found in the glottis.

**Histologic Findings**

- The surface epithelium shows atypia and ulceration, with a spindled proliferation infiltrating throughout the submucosa (Fig. 3.15).
- There is blending between the surface epithelium and the spindled proliferation (Fig. 3.16).
- The spindled proliferation has marked pleomorphism and mitotic activity.

**Differential Diagnosis**

- Squamous cell carcinoma, classic type
- Sarcomatoid squamous cell carcinoma
- Vocal cord polyp with ulceration
- Rhabdomyosarcoma
- Synovial sarcoma

**Immunohistochemical Studies**

- A cytokeratin cocktail (AE1/AE3, Cam5.2, MNF-116) is positive in the epithelial cells and negative in the spindle cells (Fig. 3.17).

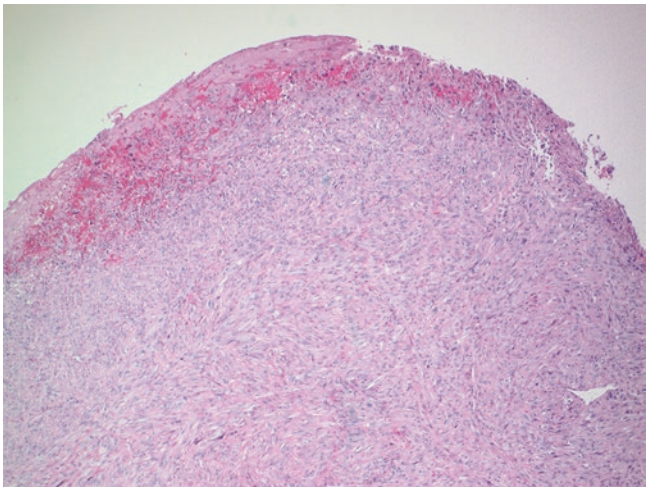

**Fig. 3.15** Case 2: A spindled proliferation infiltrating throughout the submucosa, with surface epithelium showing atypia and ulceration

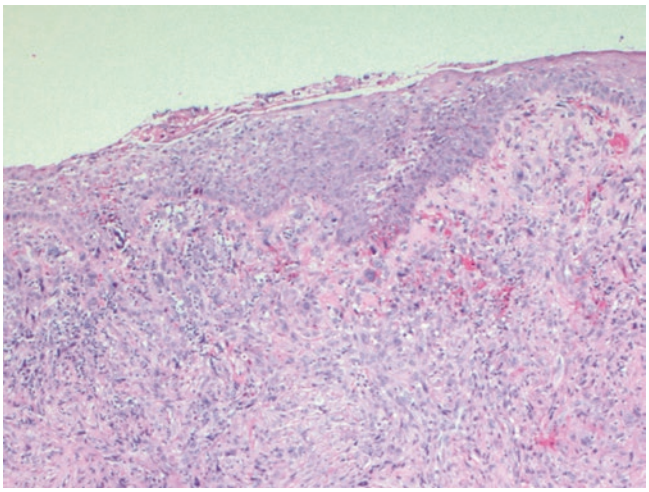

**Fig. 3.16** Case 2: Blending between the surface epithelium and the spindled proliferation

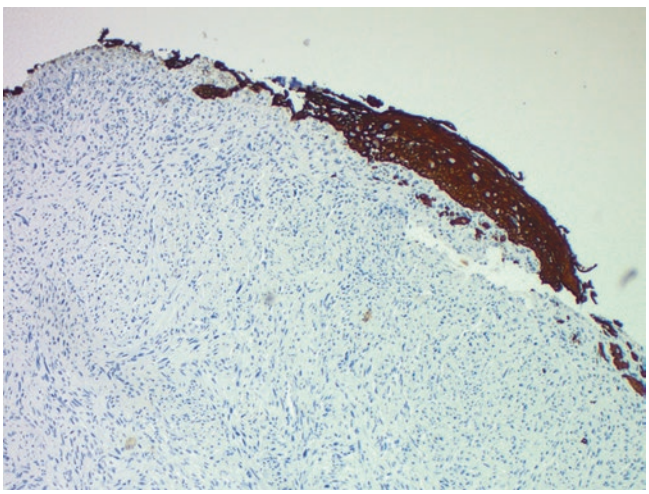

**Fig. 3.17** Case 2: A cytokeratin cocktail is positive in the epithelial cells and negative in the spindle cells

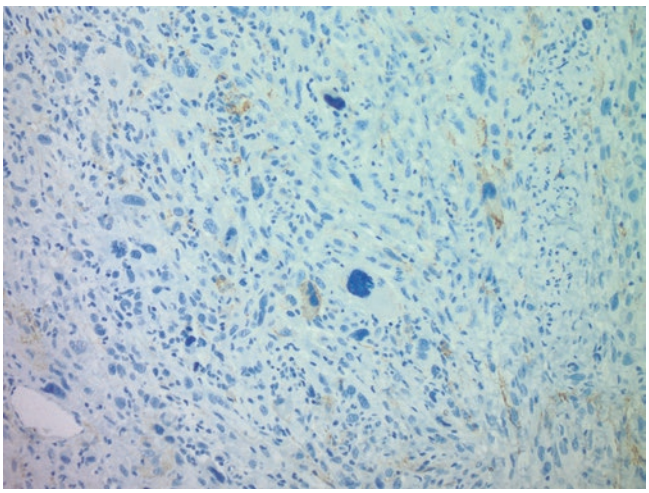

**Fig. 3.18** Case 2: EMA shows faint, focal reactivity in the spindle cells

- EMA shows faint, focal reactivity in the spindle cells (Fig. 3.18).
- Not pictured: P40, melanoma markers, and muscle markers were negative.

**Final Diagnosis** *Sarcomatoid squamous cell carcinoma*

**Take-Home Messages**

1. Sarcomatoid squamous cell carcinoma is more common than sarcomas, in the larynx.
2. Up to a third of sarcomatoid SCC may lack expression of epithelial markers.
3. Vocal cord polyps may have a spindled or reactive fibroblastic proliferation; however, marked atypia is absent.
4. Sarcomatoid SCC shows a blending of the spindle cells with the atypical surface epithelium.
5. In sarcomatoid SCC, areas of classic SCC may be very limited or lacking entirely.

References: [34, 39, 41, 46]

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# Sinonasal Tract

4

Riya Kuklani, Aatika Malik, Kathleen T. Montone, and He Wang

## Frequently Asked Questions

1. What are the leading developmental abnormalities of the sinonasal tract, and how are they diagnosed?
2. What is rhinosinusitis and how is it classified?
3. What is Samter's Triad?
4. How is fungal rhinosinusitis classified and what are the histopathologic features?
5. What is the differential diagnosis of nonneoplastic nasal polyps?
6. What is the differential diagnosis of necrotizing sinonasal lesions?
7. What are the principal inflammatory disorders of the sinonasal tract?
8. What are the common hamartomas of the sinonasal tract?
9. What are the different types of sinonasal papillomas, their associated risk of malignancy, and relationship to human papillomavirus?
10. What are the common sinonasal tumors with established genetic alterations?
11. Which features distinguish sinonasal glomangiopericytoma from solitary fibrous tumor?
12. Are there any features of sinonasal squamous cell carcinomas which are unique to this region?
13. What is the differential diagnosis of sinonasal undifferentiated carcinoma?
14. What is olfactory neuroblastoma and how is it graded?
15. What are the histopathologic features of sinonasal melanoma, how do they differ from cutaneous melanomas, and which features are prognostic indicators?
16. What is the differential diagnosis of small round blue cell tumors in the sinonasal tract?
17. What are the most common salivary gland tumors of the sinonasal tract?
18. What are the morphologic, immunohistochemical, and molecular features of HPV-related multi-phenotypic carcinoma?
19. What are the types of non-salivary sinonasal adenocarcinomas?
20. What are the morphologic and genetic features of biphenotypic sinonasal sarcoma?
21. What are the most common soft tissue tumors of the sinonasal tract?
22. Which hematolymphoid tumors are more common in the sinonasal tract?
23. What are the secondary tumors of the sinonasal tract and their differential diagnosis with primary tumors?

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1. *What are the leading developmental abnormalities of the sinonasal tract, and how are they diagnosed?*

   The developmental lesions of the sinonasal tract include nasal glial heterotopia, nasal dermoid cyst and sinus, and primary ciliary dyskinesia (Table 4.1). With the exception of the latter, these abnormalities are isolated events with few, if any, associated anomalies.
   References: [1–4]
2. *What is rhinosinusitis and how is it classified?*
   - Rhinosinusitis (RS) is inflammation of the sinonasal tract and is caused by specific and non-specific

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etiologies. It is the most common disorder of the sinonasal tract and may be limited to the nasal cavity (rhinitis), paranasal sinuses (sinusitis), or involve both (rhinosinusitis).

- The pathology and clinical classification of rhinitis is typically divided into non-allergic and allergic rhinitis, though concomitant sinus involvement can be seen (Table 4.2):
  - Non-allergic rhinitis
    - Non-allergic rhinitis with eosinophilia
    - Infectious (acute) RS (<12 weeks duration)
    - Atrophic RS
  - Allergic rhinitis (AR) has many subtypes based on the allergen, including seasonal, perennial, intermittent, persistent, and episodic.
    - By definition, AR is an IgE-mediated, type 1 inflammatory immune reaction affecting nasal mucosa.
- Rhinosinusitis has two main categories:
  - Chronic RS (>12 weeks duration)
    - CRS with polyps
    - CRS without polyps
    - Allergic fungal RS
    - Aspirin-exacerbated respiratory disease (AERD)
  - Fungal RS
    - Invasive fungal RS
    - Noninvasive RS
- Chronic rhinosinusitis (CRS) is a general term used to describe a constellation of symptoms characterized by inflammation of the sinonasal mucosa that exceeds a 12-week duration. Patients typically have at least two of the following symptoms:
  - Facial pain
  - Rhinorrhea
  - Nasal congestion
  - Olfactory dysfunction
- The etiology, histologic features, and clinical findings of CRS vary. The pathogenesis is related to a variety of host immune, environmental, and mechanical (obstructive) factors. CRS is commonly divided into CRS without polyps (Fig. 4.1) and with polyps (Table 4.3).
  - The intensity of the inflammatory infiltrate and proportion of eosinophils in CRS correlate with disease severity as defined by computed tomography (CT) findings. However, neither has proven to correlate with symptom severity.

References: [5–15]

**Table 4.1** Developmental abnormalities of the sinonasal tract

| | Nasal glial heterotopia | Nasal dermoid cyst | Primary ciliary dyskinesia |
|---|---|---|---|
| Clinical presentation | Congenital<br>May be intranasal, subcutaneous (nasal bridge), or both<br>Nasal obstruction, discharge, polyps, chronic rhinosinusitis, or subcutaneous mass 1–7 cm | Birth to adulthood<br>Midline, at nasal bridge or lower lateral regions of nose near ala | Recurrent respiratory tract infections, sinusitis, bronchitis<br>50% of patients have situs inversus |
| Morphology | Mixture of mature astrocytes, neuroglial fibers, and a fibrotic stroma<br>Absent or scant neurons and ependymal cells<br>Subjacent to skin or mucosa<br>±Focal calcifications and inflammation<br>No connection with CNS | Cyst lined by stratified squamous epithelium with cutaneous appendages including hair follicles, sebaceous glands, sweat glands<br>No mesodermal or endodermal elements | Nasal cavity biopsy shows foci of squamous metaplasia secondary to chronic rhinitis<br>Tracheal brushings or biopsy show abundant amounts of cilia |
| Differential diagnosis | Encephalocele: connects with CNS<br>Fibrosed nasal polyp: has seromucinous glands and lacks glial tissue<br>Nasal teratomas<br>True gliomas | Normal skin<br>Nasopharyngeal dermoid: not cystic<br>Nasal glial heterotopia | Normal cilia |
| Ancillary | Trichrome stain: fibrosis is blue and neurons are magenta<br>Collagen type IV and laminin stains highlight fibrosis<br>GFAP+, S100+ | Imaging required to exclude intracranial extension | TEM: Absence of dynein arms, but is not reliable alone<br>Mutational studies confirm the diagnosis (autosomal recessive) |

*CNS* central nervous system, *TEM* transmission electron microscopy

**Table 4.2** Clinicopathologic features of different types of rhinitis

| | Allergic rhinitis | Non-allergic rhinitis with eosinophilia | Infectious (acute) rhinosinusitis | Atrophic rhinosinusitis |
|---|---|---|---|---|
| Etiology | IgE-mediated, type I immune reaction<br>Exposure to allergens: mold, pollen, dust mites, animal dander | Non-immune mediated<br>May be precursor to AERD, asthma, and nasal polyps | Viral etiology is most common: rhinoviruses, influenza, RSV, adenoviruses<br>Bacteria: S. pneumoniae, H. influenza | In the West: iatrogenic, due to aggressive sinus surgery, underlying granulomatous disease, XRT<br>In developing countries: chronic bacterial infection, nutritional deficiencies, chronic irritants, autoimmune disease |
| Symptoms | Nasal congestion, rhinorrhea, sneezing, pruritis<br>Anosmia is not frequent<br>May develop chronic RS | Nasal congestion, rhinorrhea, sneezing, pruritis<br>Anosmia is more common | Nasal congestion, watery nasal discharge, pain | Nasal obstruction, headaches, nasal crusting, anosmia, epistaxis, halitosis, foul-smelling nasal odor |
| Diagnosis | Positive skin test to determine allergen | Negative skin test<br>Negative anti-allergen serum IgE | Clinical diagnosis based on disease duration<br>±Culture results | Clinical diagnosis |
| Morphology | Submucosal edema, eosinophil-predominant, mixed inflammatory infiltrate<br>±Neutrophils | Submucosal edema, eosinophil-predominant, mixed inflammatory infiltrate | Not typically sampled | Atrophic seromucinous glands, submucosal edema, chronic inflammation, vascular dilatation, fibrosis, squamous metaplasia |
| Treatment | Reduce allergen exposure, topical antihistamines and corticosteroids | Topical corticosteroids<br>±Antihistamines | ±Antibiotics | Antibiotics, nasal irrigation |

*RSV* respiratory syncytial virus, *AERD* aspirin exacerbated respiratory disease

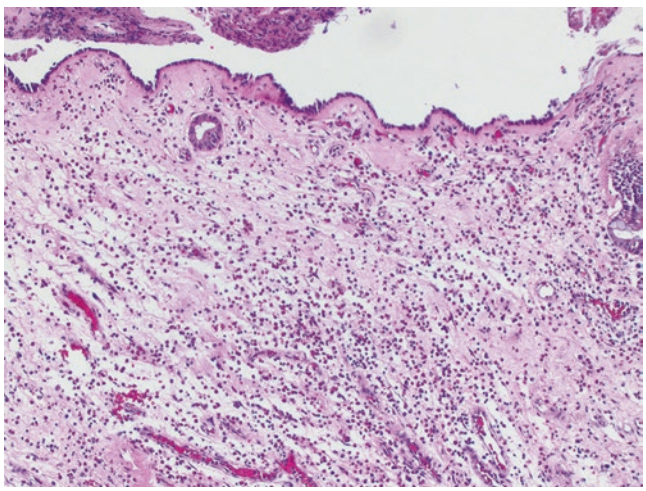

**Fig. 4.1** Chronic sinusitis. Edematous respiratory mucosa with subepithelial sclerosis and a mixed inflammatory infiltrate of predominantly eosinophils

**Table 4.3** Clinicopathologic features of chronic rhinosinusitis

| | CRS with polyps | CRS without polyps |
|---|---|---|
| Frequency among CRS | 20% | 60% |
| Prominent symptoms | Obstruction, olfactory dysfunction | Facial pain, discharge |
| Inflammatory infiltrate | Eosinophils predominate | Mononuclear cells predominate |
| Thickened BM | Present | Present |
| Submucosal edema | Present | Absent/minimal |
| Decreased/atrophic glands | Yes | No, ± goblet cell hyperplasia |
| Clinical course | More refractory to medical therapy<br>Multiple surgeries | Typically responds to medical therapy |

*BM* basement membrane

3. *What is Samter's Triad?*

Samter's Triad is a condition characterized by aspirin hypersensitivity, asthma, and sinus inflammation with recurring nasal polyps. It is also known as aspirin-exacerbated respiratory disease or acetylsalicylic acid triad.

- When patients are exposed to aspirin or other nonsteroidal anti-inflammatory drugs, they develop an adverse reaction with upper and lower respiratory symptoms including bronchoconstriction, rhinorrhea, rash and abdominal pain with vomiting, and diarrhea.
- Many patients also have marked eosinophilia of both bronchial and nasal secretions as well as in the circulating blood.

- Histologically, sinus contents show chronic rhinosinusitis with eosinophils and thick mucin containing numerous eosinophils (allergic mucin).

References: [16–18]

4. *How is fungal rhinosinusitis classified and what are the histopathologic features?*

Fungal rhinosinusitis is classified as invasive (Fig. 4.2) and noninvasive. The clinicopathologic features of invasive fungal disease are summarized in Table 4.4.

- Noninvasive fungal rhinosinusitis is divided into three main categories:
  - Saprophytic – asymptomatic colonization of sinus mucosa, usually associated with chronic RS and multiple surgeries. Discovered incidentally and generally should not be treated.
  - Fungal ball – patients are usually symptomatic females with nasal congestion, discharge, headaches, and pain. Diagnostic criteria include:
    - Sinus opacification, mucopurulent sinus contents, aggregates of fungal hyphae which are separate from the mucosa, and chronic inflammation (Fig. 4.3).
    - No predominance of eosinophils.
    - Aspergillus species is the etiologic agent, but up to 30% of cultures will be negative.
  - Allergic fungal rhinosinusitis (AFRS) is a chronic RS.
    - Generalized inflammation along with viscus allergic mucin containing eosinophilic aggregates, degranulation, and Charcot-Leyden crystals obstructs normal drainage.

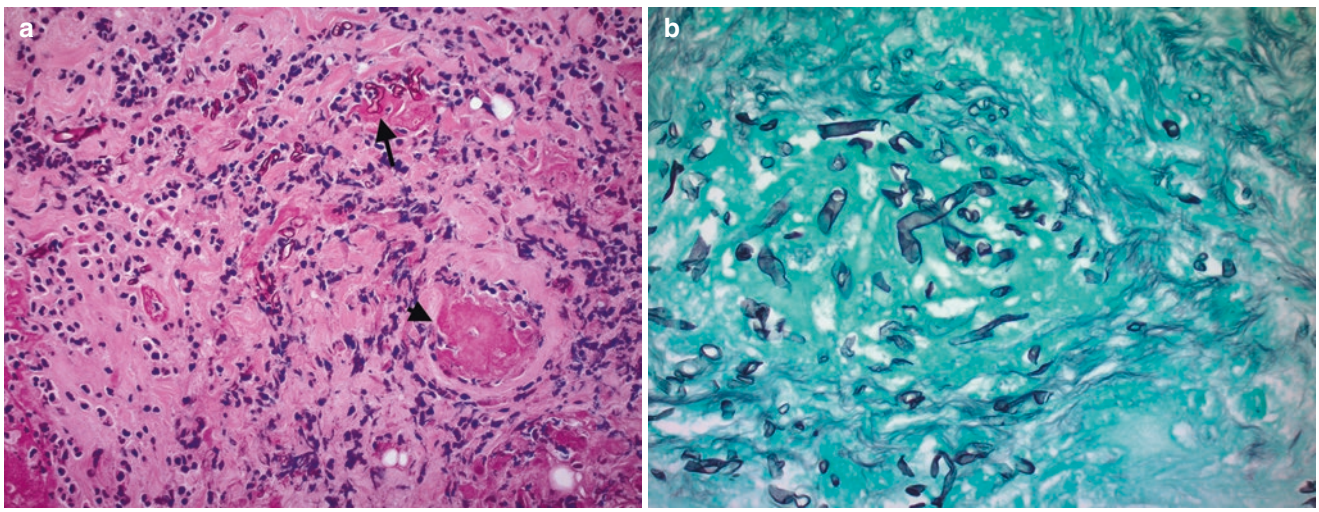


**Fig. 4.2** Acute invasive fungal rhinosinusitis in a transplant patient. (**a**) Extensive acute inflammation with tissue necrosis, fibrin thrombi (arrowhead), and easily identified fungal hyphae (arrow) on routine staining. (**b**) A GMS stain highlights broad, irregular, pauci-septate fungal hyphae consistent with zygomycetes

**Table 4.4** Features of the different types of invasive fungal rhinosinusitis (IFRS)

| | Acute (necrotizing) IFRS | Chronic IFRS | Granulomatous IFRS |
|---|---|---|---|
| Duration of symptoms | <4 weeks (Fulminant) | >12 weeks | >12 weeks |
| Risk factors<br>Epidemiology | Neutropenic patients, profound immunosuppression: transplant, chemotherapy, diabetes | Low-level immunosuppression: AIDS, diabetes, corticosteroid use | Immunocompetent patients of Sudan, India, Saudi Arabia |
| Symptoms | Fever, nasal obstruction, epistaxis, pain | Chronic sinusitis symptoms refractory to medical therapy<br>May progress to eye swelling and vision abnormalities | Enlarging mass of cheek, orbit, nose<br>Proptosis, enlarging mass of orbit, nasal cavity or sinuses |
| Histology | Vascular invasion by fungal hyphae<br>Necrosis, thrombosis, hemorrhage<br>±Neutrophils | High density of fungi<br>±Vascular invasion<br>Scant inflammation | Noncaseating granulomas<br>±Vasculitis<br>Rare hyphae |
| Organism | Aspergillus species<br>Zygomycetes | Dematiaceous molds<br>Aspergillus species | Aspergillus flavus |

- Histological features of AFRS include eosinophilic mucin mixed with sloughed epithelial cells, Charcot-Leyden crystals, and eosinophilic debris.
- Fungal hyphae are present in the mucin and often difficult to detect on routine microscopy. Gomori's methenamine silver (GMS) and periodic acid Schiff (PAS) stains are helpful ancillary tests.
- Aspergillus species and the dematiaceous molds (Alternaria species and Cladosporium species) are most common.

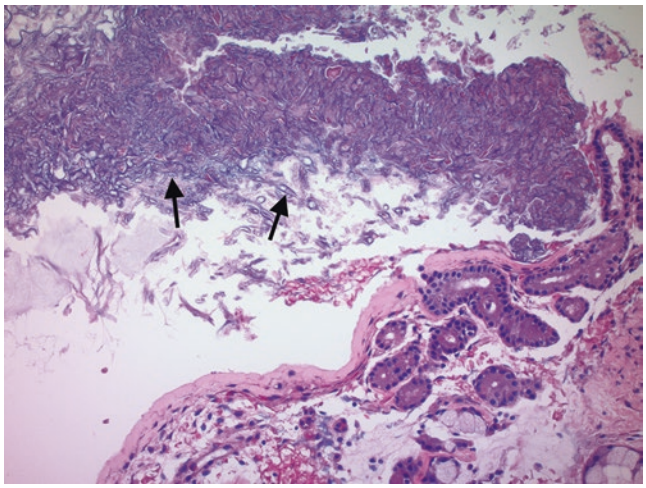

**Fig. 4.3** Noninvasive fungal rhinosinusitis with a fungal ball. Minimal inflammation is present, and the fungal aggregate is separate from the mucosa. Individual, slender, acutely branching hyphae of *Aspergillus* species can be seen (arrows) at the edges

- Treatment includes surgery to relieve obstruction along with variable steroid use.

References: [19–26]

5. *What is the differential diagnosis of nonneoplastic nasal polyps?*

The clinical differential diagnosis of nasal polyps (NP) is broad and includes neoplasms and nonneoplastic conditions. The former are usually unilateral. The histomorphologic differential diagnosis for nonneoplastic nasal polyps is primarily between inflammatory nasal polyps and antrochoanal polyps (Fig. 4.4). The differences between these two polyps are summarized in (Table 4.5). Hamartomatous lesions are discussed later (see question 8).

- Inflammatory nasal polyps are most commonly associated with chronic rhinosinusitis (CRS). These polyps are usually bilateral and multiple (i.e., nasal polyposis).
  - The most common types of RS associated with NP all fall under the heading of eosinophilic CRS:
    - Allergic fungal RS
    - Eosinophilic fungal RS
    - Aspirin-exacerbated respiratory disease
  - 80% of patients with CRS and NP in the West are characterized by a T-helper 2 response, IL-5, and eosinophils.
  - 60% of patients have allergic inflammation of the upper and lower airways, including asthma.
  - Other inflammatory conditions associated with nasal polyposis include eosinophilic granulomatosis polyangiitis.

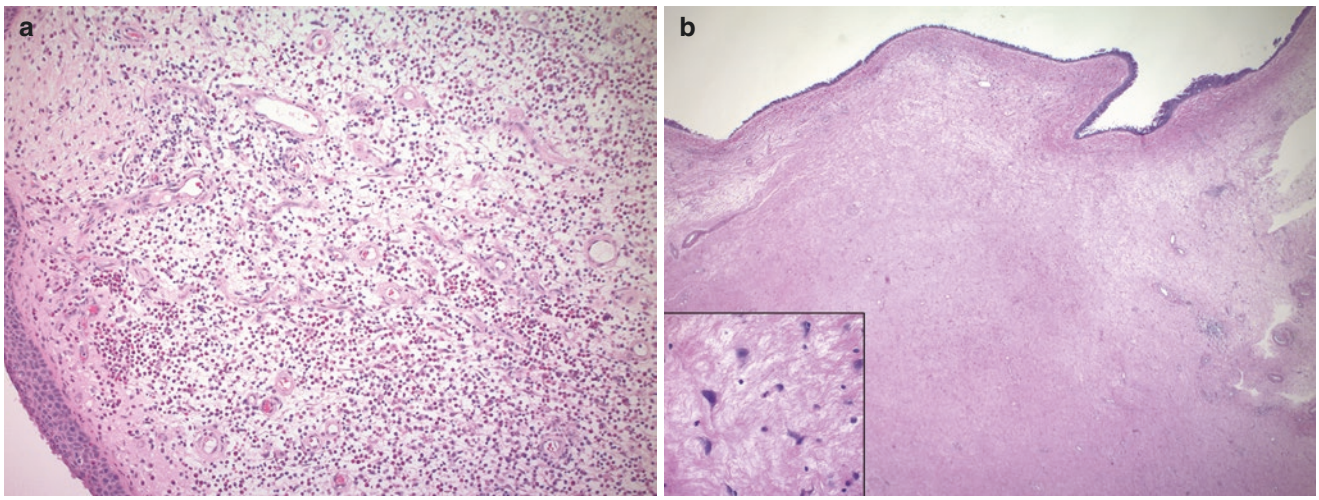


**Fig. 4.4** Nasal polyps. (**a**) An inflammatory nasal polyp with extensive submucosal edema and an eosinophilic-predominant infiltrate. (**b**) An antrochoanal polyp shows significant fibrosis with sparse lymphocytes, absence of seromucinous glands, and (inset) stromal atypia

- Given the clinical implications of allergy and associated systemic disease with CRS with NP versus without NPs, the diagnosis should adhere to strict histologic criteria.
  - NPs are inflamed nasal mucosa that is markedly edematous, polypoid, and generally devoid of seromucinous glands (Fig. 4.4a).
  - Mildly edematous rhinitis does not qualify as NPs.
- The principal unilateral, nonneoplastic nasal polyp is an antrochoanal polyp (ACP).
- ACPs arise from the maxillary sinus and grow through the maxillary ostium into the nasal cavity.
- Patients present with nasal obstruction.
- Up to 35% of ACPs occur in children.
  - Nasal polyps of any type in children should raise concern for cystic fibrosis.
  - NPs in cystic fibrosis usually have a neutrophilic infiltrate.

References: [27–34]

6. *What is the differential diagnosis of necrotizing sinonasal lesions?*

The sinonasal tract may be involved by various conditions which result in necrosis, midline tissue destruction, and deformities. The differential diagnosis is broad and includes infectious, autoimmune, inflammatory, and neoplastic conditions. The infectious diseases are summarized in Table 4.6, while the noninfectious disorders are addressed separately in question 7.

- Extranodal natural killer/T-cell lymphoma may present as a necrotizing, nasal cavity lesion secondary to angioinvasion of the atypical lymphoid cells. The reader is referred to Chap. 10 for a discussion of this entity.

References: [35–43]

7. *What are the principal inflammatory disorders of the sinonasal tract?*

The major noninfectious inflammatory diseases of the sinonasal tract are the ANCA-associated vasculitides, granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Eosinophilic angiocentric fibrosis (EAF) is also included here because of its primary involvement of the nasal cavity and similar vascular, inflammatory, and clinical manifestations. All three diseases typically present with sinonasal tract involvement and are summarized in Table 4.7.

- Cocaine-induced midline destructive disease is in the differential diagnosis of necrotizing and inflammatory disorders of the sinonasal tract (SNT).
  - Patients present with nasal cavity ulceration and epistaxis and may have septal perforation.
  - Biopsies show ulceration and necrosis with acute and chronic inflammation, foreign body giant cell reaction, and granulomatous changes.
  - Polarized light microscopy may show foreign material associated with cocaine inhalation such as talc crystals.
  - The pathogenesis is related to vasoconstriction with subsequent ischemic necrosis and destruction of tissues.

References: [35, 37–39, 44–52]

8. *What are the common hamartomas of the sinonasal tract?*

Hamartomas are nonneoplastic lesions with aberrant differentiation, which may produce growth of disorganized, mature, specialized cells or tissue indigenous to that particular site. The growth of hamartomas is a self-limited process. The most common hamartomas of the sinonasal tract are highlighted in Table 4.8.

- The epithelial-predominant hamartomas (Figs. 4.5 and 4.6) may show a complex glandular arrangement, raising the possibility of an adenocarcinoma. Diagnostic clues to the correct diagnosis include:
  - Maintenance of a normal lobular architecture
  - Absence of atypia and mitoses

**Table 4.5** Comparison of inflammatory nasal polyps and antrochoanal polyps

| | Nasal inflammatory polyp (polyposis) | Antrochoanal polyp |
|---|---|---|
| Median age (years) | 50 | 27 (35% occur in children) |
| Source | Ethmoid sinus | Maxilla |
| Bilateral | Yes | No |
| Inflammation | Eosinophilic, mononuclear | Minimal, lymphocytes |
| Histomorphology | Massively edematous sinonasal polyp<br>Sparse seromucinous glands<br>±Thickened basement membrane | Polyp with fibrotic, eosinophilic submucosa with slender stalk<br>Largely devoid of seromucinous glands<br>±Increased vasculature<br>Secondary changes: infarction, stromal atypia |
| % association with CRS | 100% | Up to 65% |
| Association with allergy | High | Low/unclear |
| Recurrences | Increase with eosinophilia | Rare, <2% |
| Treatment | Medical, ±surgery | Surgery |

**Table 4.6** Differential diagnosis of necrotizing sinonasal lesions

| | Etiology/exposure | Histology | Diagnostic and Ancillary studies |
|---|---|---|---|
| **Bacterial** | | | |
| Rhinoscleroma | Endemic in Northern Africa, South America<br>Poor hygienic conditions | Granulomatous, fibrotic process<br>Foamy macrophages containing bacterial organisms (Mikulicz cells) in a background of plasma cells<br>Gram negative, Klebsiella rhinoscleromatis | Gram stain, Warthin-Starry, Brown-Hopps stains |
| Mycobacterial leprosy | Transmission via close contact and possibly secretions<br>Mycobacterium leprae | Nasal biopsy with noncaseating granulomatous inflammation<br>Foamy macrophages with abundant organisms (lepra cells) | Ziehl-Neelsen, Fite stains |
| Mycobacterial tuberculosis | Airborne, respiratory infection with *Mycobacterium tuberculosis* | Sheets of histiocytes intermixed with multinucleated giant cells and areas of caseating necrosis | Ziehl-Neelsen/acid-fast stain, culture, biopsy, PPD skin test |
| Syphilis | Sexually transmitted organism<br>Treponema pallidum | Non-specific mucosal ulceration or hyperplastic epithelium with extensive plasma cells and exocytosis of neutrophils | Warthin-Starry or Steiner stains, direct fluorescent antibody, nucleic acid amplification testing, serologic screening tests |
| **Fungal** | | | |
| Aspergillus | Inhalation exposure<br>Infection ranges from colonization to invasive fungal disease<br>Aspergillus flavus and fumigatus | Necrosis with narrow, septate, acutely branching fungal hyphae, ±fruiting bodies, granulomatous inflammation | Histopathologic findings, PAS or GMS stains, culture |
| Zygomycosis | Airborne exposure affects immunocompromised patients (diabetes, transplant, AIDS)<br>*Mucoromycotina Mucor*, *Absidia*, *Rhizomucor*, *Rhizopus* | Sinonasal mucormycosis<br>Extensive necrosis with broad, pauci-septate, 90-degree branching fungal hyphae | Histopathologic findings, culture, PAS or GMS stains, Calcofluor white with fluorescence microscopy |
| Rhinosporidiosis | Endemic, chronic upper respiratory disease in India and South America<br>*Rhinosporidium seeberi* | Nodular, polypoid tissue with granulomatous inflammation of submucosa, mixed inflammatory infiltrate<br>Large cystic, spore-containing structures (up to 100 um) | Histopathologic findings, PAS or GMS stains, mucicarmine |
| **Parasitic** | | | |
| Leishmaniasis | Parasitic infection transmitted by a sand fly<br>Leishmania species | Ulceration with necrosis, granulomatous, or lymphohistiocytic infiltrate<br>Small, round (1–3 μm) intracytoplasmic organisms in histiocytes | Giemsa or Brown-Hopps stains, PCR, in situ hybridization, TP with Leishman method |

*PPD* purified protein derivative, *PAS* periodic acid-Schiff, *GMS* Gomori methenamine silver, *PCR* polymerase chain reaction, *TP* touch preparation

- The use of basal and myoepithelial markers to demonstrate invasion may be confounding, as some hamartomas lack these abluminal cells.

References: [33, 53–60]

9. *What are the different types of sinonasal papillomas, their associated risk of malignancy, and relationship to human papillomavirus?*

Sinonasal papillomas are benign epithelial neoplasms. There are three types of papillomas that arise from the SNT: exophytic (fungiform), inverted, and oncocytic (cylindrical cell) (Table 4.9). They represent 10–25% of all tumors of the SNT. Half of them arise from the mucosa of the lateral nasal wall; the remainder arise from the maxillary and ethmoid sinuses.

- The inverted type (Fig. 4.7) have an increased risk of synchronous and metachronous squamous cell carcinoma (5–15%).
  - Specimens with inverted papillomas should be wholly submitted for histologic evaluation to rule out malignancy and high-grade dysplasia.
  - Among the inverted papillomas, the incidence of HPV increases approximately two-fold with the presence of dysplasia.
- The oncocytic type (Fig. 4.8) also has an increased risk of malignant transformation.

References: [54, 61–67]

**Table 4.7** Clinicopathologic features of inflammatory diseases of the sinonasal tract

| | Granulomatosis polyangiitis | Eosinophilic granulomatosis polyangiitis | Eosinophilic angiocentric fibrosis |
|---|---|---|---|
| Gender, age (years) | M = F, fourth to fifth decade of life | M > F, third to sixth decade | F:M = 4:1, 19–79 (mean 50) |
| Symptoms | Cough hemoptysis, hematuria, nasal obstruction, epistaxis, rhinorrhea | Allergic rhinitis, polyposis, sinusitis, asthma | Slow progression of nasal obstruction and discharge with swelling, nasal mass and obstruction |
| Clinical findings | Triad: localized or systemic lung, kidney, and sinonasal disease<br>Pulmonary infiltrates, ulcerative mucosal lesions with necrosis, renal impairment | Asthma, nasal polyps, peripheral eosinophilia, pulmonary infiltrates, polyneuropathies | Allergic rhinitis, chronic urticaria, sensitivity to penicillin |
| Site | Nasal cavity>>sinuses | Nasal cavity, lungs, CNS, kidneys | Nasal septum, lateral nasal wall, orbit |
| Associated conditions | Focal glomerulonephritis, necrotizing granulomatous pulmonary disease | Pauci-immune crescentic glomerulonephritis, polyneuropathies | Granuloma faciale, IgG4-related diseases |
| Sinonasal histopathology | Granulomatous inflammation, subepithelial abscess, ulceration, leukocytoclastic vasculitis, or classic vasculitis with fibrinoid necrosis<br>Irregular areas of necrobiotic necrosis with degenerated collagen and basophilic debris | Eosinophilic inflammatory infiltrate with microabscesses<br>Granulomatous vasculitis with eosinophils<br>Necrotizing vasculitis is rare but may show eosinophilic infiltration of vessels | Prominent fibrosis is the hallmark<br>Early: dense, inflammation with eosinophils around vessels, perivascular concentric fibrosis<br>±Plasma cells with phlebitis<br>Late: dense stromal fibrosis in whorls, hypocellular, mixed inflammation with eosinophils |
| Inflammatory infiltrate | Mixed, lymphocytes, histiocytes, plasma cells, rarely eosinophils predominate | Eosinophils predominate | Eosinophils, plasma cells |
| Granulomatous inflammation | Yes | Yes | No |
| Vasculitis | Small, medium vessels | Small, medium vessels | ±Phlebitis, no thrombosis |
| Necrosis | Yes | Yes | No |
| Serology | Autoantibodies to c-ANCA and PR3 | ±c-ANCA and PR3 (~30%) | Elevated serum IgG4<br>Normal ANCA and ESR |
| Treatment | Steroids, immune modulation | Steroids, immune modulation | Surgical |

*CNS* central nervous system, *c-ANCA* cytoplasmic antineutrophil cytoplasmic antibodies, *PR3* proteinase 3, *ESR* erythrocyte sedimentation rate

10. *What are the common sinonasal tumors with established genetic alterations?*

    Specific genetic markers are emerging for an increasing number of sinonasal tumors. Genetic changes define a handful of new tumor entities. These markers not only help to establish the diagnosis but are targets of novel therapies. Table 4.10 includes both tumors that occur exclusively in the sinonasal tract and tumors which arise in other sites but also show a preference for the sinonasal tract.
    References: [68–73]

11. *Which features distinguish sinonasal glomangiopericytoma from solitary fibrous tumor?*

    See Table 4.11.
    References: [74–81]

12. *Are there any features of sinonasal squamous cell carcinomas which are unique to this region?*

    Although the sinonasal tract is the least common site for head and neck squamous cell carcinomas, it is the most common malignancy of this region.

    - As in other locations, SCC shows a male predominance with a median age of 50–60 years old.
    - The principal risk factor is smoking, but occupational exposures to wood dust, nickel, chromium, and formaldehyde play a significant role.
    - Most tumors arise in the nasal cavity and maxillary sinus.
    - Nonkeratinizing squamous cell carcinoma (NK-SCC) accounts for up to 45% of SCC in the SNT.

**Table 4.8** Common hamartomas of the sinonasal tract

| | Respiratory epithelial adenomatoid hamartoma | Seromucinous hamartoma | Nasal chondromesenchymal hamartoma |
|---|---|---|---|
| Age, gender | M > F, third to ninth decades (median sixth decade) | M > F, second to ninth decades | M > F, first 3 months of life up to the second decade |
| Site | Posterior nasal septum>>lateral nasal wall, middle meatus, inferior turbinate, nasopharynx | Posterior nasal septum, lateral nasal cavity, nasopharynx | Nasal cavity>>nasopharynx, sinuses |
| Symptoms | Nasal obstruction, stuffiness, deviated septum, epistaxis, rhinorrhea, chronic recurrent rhinosinusitis, facial pain | Nasal obstruction, nasal stuffiness, epistaxis, and chronic recurrent rhinosinusitis | Respiratory difficulty, facial swelling |
| Clinical | Slow growing, expansile, no bony erosion, up to 6 cm size<br>Rare association with SFT, SN papillomas | Associated with chronic sinusitis, inflammatory polyps, rheumatoid arthritis, and Parkinson disease | Intranasal mass or facial swelling, ±erosion through the cribriform plate<br>Associated t(12;17) translocation |
| Morphology | Proliferation of widely spaced, small- to medium-sized, round to oval glands, surrounded by a thickened, eosinophilic BM<br>The glands are surface epithelium which invaginates downward into the submucosa<br>Lining is multilayered, ciliated respiratory epithelium and admixed goblet cells<br>Edematous stromal tissue with mixed inflammatory infiltrate<br>May have squamous, osseous, or chondroid metaplasia | Submucosal epithelial proliferation of small serous glands with retention of lobular architecture<br>Glands may be densely packed and back-to-back, or haphazard arrangement with larger glands and cysts<br>Lining is cuboidal to flat epithelial cell with round to oval nuclei and basophilic to eosinophilic cytoplasm<br>Peri-glandular hyalinization and invagination of surface respiratory epithelium also present<br>Nuclear pleomorphism, mitotic figures, necrosis, and mucinous cell component are absent | Admixture of chondroid and stromal elements with cystic changes<br>Submucosal proliferation of irregular, cellular nodules of cartilage in a background of bland spindled cells<br>Chondromesenchymal elements are relatively cellular and immature.<br>Loose spindle cell stroma or abrupt transition to hypocellular fibrous stroma at periphery of cartilaginous nodules<br>Cystic areas may be composed of blood-filled cystic spaces or microcysts within myxoid areas<br>Uncommonly shows calcifications, immature bone, perivascular hyalinization, mitotic activity |

*SFT* solitary fibrous tumor, *SN* sinonasal

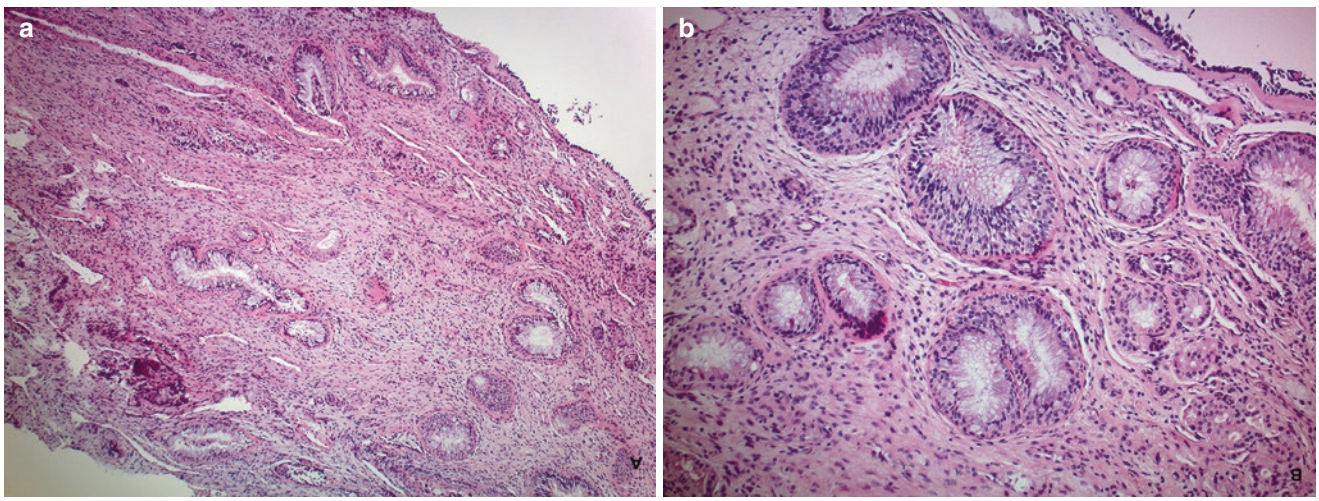


**Fig. 4.5** Respiratory epithelial adenomatous hamartoma. (**a**) A polypoid mucosal lesion with widely spaced glands surrounded by a thick basement membrane. (**b**) The glands are lined by surface ciliated respiratory mucosa

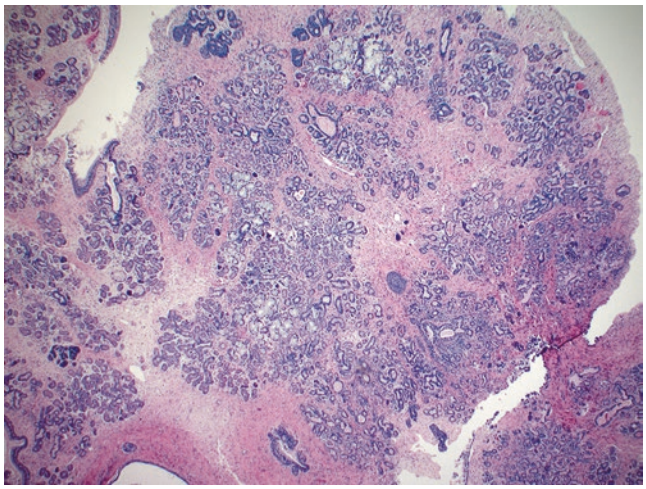

**Fig. 4.6** Sinonasal hamartoma. Proliferation of densely packed, predominantly serous glands, arranged in a lobular architecture. Rare mucinous glands are present toward the center of the lesion

  - The neoplastic cells are basaloid and arranged in ribbons and large nests with a pushing border, reminiscent of transitional cell carcinoma (Fig. 4.9).
  - The morphologic features of nonkeratinizing SCC are highlighted in Table 4.12 where it is compared to the wide range of entities in the differential diagnosis.
  - Up to 50% of cases are associated with high-risk HPV and appear to convey some improved prognosis.
- Keratinizing SCC (K-SCC) of the sinonasal is morphologically similar to SCC at other sites, though the undulating ribbons of tumor typical of NK-SCC can be seen in the keratinizing form as well (Fig. 4.10).
  - K-SCC is the type most frequently associated with malignant transformations of sinonasal papillomas.
  - There is no significant association with HPV.

**Table 4.9** Clinicopathologic features of sinonasal papillomas

| | Exophytic papilloma | Inverted papilloma | Oncocytic papilloma |
|---|---|---|---|
| Proportion of all SN papillomas | 18–50% | 50–78% (most common type) | <7% |
| HPV frequency & types | 50% of cases type 6, 11 | 20-38% of cases type 6, 11 less frequent 16, 18 | Typically absent<br>types 6,11,16,18 (low frequency) |
| Location | Nasal septum | Lateral nasal wall, paranasal sinus | Maxillary antrum, lateral nasal wall, ethmoid sinus |
| Gender | M:F = 2:1 | M:F = 3:1 | M >> F |
| Age (years) | 20–50 | 20–50 | 20–50 |
| Clinical symptoms | Unilateral nasal obstruction, epistaxis | Unilateral nasal obstruction, epistaxis, pain, purulent discharge | Unilateral nasal obstruction |
| Clinical features | Broad-based nodule with papillary or warty surface | Polypoid or nodular growth<br>Multiple lesions may be present<br>Bony erosion due to pressure | Multinodular, brown mass<br>Single or multiple |
| Histology | Stratified, squamous to transitional epithelium with mucous cells, mucin-filled microcysts<br>Exophytic, delicate fibrovascular cores<br>Rare mitoses and dysplasia | Stratified, squamous to transitional epithelium<br>Endophytic growth with scattered mucous cells, mucin-filled microcysts within epithelium<br>Chronic inflammation in stroma<br>Mitoses in basilar or parabasal cells<br>±Dysplasia | Multilayered columnar cells with eosinophilic, granular cytoplasm and small, dark nuclei<br>Endophytic and exophytic growth<br>Surface cilia, intraepithelial neutrophils, mucin-filled microcysts |
| Potential for malignant transformation | Minimal, rare | 3–24% of cases<br>Most commonly K-SCC | 4–17%<br>Most commonly K-SCC, also MEC |
| Recurrence rate | Up to 30% | Up to 75% with conservative excision<br>20% with aggressive surgery | Lower than that of inverted papilloma |

*HPV* human papillomavirus, *K-SCC* keratinizing squamous cell carcinoma, *MEC* mucoepidermoid carcinoma

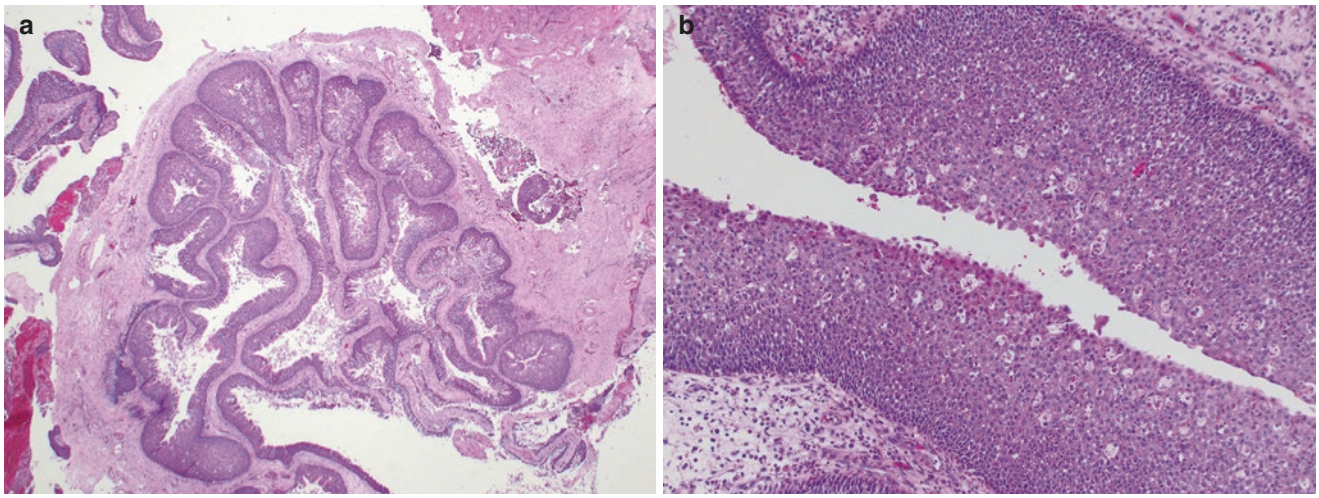


**Fig. 4.7** Inverted sinonasal papilloma. (**a**) Undulating folds of hyperplastic transitional-type epithelium extend deep into the submucosa. (**b**) The lining epithelium is several layers thick, lacks atypia, and contains intraepithelial neutrophils and characteristic microcysts

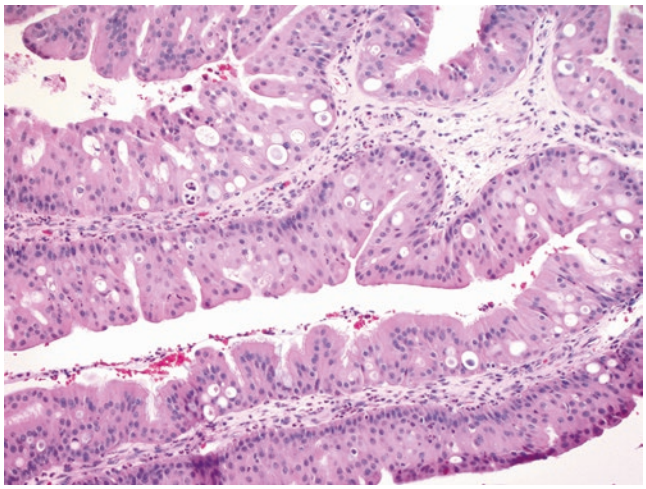

**Fig. 4.8** Sinonasal papilloma, oncocytic type. The lining epithelium is thickened and composed of eosinophilic cells with granular cytoplasm and occasional cilia; prominent microcysts and rare intraepithelial inflammatory cells are also present

- Spindle cell, papillary, and verrucous squamous cell carcinomas are rare in the sinonasal tract.

References: [66–68, 82–84]

13. *What is the differential diagnosis of sinonasal undifferentiated carcinoma?*

Sinonasal undifferentiated carcinoma (SNUC) is a rare, highly aggressive, undifferentiated carcinoma that shows no squamous or glandular differentiation (Fig. 4.11). It is a clinicopathologically distinct neoplasm of the nasal cavity and paranasal sinuses. Loss of a functioning retinoblastoma tumor suppressor gene is implicated in the pathogenesis.

- The differential diagnosis includes other undifferentiated and poorly-differentiated tumors of the SNT and adjacent structures. Table 4.12 compares SNUC with epithelial tumors. Non-epithelial and neuroectodermal tumors that are in the differential diagnosis are discussed later (see question 16).
  - In reviewing Table 4.12, the reader is reminded that, as expected, undifferentiated tumors may show focal staining of various lineage-specific markers (e.g., neuroendocrine, squamous, etc.). The information provided represents the prevailing features and staining patterns.
- Large cell lymphomas are also a diagnostic consideration and easily excluded with the use of lymphoid markers such as CD45, CD20, and CD3.
- SMARCB1-deficient carcinoma is a newly defined subset of undifferentiated sinonasal carcinomas characterized by the loss of SWI/SNF-related matrix-associated, actin-dependent regulator of chromatin, subfamily B, member-1 (SMARCB1) (INI1).
  - The majority of SMARCB1-deficient sinonasal carcinomas display a prominent basaloid morphology with scattered plasmacytoid/rhabdoid cells (Fig. 4.12).
  - The second most common morphologic type comprises sheets and nests of eosinophilic cells (Fig. 4.13). This type is dominated by more rhabdoid-type cells with a moderate amount of eccentric, pink cytoplasm.
- Others in this category contained dyshesive, oncocytic cells with abundant cytoplasm.

**Table 4.10** Genetic alterations associated with sinonasal tumors

| Tumors | Genetic abnormalities | Percentage of cases |
|---|---|---|
| NUT carcinoma | Rearrangement of the nuclear protein in testis gene (NUTM1) | 100% |
| SMARCB1-negative sinonasal undifferentiated carcinoma | Loss of SWI/SNF-related matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 (SMARCB1)/(INI1) | 100% |
| Biphenotypic sinonasal sarcoma | Paired box 3-mastermind-like transcriptional coactivator 3 (PAX3-MAML3) gene fusion | Almost all cases |
| Sinonasal glomangiopericytoma | Beta-catenin gene (CTNNB1) heterozygous mutation | n/a |
| Mucosal melanoma | Cluster of differentiation 117 (CD117) mutation | 25% |
| | Neuroblastoma RAS viral oncogene homolog (NRAS) mutation | 15–20% |
| | BRAF proto-oncogene, serine/threonine kinase (BRAF) mutation | <6% |
| Rhabdomyosarcoma | Paired box 3-forkhead box O1 (PAX3-FOXO1) gene fusion | 70–80% |
| | Paired box 7-forkhead box O1 (PAX7-FOXO1) gene fusion | Uncommon |
| Malignant peripheral nerve sheath tumor | Loss of neurofibromin 1 (NF1) | n/a |
| | Loss of tumor protein 53 (TP53) | n/a |
| Synovial sarcoma | t(X;18) chromosomal translocation | >90% |
| Solitary fibrous tumor | NGFI-A-binding protein 2-signal transducer and activator of transcription 6 (NAB2-STAT6) gene fusion | n/a |
| Epithelioid hemangioendothelioma | WW domain containing transcription regulator 1-calmodulin-binding transcription activator 1 (WWTR1-CAMTA1) | Most cases |
| | Yes-associated protein 1-transcription factor binding to IGHM enhancer 3 (YAP1-TFE3) | Small subset |

*n/a* not available

  - Other uncommon morphologic variants include tumors with:
    - Variably glandular features and mucin production
    - Frank sarcomatoid features (focal or dominant)
  - The immunoprofile of SMARCB1-deficient carcinomas:
    - Positive IHC: strong, diffuse pan-cytokeratin, variable expression of CK5, CK7, p63, and SMARCA4
    - Negative IHC: SMARCB1, NUT, EBV, high-risk HPV
- NUT carcinoma is a recently described, poorly differentiated carcinoma, often with evidence of squamous differentiation (Fig. 4.14), and characterized by a rearrangement of the nuclear protein in testis (NUTM1) gene on chromosome 15q14. In approximately 70% of cases, the partner fusion gene is BRD4 (bromodomain-containing protein 4) on 19p13.1 and less frequently BRD3 or WHSC1L1. The clinicopathologic features are outlined in Table 4.12.
  - Affects patients of all ages with a predilection for young adults.
  - The tumors are generally midline with over 60% of cases arising in the nasal cavity and paranasal sinuses.
  - The diagnosis requires the identification of NUTM1 gene rearrangement or diffuse (>50%) nuclear staining for NUT (monoclonal antibody C52) by immunohistochemistry.
  - The prognosis is poor with median survival of less than a year.

References: [59, 69, 72, 73, 84–97]

14. *What is olfactory neuroblastoma and how is it graded?*

Olfactory neuroblastoma (esthesioneuroblastoma) is a rare neuroectodermal malignancy thought to arise from basal reserve cells (stem cells) of the olfactory mucosa. Olfactory neuroblastoma (ONB) comprises 3–6% of all malignancies in the sinonasal tract.

- ONB arises almost exclusively in the superior portion of the nasal cavity with involvement of the cribriform plate, superior turbinate, and the superior nasal septum.
- Patients range in age from childhood to the elderly with a peak in the fifth to sixth decades. They present with nasal obstruction and epistaxis. Paradoxically, anosmia is reported in less than 5% of patients. Rarely, patients present with production of ectopic adrenocorticotropic hormone and inappropriate secretion of antidiuretic hormone secretion.
- Imaging shows the classic "dumbbell-shaped" mass spreading across the cribriform plate.

**Table 4.11** Comparison of sinonasal glomangiopericytoma and solitary fibrous tumor

| | Glomangiopericytoma | Solitary fibrous tumor |
|---|---|---|
| Synonyms | Sinonasal-type hemangiopericytoma-like tumor | Hemangiopericytoma; giant cell angiofibroma |
| Incidence among sinonasal tumors | Rare (<0.5%) | Very rare (0.1%) |
| Age | 5–90 years (mean 70 years) | 20–80 years (median 50 years) |
| Gender | Female > Male (1.2:1) | Male = Female |
| Size (mean) | 0.8–8 cm (3 cm) | 1–6 cm (2.5 cm) |
| Site | Nasal cavity: turbinate and septum<br>Sinus: maxillary and ethmoid | Anywhere in sinonasal tract<br>Maxillary sinus > sphenoid/ethmoid > nasal cavity > nasopharynx |
| Presentation | Painless, polypoid mass<br>Nasal obstruction, epistaxis, difficulty breathing, sinusitis, headache, congestion, pain, discharge | Polypoid, firm, unilateral, slow-growing mass<br>Painless, obstructive symptoms, epistaxis and rhinorrhea |
| Radiographic findings | CT: Sinus opacification with bone erosion or sclerosis<br>MRI: T1-weighted low/intermediate signal intensity<br>T2-weighted heterogeneous, high signal intensity | CT: Well-circumscribed tumor<br>MRI: T1-weighted low/intermediate signal intensity<br>T2-weighted heterogeneous, high signal intensity |
| Histologic features | Surface epithelium usually intact<br>Bland, oval to spindled cells, cellular proliferation<br>Hypercellular, whorled-storiform pattern<br>Minimal collagenous stroma<br>Prominent perivascular hyalinization<br>Typical branching, "staghorn"-like, thin-walled vessels<br>Rare mitoses, no necrosis | Intact surface epithelium<br>Unencapsulated, circumscribed mass below an intact epithelium<br>Bland, blunt spindled cells with uniform nuclei<br>Patternless growth pattern<br>Alternating hypo- and hypercellular areas, separated by thick bands of "ropey," keloidal or hyalinized collagen<br>Rare "staghorn" vessels<br>No invasion, mitoses, necrosis, or ulceration |
| Positive IHC | (n)ß-catenin, SMA, actin-HHF-35, vimentin<br>Ki-67, low (<5%) | str diff CD34, str diff BCL-2, str CD99, str diff (n)STAT6 (NAB2–STAT6 gene fusion)<br>Ki-67, low (<5%) |
| Negative IHC[a] | S100, CD31, CK, EMA, CD34[a], BCL-2[a] | (n)ß-catenin, S100, desmin, SMA |
| Malignant potential | Rare cases<br>Profound pleomorphism, increased mitotic activity, necrosis | Rare cases, <2%<br>Infiltrative, high cellularity, pleomorphism, atypical mitoses, necrosis, mitoses >4/10 hpf<br>Histology does not reliably determine behavior |
| Treatment | Wide surgical excision, radiation used in nonsurgical candidates | Complete conservative local excision |
| Prognosis | Excellent, ~20% recurrences | Excellent, <10% recurrences |

*n* nuclear, *c* cytoplasmic, *SMA* smooth muscle actin, *str* strong, *diff* diffuse, *hpf* high power field
[a]Negative IHC may be weak or focal

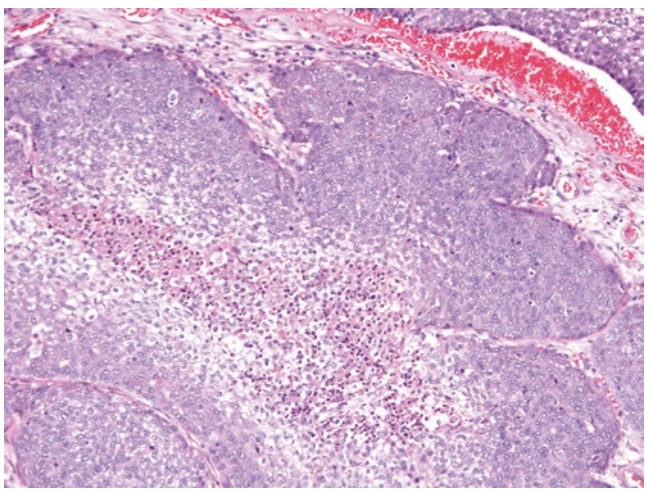

**Fig. 4.9** Nonkeratinizing squamous cell carcinoma. Interconnecting ribbons of atypical squamous epithelium invade the stroma with a broad, pushing border and central necrosis. The squamous cells have scant cytoplasm, moderate nuclear atypia, and numerous mitoses

**Table 4.12** Epithelial tumors in the differential diagnosis of sinonasal undifferentiated carcinoma

| | **Sinonasal undifferentiated carcinoma** | **Nonkeratinizing squamous cell carcinoma** | **Nasopharyngeal carcinoma/ lymphoepithelial carcinoma** | **Sinonasal neuroendocrine carcinoma[a]** | **NUT midline carcinoma** |
|---|---|---|---|---|---|
| Age (years) | 53–58 (3rd–9th decades) | >60 | 40–60 | 26–77 (mean 51) | 0–82 (median 21.9) |
| Gender | M:F = 3:1 | M:F = 2:1 | M:F = 3:1 | M = F | Slight F > M |
| Site | Nasal cavity, maxillary antrum, ethmoid sinus | Maxilla>nasal cavity>ethmoid sinus | Lateral nasopharyngeal wall, rarely primary to SNT (nasal cavity) | Nasal cavity, ethmoid, maxillary sinus | Usually midline Nasal cavity, paranasal sinuses |
| Symptoms and presentation | Nasal obstruction, discharge, epistaxis, swelling, and pain Infiltrative, rapidly growing large mass, locally extensive disease | Nasal obstruction or discharge, epistaxis | Hearing loss, otitis media, pharyngeal pain, nasal obstruction, epistaxis frequently presents with neck mass and nodal disease | Epistaxis, exophthalmos, nasal obstruction, large mass Presents with advanced local and distant disease | Non-specific symptoms with rapidly growing mass, nasal obstruction, pain, epistaxis, nasal discharge, proptosis |
| Morphology | Sheets and lobules of malignant cells with round, vesicular nuclei with prominent nucleoli and variably sized cytoplasm Nuclear pleomorpism is not typical ±High N:C ratio Necrosis, LVI, brisk mitotic activity No squamous differentiation or keratin formation ±Surface dysplasia | Broad interconnecting bands, ribbons, or nests of cells Pushing, endophytic growth ±Papillae Oval nuclei, coarse chromatin, scant cytoplasm, focal palisading None/rare keratinization Numerous mitoses, necrosis | Syncytial sheets, cords or single spindle cells with large vesicular nuclei, scant cytoplasm Prominent lymphoplasmacytic infiltrate may obscure the tumor cells | Nests, sheets or ribbons of small or large cells with scant cytoplasm Hyperchromatic to fine chromatin Individual cell necrosis, nuclear molding in small cells Frequent mitoses, necrosis, LVI, PNI | Sheets of large, monomorphous cells with scant to moderate, pale cytoplasm Round to oval, vesicular nuclei, conspicuous nucleoli High mitotic activity, necrosis Abrupt keratinization or large foci of squamous differentiation |
| **Immunohistochemistry** | | | | | |
| | **SNUC** | **NK-SCC** | **NPC/LEC** | **SNEC** | **NUT-MC** |
| Pan-cytokeratin | Positive | Positive | Positive | Positive (perinuclear, dot-like) | Positive |
| Cytokeratin 5/6 | Negative | Positive | Positive | Negative[b] | Positive |
| p63/p40 | Var positive/Negative | Positive/Positive | Positive/Positive | Negative[b]/Negative | Positive/Positive |
| EBV/EBER | Negative | Negative | Positive | Negative | Negative |
| p16 (HR-HPV) | Positive (Variable) | Positive (50% positive) | Negative | Positive (Rare) | Occasional positive |
| Neuroendocrine markers | Negative[b] | Negative | Negative | Positive | Occasional positive |
| Additional positive stains | NSE, EMA, CK7, CK8/18, p53, c-Kit | CK14, CK13, (n) SMARCB1/INI | CK14 | TTF-1, CK7, EMA, var S100 | str diff (n)NUTM1 (speckled), str diff CD34 |
| Additional negative stains | CEA, S100, CD45 | CK7, S100, NUT | CK7, CK20 | p63, p40, SOX10 | Myoglobin, PLAP, desmin, CD99 |

*Var* variable expression, *str* strong, *diff* diffuse, *(n)* nuclear, *PLAP* placental alkaline phosphatase

[a]Includes small cell and large cell variants

[b]Rare focal positive cells, rare cases positive

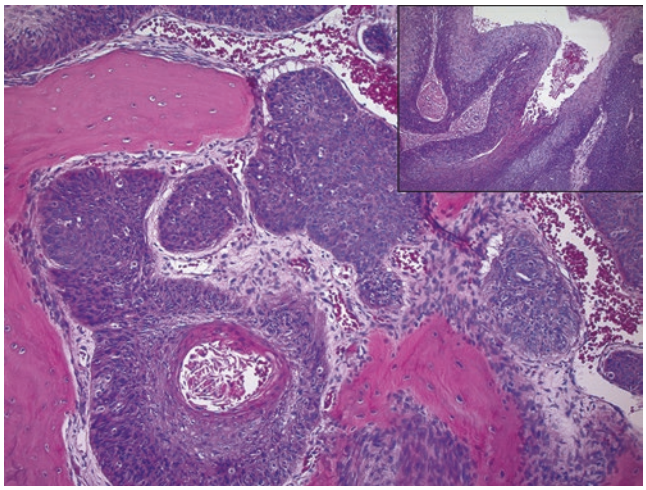

**Fig. 4.10** Keratinizing squamous cell carcinoma of the maxillary sinus. Nests of carcinoma cells invade maxillary bone; keratin pearl formation is evident. Inset shows the classic ribbons and trabecular of sinonasal squamous cell carcinoma

- Morphology varies by grade and tends to reflect differentiation. ONB is characterized by a nested or lobular growth pattern and rosette formation.
  - Low-grade tumors are composed of well-circumscribed nests and lobules separated by fibrovascular stroma. The majority of tumors have a variable amount of fibrillary stroma.
    - The tumor cells are uniform, small- or medium-sized with pale, eosinophilic cytoplasm and indistinct borders. The nuclei are round with fine to vesicular chromatin and absent or inconspicuous nucleoli. There may be mild nuclear atypia or a low mitotic rate.
    - Flexner-Wintersteiner rosettes are true rosettes with a central lumen, indicative of olfactory differentiation, but are rarely seen.
  - High-grade tumors show more marked nuclear atypia, pleomorphism, prominent nucleoli, and increased mitotic activity. The fibrillary back-

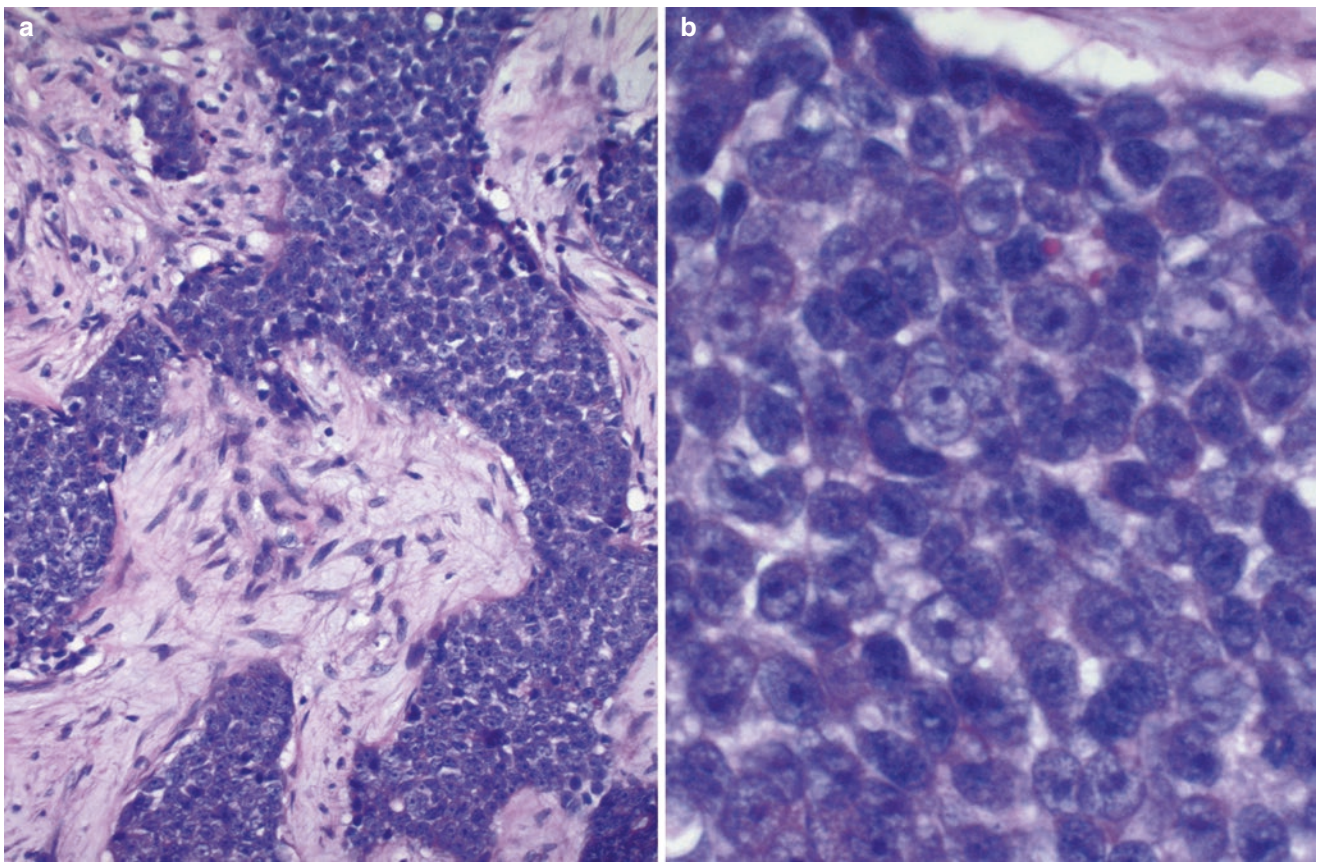


**Fig. 4.11** Sinonasal undifferentiated carcinoma. (**a**) Trabeculae of tumor cells in a fibrous stroma. (**b**) The cells look overtly malignant but lack anisonucleosis. They have a scant to moderate amount of cytoplasm; round, vesicular nuclei; and prominent nucleoli

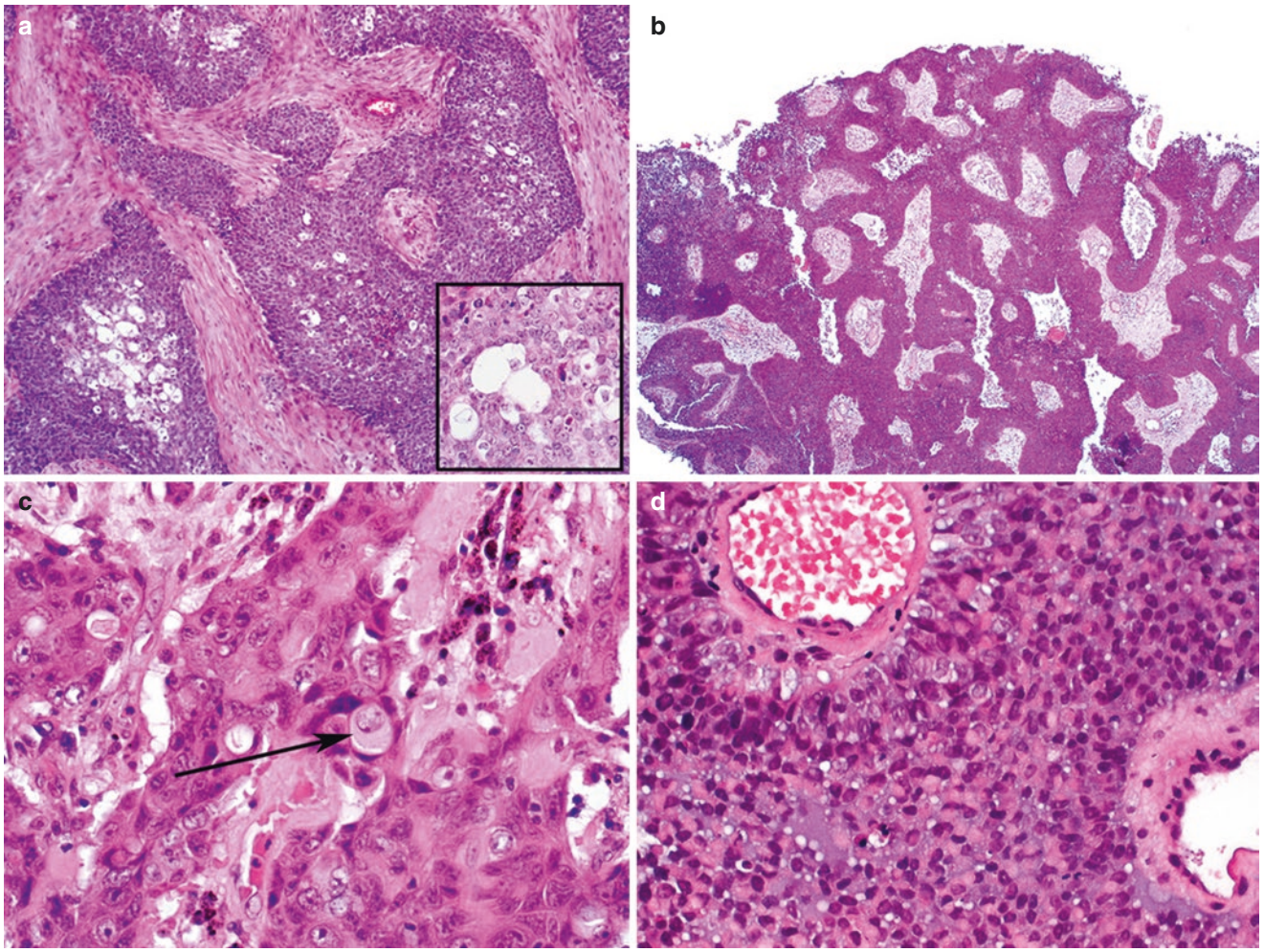


**Fig. 4.12** SMARCB1-deficient sinonasal carcinoma. (**a**) A common histologic pattern shows nests of basaloid cells with occasional vacuoles (inset) and high N:C ratios in a desmoplastic stroma. (**b**) An inverted growth pattern similar to inverted Schneiderian papilloma may be seen. (**c**) Rare, singly dispersed plasmacytoid or rhabdoid cells (arrow) may be present. (**d**) In rare cases, the basaloid tumors demonstrate a predominantly plasmacytoid/rhabdoid morphology, as noted in this lung metastasis

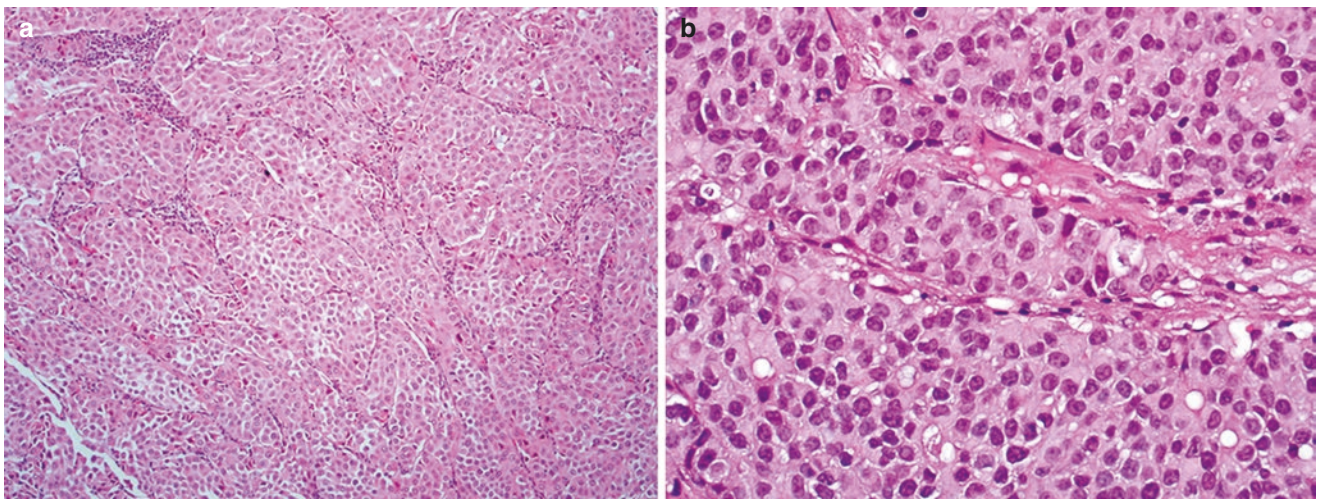


**Fig. 4.13** SMARCB1-deficient sinonasal carcinoma. (**a**) The second most common appearance shows a nested or solid proliferation of oncocytic cells with cellular dyshesion. (**b**) The tumor cells have abundant, pink, eccentrically located cytoplasm with a rhabdoid appearance. (**c**) Rare cases grow in a multinodular, "pseudogranulomatous" pattern. (**d**) Other areas show glandular differentiation with mucin

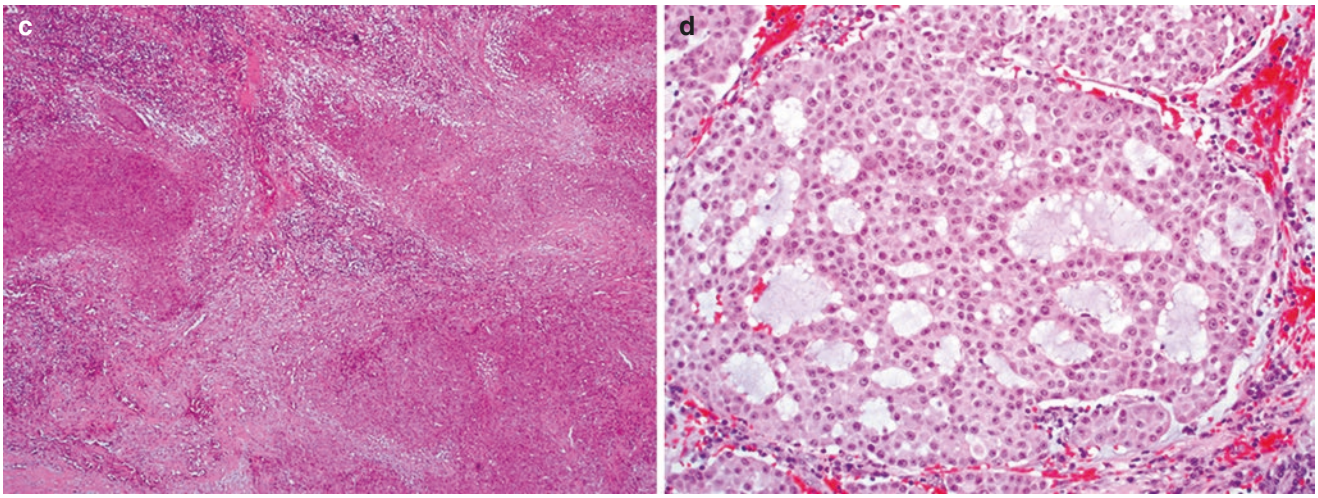


**Fig. 4.13** (continued)

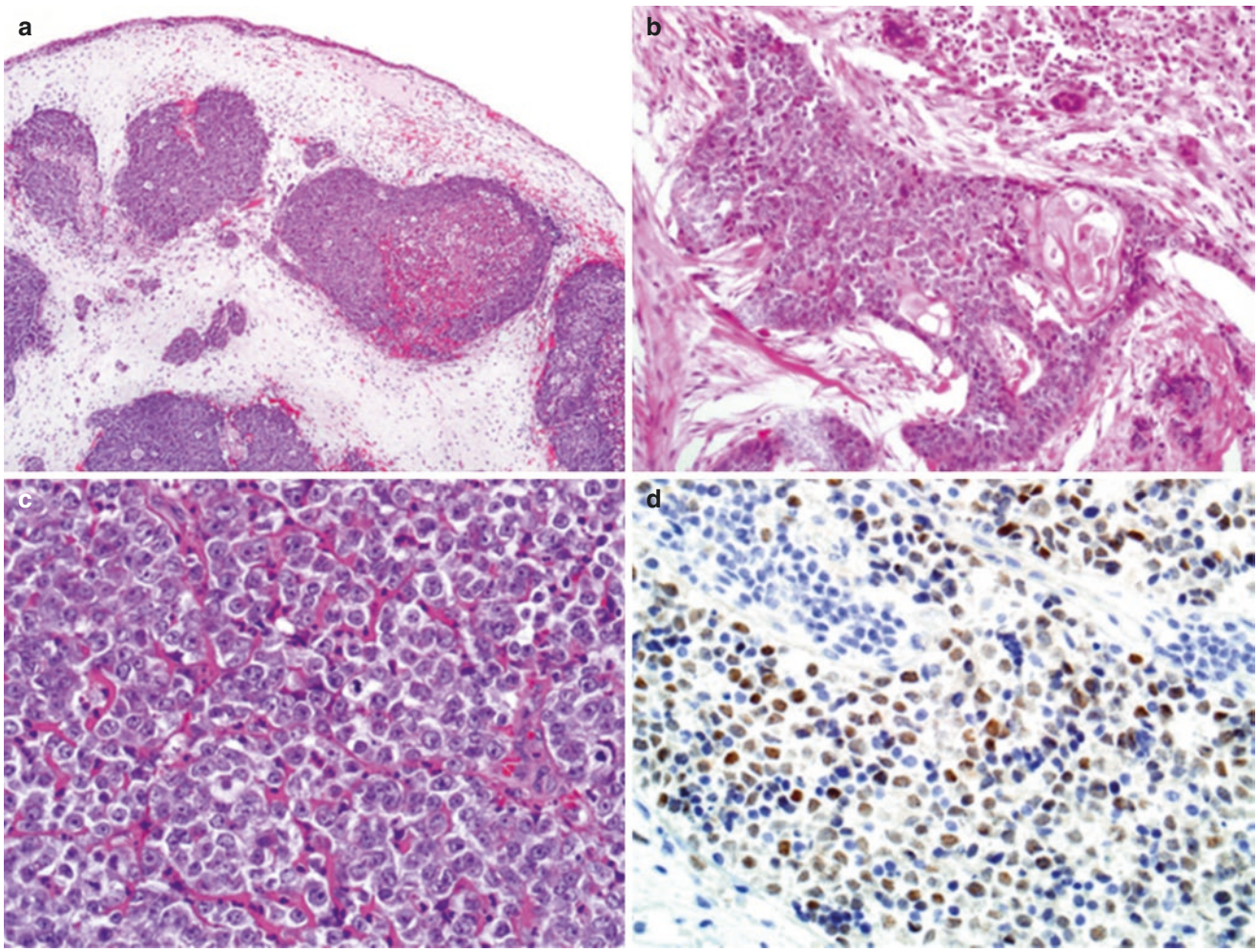


**Fig. 4.14** NUT midline carcinoma. (**a**) The tumor cells grow in nests in the sinonasal submucosa. (**b**) Abrupt keratinization is typical. (**c**) The cells are monotonous with minimal pleomorphism but brisk mitotic activity. (**d**) Immunohistochemistry for NUT-1 is diffusely positive in tumor nuclei with a speckled pattern

**Table 4.13** Hyams grading system for olfactory neuroblastoma

| Grade | Lobular architecture | Fibrillary matrix | Rosettes | Nuclear pleomorphism | Mitotic index | Necrosis |
|---|---|---|---|---|---|---|
| I | + | Prominent | HW rosettes | None | None | None |
| II | + | Present | HW rosettes | Moderate | Low | None |
| III | ± | Low | FW rosettes | Prominent | Moderate | Rare |
| IV | ± | Absent | Rare | Marked | High | Common |

*HW* Homer Wright rosettes, *FW* Flexner-Wintersteiner rosettes

ground is much less prominent, and necrosis may be present.
    - Pseudorosettes (Homer-Wright rosettes) with peripherally located nuclei around a fibrillary center are typical but may only be focal.
  - Glandular, squamous, myogenic, ganglion, or melanocytic differentiation is possible but exceedingly rare.
- The Hyams grading system (Table 4.13) takes into account the above morphologic features. A high tumor grade (III and IV) significantly correlates with poor outcomes but not necessarily with stage.
  - The presence of necrosis, frequent mitoses, and pleomorphism are the best determinants of high-grade tumors.
- The differential diagnosis of ONB includes the small round blue cell tumors seen in the sinonasal tract (see question 17).

References: [98–106]

15. *What are the histopathologic features of sinonasal melanoma, how do they differ from cutaneous melanomas, and which features are prognostic indicators?*

The sinonasal tract is the most common head and neck mucosal site for melanomas. The nasal cavity is the most frequent location. Patients are usually middle-aged (range 30–90 years old), and there is no significant gender predominance.

- The presentation is related to mass effect and includes nasal obstruction, nasal polyp, and epistaxis.
  - Approximately 40% of patients present with advanced disease in the form of extensive local progression and distant metastases.
- The majority of sinonasal melanomas are amelanotic. Some show an intraepithelial or junctional component in the overlying mucosa. The tumors have diverse morphology like its cutaneous counterpart and include epithelioid, spindled, small cell, and pleomorphic types.
  - Tumor cells have round nuclei and prominent nucleoli with a moderate to abundant amount of eosinophilic or amphophilic cytoplasm. Nuclear pleomorphism is the rule, though spindled and small cell forms may show more monotony.
  - The cells are arranged in sheets or large nests and demonstrate a slightly dyshesive quality.
  - Variants may show plasmacytoid, dense, pink cytoplasm and more hyperchromatic nuclei mimicking rhabdoid tumors.
- Histologic features such as ulceration, depth, growth phases, and pagetoid spread have no impact on prognosis.
- Unlike skin melanomas, only a minority of cases harbor BRAF gene mutations, limiting targeted therapy options.
- Five-year survival averages 30%; median survival is 2 years.

References: [107–115]

16. *What is the differential diagnosis of small round blue cell tumors in the sinonasal tract?*

The differential diagnosis of small round cell tumors in the sinonasal tract includes a wide variety of epithelial, neuroectodermal, and mesenchymal tumors. J. S. Lewis put forth the helpful acronym "NOSE ALARM": *N*UT-midline carcinoma, *O*lfactory neuroblastoma, *S*mall cell and sinonasal undifferentiated carcinomas, *E*wing sarcoma, *A*denoid cystic carcinoma, *L*ymphoma, *A*lveolar *R*habdomyosarcoma, and *M*elanoma. Table 4.12 addresses the epithelial tumors and Table 4.14 addresses the non-epithelial entities on the list.

- With the exception of adenoid cystic carcinoma, all of the above are relatively rare. Though, olfactory neuroblastoma and melanoma are among the most common.
- RMS is the most common sinonasal tract sarcoma in adults and children.
- Not included in this list, but an important consideration, is an extracranial or ectopic pituitary adenoma which can mimic neuroendocrine carcinomas and should be considered in this differential diagnosis (see question 22). Use of pituitary hormone IHC can aid in the diagnosis.

References: [70, 71, 107, 113–127]

**Table 4.14** Small blue cell tumors of the sinonasal tract

| | Sinonasal undifferentiated carcinoma | Sinonasal neuroendocrine carcinoma | PNET/Ewing sarcoma | Olfactory neuroblastoma | Rhabdomyosarcoma | Sinonasal melanoma |
|---|---|---|---|---|---|---|
| Age (years) | 53–58 (3rd–9th decades) | 26–77 (mean 51) | Children/teens (median 12) | 11–90 (peaks at 15 and 50) | 1st decade of life | 50 (median 70) |
| Gender | M:F = 3:1 | M = F | M > F | M = F | M = F | M = F |
| Site | Nasal cavity, maxillary antrum, ethmoid sinus | Nasal cavity, ethmoid, maxillary sinus | Maxillary sinus, nasal cavity | Superior nasal cavity<br>Cribriform plate | Paranasal sinuses, nasal cavity | Anterior septum, inferior or middle turbinate, maxillary antrum, ethmoid sinuses |
| Presentation | Nasal obstruction, discharge, epistaxis, swelling, and pain<br>Infiltrative, rapidly growing large mass, locally extensive disease | Epistaxis, exophthalmos, nasal obstruction, large mass<br>Presents with advanced local and distant disease | Polypoid or multilobular mass with nasal obstruction, ulceration<br>Rapid growth<br>Bone pain | Polypoid, dumbbell-shaped soft tissue mass, nasal obstruction, epistaxis, pain, anosmia, visual disturbances, proptosis | Nasal obstruction, pain, facial swelling, proptosis, polypoid mass, and epistaxis | Polypoid or sessile brown to black nodules, ulceration, epistaxis, nasal obstruction, black mucus discharge |
| Morphology | Sheets and lobules of medium to large, polygonal cells with moderate amount of cytoplasm<br>Vesicular nuclei with prominent nucleoli<br>Extensive necrosis, LVI<br>Brisk mitotic activity<br>±Surface dysplasia | Nests, sheets or ribbons of small or large cells with scant cytoplasm<br>Hyperchromatic to fine chromatin<br>Individual cell necrosis, nuclear molding in small cell type<br>Frequent mitoses, necrosis, LVI, PNI | Hypercellular tumor sheets of small to medium, uniform, round cells with small round nuclei with fine chromatin, scant, pale cytoplasm<br>±HW rosettes<br>Mitoses | Submucosal, well-circumscribed mass<br>Nests and sheets of cells with small, round to ovoid nuclei, fine, speckled chromatin and pale cytoplasm<br>Pink, fibrillary stroma<br>±Rosette formation<br>Mitoses, necrosis, pleomorphism per grade | Sheets or nests of primitive round to spindle cells with scant cytoplasm, hyperchromatic nuclei<br>Spindle variant also ±Rhabdomyoblasts with dense, eosinophilic cytoplasm<br>Necrosis | Variably sized, pleomorphic epithelioid cells, moderate to abundant amphophilic cytoplasm, prominent nucleoli<br>Epitheliotropism, ±Pigment |
| Prognosis | Poor<br>20–25% OS at 5 years | Poor<br>Median survival of 14.5 mn<br>Recurrences, DM | 60% 5-year DFS | Local recurrences 29–38%<br>Metastases (LN, DM) 16–46% | Poor<br>5-year survival 40–45% | Poor<br><40% 5-year survival<br>recurrences common |
| **Immunohistochemistry** | | | | | | |
| | **SNUC** | **SNEC** | **ES** | **ONB** | **RMS** | **SNM** |
| Pan-cytokeratin | Positive | Positive | Negative[a] | Negative[a] | Negative[a] | Negative |
| Cytokeratin 5/6 | Negative | Negative[a] | Negative[a] | Negative | Negative[a] | Negative |
| EBV | Negative | Negative | Negative | Negative | Negative | Negative |
| CD99 | Positive | Negative | (m)Positive | Negative | Var positive | Negative |
| S100 | Negative | Var positive | Var positive | Sustentacular | Negative | Positive |
| Neuroendocrine markers | Negative[a] | Positive | Var positive | Positive | Negative[a] | Negative |
| Lymphoid markers | Negative | Negative | Negative | Negative | Negative | Negative |
| Melanocytic markers | Negative | Negative | Negative | Negative | Negative | Positive |
| Other positive ancillary studies | var p63, CK7,CK8, CK18, p16 | TTF-1, ±CK7, EMA | FLI-1, CD117, PAS t(11;22) fusion of EWS/FLI1 genes | NSE, CD56, CD57, var BCL-2, p53 | Desmin, myogenin, MyoD1, myoglobin, SMA, CD56 t(2;13), PAX3/PAX7-FKHR gene fusion | SOX10, tyrosinase, MiTF, FLI-1 |
| Other negative ancillary studies | CEA, CD45 | p63, p40, SOX10 | PASD, myoD1, myogenin, HMB45, desmin[a] | FLI-1[a], p63 | SOX10, p63 | p63, p16, p40 |

*SNUC* sinonasal undifferentiated carcinoma, *SNEC* sinonasal neuroendocrine carcinoma, *SmCC* small cell carcinoma, *ES/PNET* Ewing sarcoma/primitive neuroectodermal tumor, *NB* neuroblastoma, *RMS* rhabdomyosarcoma, *LVI* lymphovascular invasion, *OS* overall survival, *LN* lymph node, *DM* distant metastases, *var* variable expression, *str* strong, *diff* diffuse, *(n)* nuclear, *(m)* membranous, *CEA* carcinoembryonic antigen, *MiTF* microphthalmia-associated transcription factor

[a]Rare focal positive cells

17. *What are the common salivary gland tumors of the sinonasal tract?*

Salivary gland tumors of the sinonasal tract are relatively common. The histopathological appearance of these tumors is similar to those arising in the major and minor salivary glands.

- Pleomorphic adenoma (PA) is the most frequent salivary gland tumor of the sinonasal tract, comprising approximately 25% of all sinonasal glandular tumors. PA usually presents in the third to sixth decades of life, with a mean of 40 years and slight female predominance.
  - Most cases arise in the submucosa of the bony or cartilaginous nasal septum and less common in nasal turbinates and lateral wall. Patient presentation depends on the site and includes unilateral nasal obstruction, epistaxis, and sinusitis.
  - Tumors range in size from 0.5 to 5 cm and present as a mucosa-covered, firm, polypoid mass with a broad base.
  - Histologically, PA of the sinonasal tract does not differ significantly from those of minor salivary gland. They are typically unencapsulated but well-circumscribed. Tumors may show a myoepithelial predominance with less stroma.
  - 2–10% of PAs in the nasal cavity undergo malignant transformation (usually adenoid cystic carcinoma).
- Adenoid cystic carcinoma (AdCC) is the most common salivary gland carcinoma of the sinonasal tract. It is the second most common sinonasal malignancy overall (after squamous cell carcinoma), representing 10–18% of all sinonasal malignancies. AdCC usually occurs in the maxillary sinus or the nasal cavity.
  - Histologic features of sinonasal AdCC are identical to those of the major salivary glands. Similarly, most harbor the MYB-NFIB gene rearrangement.
  - Long-term prognosis of AdCC is poor due to aggressive, local spread.
  - AdCC should be distinguished from the recently identified entity HPV-related multi-phenotypic carcinoma (see question 17). These tumors are biphasic but negative for MYB rearrangements and positive for p16 and HR-HPV. They also tend to show some associated squamous dysplasia.
- Mucoepidermoid carcinoma is less common in this region, accounting for approximately 5% of sinonasal glandular tumors.

References: [101, 128–132]

18. *What are the morphologic, immunohistochemical, and molecular features of HPV-related multi-phenotypic carcinoma?*

HPV-related multi-phenotypic carcinoma is a sinonasal-specific carcinoma of both surface epithelial and salivary gland origin. The salivary gland component may resemble adenoid cystic carcinoma, basal cell adenocarcinoma, or epithelial-myoepithelial carcinoma. HPV-related multi-phenotypic carcinoma is a rare, but likely distinct, entity with reports currently limited to small series. It shows a slight female predominance with a wide age range (mean 54 years).

- The tumor is submucosal and shows predominantly large, solid nests of basaloid cells with angulated, hyperchromatic nuclei and scant cytoplasm (Fig. 4.15).
  - Some areas show the classic cribriform architecture of adenoid cystic, with microcysts filled with basophilic, mucoid material. Others show a more ribbon-like architecture with pushing borders similar to nonkeratinizing squamous cell carcinoma.
  - The basaloid cells may demonstrate myoepithelial differentiation, and true duct formation can be seen. Overt squamous differentiation is not typical, but overlying surface dysplasia can be seen.
  - The myoepithelial and ductal cells stain for typical, lineage-specific markers, and both cell types stain for p16.
  - Mitoses and necrosis are common.
  - The tumors characteristically harbor transcriptionally active high-risk HPV, most commonly HPV types 33 and 35; type 16 is rare in contrast to

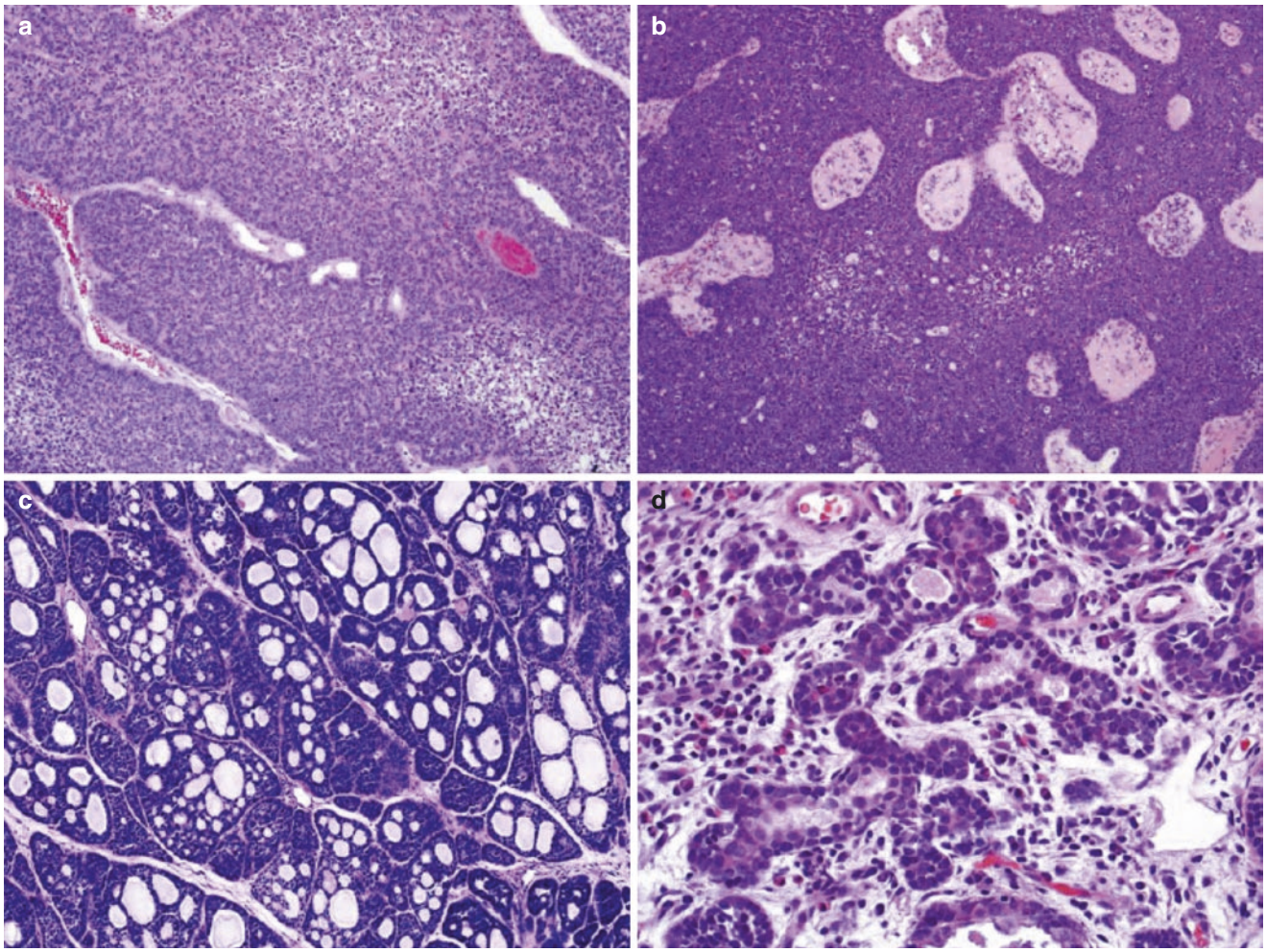


**Fig. 4.15** HPV-related multi-phenotypic sinonasal carcinoma. The tumor demonstrates varied growth patterns including (**a**) a predominantly solid growth with (**b**) an inverted pattern and fibrovascular cores. (**c**) A cribriform growth pattern resembling adenoid cystic carcinoma is common. (**d**) Focal tubular growth is noted in this case

most head and neck carcinomas. All the tumors tested are negative for MYB gene fusions that are typical of true adenoid cystic carcinomas.

- Despite the high-grade histology, it demonstrates a relatively indolent behavior.

References: [59, 97, 130, 132, 133]

19. *What are the types of non-salivary sinonasal adenocarcinomas?*

Sinonasal adenocarcinomas comprise 10–20% of sinonasal primary malignancies. They are divided into two main categories: intestinal-type adenocarcinoma (ITAC) and non-intestinal-type adenocarcinoma (non-ITAC) which is further divided into low and high grades.

- ITAC is the most common sinonasal tract adenocarcinoma (after adenoid cystic carcinoma). It predomi-

nantly affects men in the 60th decade of life. Wood and leather dust exposure is a significant risk factor.
- There are four different morphologic patterns (Table 4.15) with varying amounts of papillae, glands, and tubules.
- Cells have a typical colonic adenocarcinoma appearance with cigar-shaped, hyperchromatic nuclei and a pseudostratified epithelium (Fig. 4.16). Grade varies from well to poorly differentiated.
- The mucinous type may show more cuboidal cells and signet ring cells in pools of mucin.
- Tumors show obvious invasion and complex architecture with perineural invasion, luminal necrosis, and bone involvement.
- In contrast to primary gastrointestinal tumors, ITAC shows weak expression of CEA and focal chromogranin and synaptophysin staining.

**Table 4.15** Comparison of the morphologic categories of ITAC and survival rates

| Barnes et al. | Kleinsasser, Schroeder | Morphology | 3-year overall survival |
|---|---|---|---|
| Papillary (18%) | PTCC-I | Predominantly papillary with rare tubules, villi can be seen | 82% |
| Mixed | Transitional | Various morphologies | 71% |
| Colonic (40%) | PTCC-II | Glands and tubules mimic colonic adenocarcinoma | 54% |
| Solid | PTCC-III | Poorly differentiated, solid growth | 36% |
| Mucinous | Alveolar goblet | Pools of mucin with floating cells | 48% |
| | Signet ring | | 0% |

*PTCC* papillary tubular cylinder cell

- The morphologic types of ITAC correspond to overall survival (see Table4.15) in the two systems proposed by Barnes et al. and Kleinsasser and Schroeder. Lymph node and distant metastases average 3% and 12%, respectively. However, the overall prognosis is poor.

- Non-ITAC shows a wide age range from childhood to the seventh decade of life with a median age of 60. There is a slight male predominance among the high-grade tumors; low-grade tumors have an equal gender distribution. The ethmoid sinus and nasal cavity are the most common locations, though cases occur in the nasopharynx as well. Table 4.16 compares the non-ITAC to ITAC.
  - Low-grade non-ITAC has a highly variable architecture but is mainly glandular and papillary.
    - Tumors show complex, back-to-back, closely packed glands with minimal stroma, desmoplasia, and an absent basal cell layer (Fig. 4.17).
    - The glands typically have only a single layer of cuboidal to low columnar cells, with pale cytoplasm and round, bland, basally located nuclei.
  - High-grade non-ITAC, in contrast, shows necrosis, cellular pleomorphism, and significant mitotic activity. Solid growth is more common (Fig. 4.18).

References: [54, 134–139]

20. *What are the morphologic and genetic features of biphenotypic sinonasal sarcoma?*

Biphenotypic sinonasal sarcoma (BSNS) is a low-grade spindle cell sarcoma with neural and myogenic differentiation. Less than 50 cases are reported in the literature. BSNS typically arises in the superior aspects of the nasal cavity and ethmoid sinuses. It is more com-

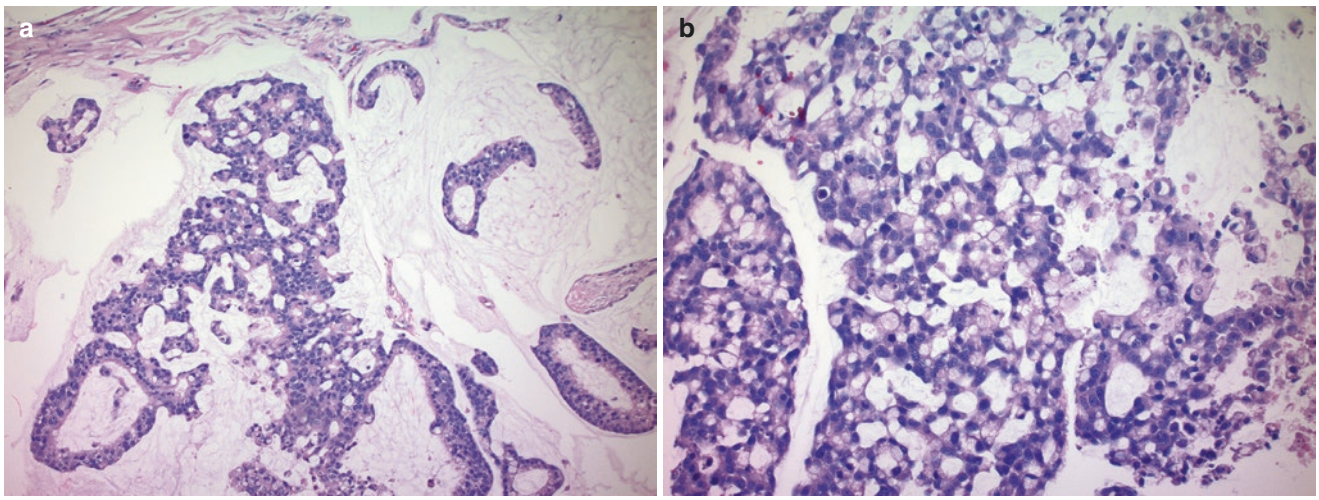


**Fig. 4.16** Sinonasal intestinal-type adenocarcinoma. (**a**) Cribriform glands floating in mucin pools. (**b**) Tumor nuclei are round to oval with conspicuous nucleoli, some signet ring forms, and frequent mitoses. Necrosis is present (lower right)

**Table 4.16** Comparison of non-salivary sinonasal adenocarcinomas

| | ITAC | | Non-ITAC, LG | | Non-ITAC, HG | |
|---|---|---|---|---|---|---|
| Associations | Hardwood and leather dust workers (30-fold risk) | | 20% concurrent hamartomas | | Oncocytic sinonasal papilloma | |
| Architecture | Varies from well to poorly differentiated based on type<br>Most common type is colonic mainly exophytic with papillary, glandular and tubular growth | | Complex growth with back-to-back glands and minimal intervening stroma<br>Clear invasion with desmoplasia | | Solid, nested, trabecular growth | |
| Cytology | Atypical columnar cells with oval, cigar-shaped nuclei, vesicular chromatin, variable nucleoli<br>Pseudostratified nuclei<br>±goblet cells, ±Paneth cells<br>Luminal necrosis, mitoses | | Bland cuboidal, low columnar cells with round nuclei, absent or inconspicuous nucleoli<br>Single cell layer, basally located nucleus<br>No necrosis, rare mitoses | | High-grade nuclei, pleomorphic, coarse chromatin<br>Necrosis, numerous mitoses | |
| CK7 | Variable | | Positive | | Positive | |
| GI markers: CK20, CDX2, MUC2 | Positive | | Negative | | Negative | |
| Differential diagnosis and contrasting IHC | ITAC:<br>wk CEA+<br>Chromo+<br>Synapto+ | Colon metastasis:<br>str CEA+<br>Chromo–<br>Synapt– | Non-ITAC:<br>GI markers–<br>Basal/myoep cells absent (calponin–, SMA–, p63–) | ITAC: GI markers+<br>Hamartomas: Basal/myoep cells present (calponin+, SMA+, p63+) | Non-ITAC: p63– | Salivary gland carcinoma: p63+ |
| Prognosis | Poor, 50% recur, 60% DOD | | Excellent, very rare DM or deaths | | Poor | |

*GI* gastrointestinal, *chromo* chromogranin, *synapto* synaptophysin, *myoep* myoepithelial, *DOD* dead of disease, *DM* distant metastases

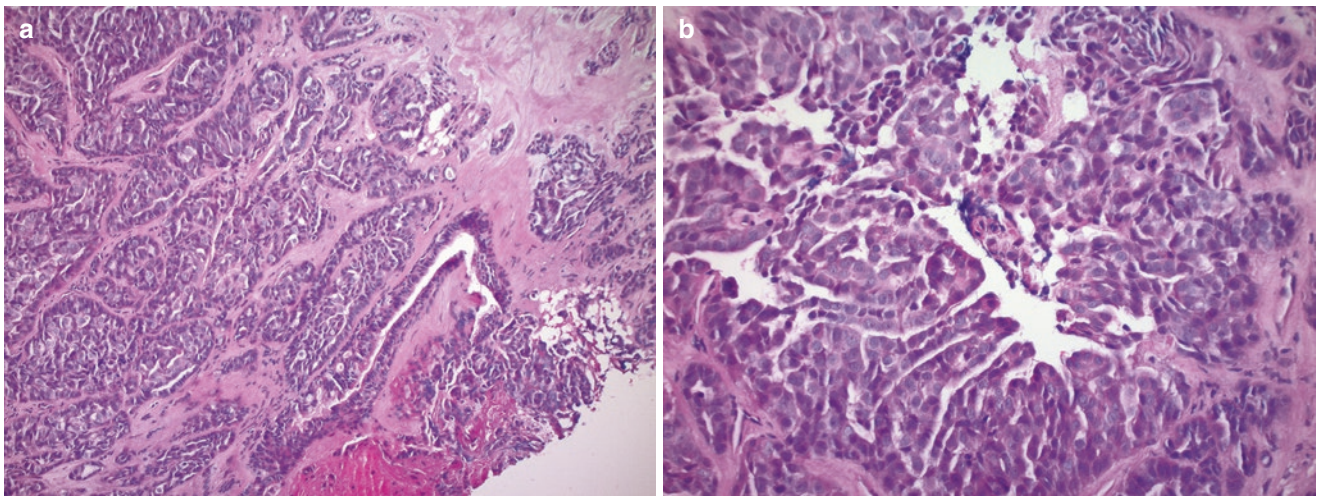


**Fig. 4.17** Sinonasal non-intestinal-type adenocarcinoma, low grade. (**a**) Complex glands and papillary structures are (**b**) lined by low cuboidal cells with pale nuclei and inconspicuous nuclei

mon in women, with a wide age range among adults (mean 52 years old).

- BSNS presents with obstructive nasal symptoms and a polypoid mass.
- It is an infiltrative, unencapsulated submucosal tumor composed of a hypercellular spindle cell proliferation. The tumor cells are arranged in a fascicular, herringbone pattern with branching, hemangiopericytoma-like vessels (Fig. 4.19).
  - BSNS cells are bland with elongated, uniform, hypochromatic nuclei and rare mitoses. Necrosis is absent.
  - A distinguishing feature is the proliferation and invagination of benign respiratory epithelium into the tumor. This epithelial proliferation is located

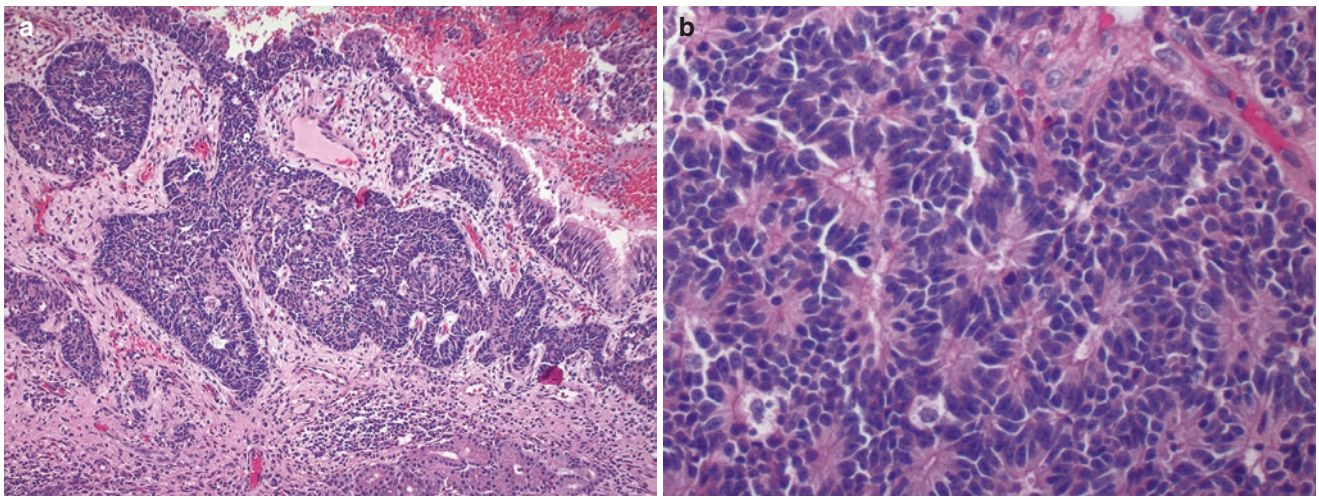


**Fig. 4.18** Sinonasal non-intestinal-type adenocarcinoma, high grade. (**a**) Trabeculae of blastomatous-like epithelium extend from the surface epithelium. (**b**) Rosette-like glands with oval nuclei and coarse chromatin and occasional mitoses are noted

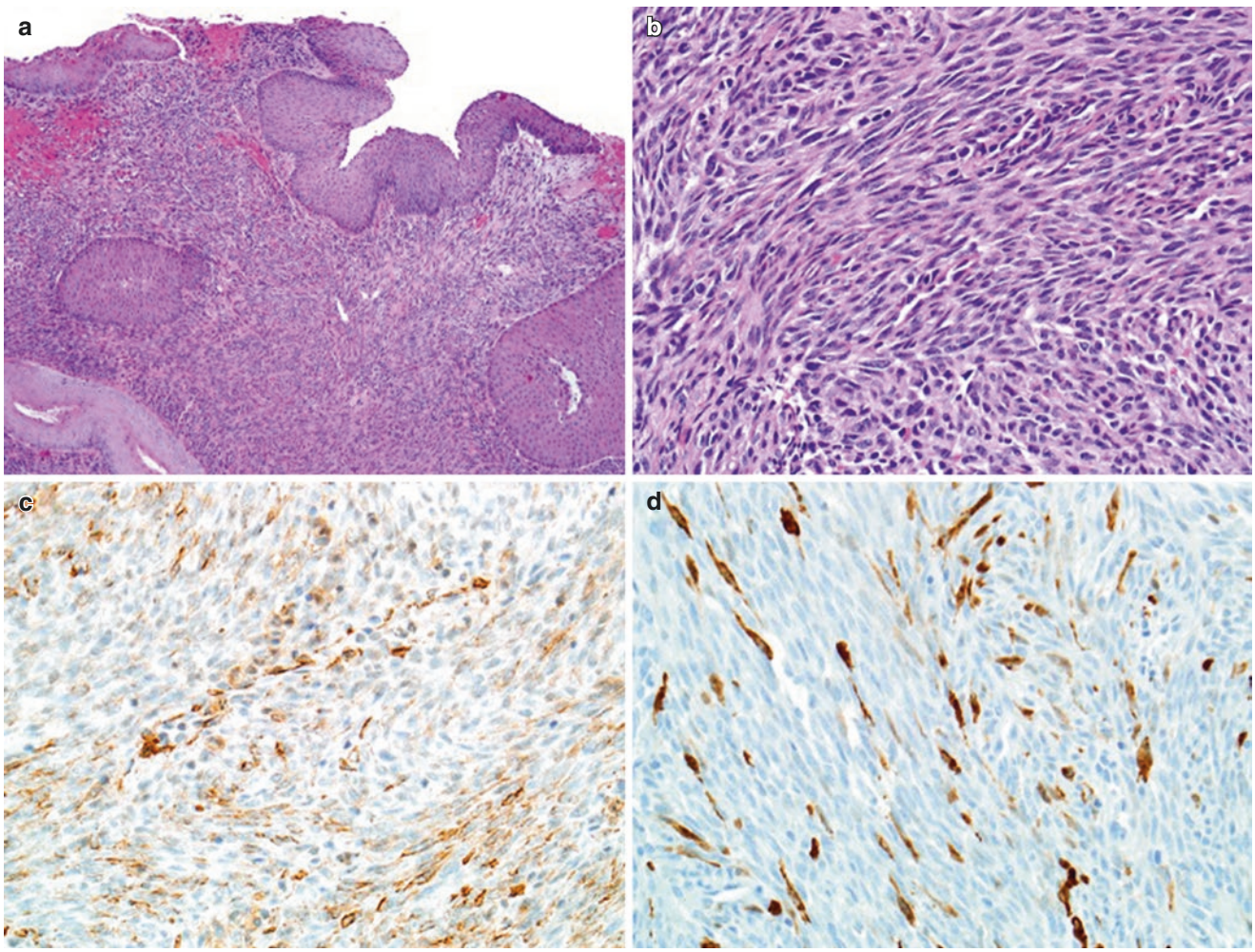


**Fig. 4.19** Biphenotypic sinonasal sarcoma. (**a**) A cellular spindle cell tumor that frequently shows nonneoplastic surface epithelium entrapped within the tumor. (**b**) The tumor cells are bland and arranged in broad fascicles intersecting to form a "herringbone" pattern. Biphenotypic sinonasal sarcoma is always, at least focally, positive for both (**c**) actins and (**d**) S100

close to the mucosal surface. It is so closely associated with the spindled proliferation that it appears to be an integral part of the tumor.
  - Rhabdomyoblastic differentiation may be focal, manifested by cells with eosinophilic cytoplasm and cross-striations.
- By immunohistochemistry, all tumors show at least focal staining for S100, SMA, and muscle-specific actin (MSA). Additional antigen expression may be focal and includes:
  - Positive IHC: nuclear beta-catenin, calponin, desmin, myogenin, EMA, CD34, and cytokeratins
  - Negative IHC: SOX10
  - Almost all examples of BSNS harbor rearrangements of PAX3. The most frequent and specific translocation partner is MAML3.
    - A subset of BSNS cases with focal rhabdoid differentiation harbors PAX3-FOXO1 and PAX3-NCOA1, the same fusion transcripts seen in alveolar rhabdomyosarcoma.
  - Given the variable immunoprofile and uniform morphology, a handful of benign and malignant mesenchymal tumors are in the differential diagnosis for BSNS (Table 4.17).
- BSNS has an indolent clinical course with frequent recurrences, a rare tumor-related death, and no metastases.

References: [59, 133, 140–143]

21. *What are the most common soft tissue tumors of the sinonasal tract?*

Primary soft tissue tumors of the sinonasal tract are rare. Despite the many mesenchymal tumors reported in this location, only a handful is unique to this site. Sinonasal hemangiopericytoma (glomangiopericytoma) and the recently characterized biphenotypic sinonasal sarcoma (BSNS) are two such lesions. The most common mesenchymal entities in this region are listed in Table 4.18. The reader is referred to Chap. 10 for a detailed discussion of these soft tissue tumors.

Reference: [59, 80, 117, 142–156]

22. *Which hematolymphoid tumors are more common in the sinonasal tract?*

Non-Hodgkin lymphomas are the third most common malignancy in the sinonasal tract and account for 10–15% of all head and neck lymphomas. Of particular significance to this site are extranodal natural killer/T-cell lymphoma, nasal-type and extraosseous plasmacytoma. A more detailed discussion of these entities can be found in Chap. 10.

**Table 4.18** Soft tissue tumors of the sinonasal tract

| Benign | Borderline/low-grade malignant | Malignant |
|---|---|---|
| Hemangioma<br>Schwannoma<br>Leiomyoma<br>Neurofibroma | Desmoid-type fibromatosis<br>Sinonasal glomangiopericytoma<br>Solitary fibrous tumor<br>Epithelioid hemangioendothelioma | Rhabdomyosarcoma<br>Fibrosarcoma<br>Undifferentiated pleomorphic sarcoma<br>Synovial sarcoma<br>Malignant peripheral nerve sheath tumor<br>Biphenotypic sinonasal sarcoma<br>Angiosarcoma<br>Leiomyosarcoma |

**Table 4.17** Comparison of biphenotypic sinonasal sarcoma with mesenchymal tumors of the sinonasal tract

| | Overlapping morphologic features | BSNS contrasting morphologic features |
|---|---|---|
| Schwannoma | Variably hypercellular areas S100+ | Uniformly hypercellular |
| | Diffuse S100+, SOX10+, SMA– | var S100+, SOX10–, SMA+, MSA+ |
| Malignant peripheral nerve sheath tumor | Spindled cells<br>±Muscle or epithelial differentiation | Low nuclear grade<br>No mitoses or necrosis |
| | SOX10+ | SOX10– |
| Monophasic synovial sarcoma | Uniform spindled cells with focal cytokeratin expression | Epithelial proliferation near mucosal surface |
| | SYT-SSX fusion | PAX3 rearrangement |
| Fibrosarcoma | Herringbone growth pattern | Admixed respiratory epithelium |
| | S100–, SMA– | S100+, SMA+ |
| Glomangiopericytoma | Branching vasculature<br>Smooth muscle differentiation | Long, sweeping fascicles<br>Elongated nuclei |
| | S100– | S100+ |
| Solitary fibrous tumor | Branching vasculature (rare) | Admixed respiratory epithelium |
| | Hypercellular areas | No ropey collagen<br>Infiltrative growth |
| | Diffuse CD34+, STAT6+ | S100+, MSA+, SMA+ |

*BSNS* biphenotypic sinonasal sarcoma, *PAX3* paired box 3, *SYT* synovial sarcoma translocated to X chromosome, *SSX* synovial sarcoma, *X* breakpoint, *MSA* muscle-specific actin

**Table 4.19** Secondary tumors of sinonasal tract and their differential diagnosis with primary tumors

| Tumor | Source/primary location | Ancillary tests | Primary SN tumors in the differential diagnosis: contrasting stains |
|---|---|---|---|
| Meningioma | Direct extension from cranial meningiomas<br>Primary SN meningiomas are very rare | EMA+, CK18+, vimentin+, claudin-1+<br>(S100 may be positive in fibrous types) | SFT: STAT6+, claudin-1–<br>Glomangiopericytoma: (n)ß-catenin+<br>Carcinomas: p63+, p40+, CK5/6+<br>Neural tumors: SOX10+, S100+ |
| Angiofibroma | Large nasopharyngeal tumors may involve SN tract | AR+ | SFT: STAT6+, CD34+ |
| Pituitary adenoma | Direct extension from cranial pituitary adenoma, primary pituitary adenomas are rare | Pituitary hormone markers+<br>Pituitary transcription factors: Pit-1, TPIT+, SF1+<br>ER-alpha+, GATA-2+ | PGL: (s)S100+, GATA-3+<br>ONB: (s)S100+<br>NEC: var S100+, high Ki-67 |
| Metastatic RCC | Kidney | RCC: PAX8+, CD10+, RCC+ | RCC-like SN carcinoma: PAX8–, CK20–, DOG1+, SOX10+<br>Salivary CCC: p63+, SOX10– |

*SN* sinonasal, *SFT* solitary fibrous tumor, *AR* androgen receptors, *PGL* paraganglioma, *s* sustentacular, *var* variable, *TPIT* T,Box Protein 19, *SF1* Splicing Factor 1, *ER* estrogen receptors, *PAX8,* Paired box gene 8, *ONB* olfactory neuroblastoma, *NEC* neuroendocrine carcinoma, *RCC* renal cell carcinoma, *CCC* clear cell carcinoma

- Extranodal NK/T-cell lymphoma (ENKTL) has a distinct predilection for the nasal cavity with over 80% of cases arising in head and neck mucosal sites.
  - This tumor has a high prevalence among East Asian and Latin American populations and is associated with Epstein-Barr virus.
  - ENKTL has an angioinvasive growth pattern, and patients may present with nasal obstruction, epistaxis, and septal perforation. The clinical picture raises concern for infectious and inflammatory etiologies.
  - Histologic findings include a dense, atypical lymphoid infiltrate in the submucosa with ulceration and necrosis.
- The majority of extraosseous plasmacytomas occur in the head and neck, and the nasal cavity is the most common site.
  - The tumor shows sheets of plasma cells in the submucosa.
  - Awareness of this entity and its more atypical variants is important in the differential diagnosis of more common epithelial and undifferentiated malignancies.
- Sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease is a benign, histiocytic proliferation that is found primarily in the lymph nodes. The sinonasal tract is a common extranodal site of disease. Patients present with multi-site involvement, nasal obstruction, and polypoid, nasal lesions.
  - Given the histologic picture, SHML should be considered in the differential diagnosis of the infectious and granulomatous inflammatory disorders of the sinonasal tract such as rhinoscleroma and leprosy.

References: [59, 68, 121, 122, 157–167]

23. *What are the secondary tumors of the sinonasal tract and their differential diagnosis with primary tumors?*

Secondary tumors of the sinonasal tract include tumors extending from surrounding sites, as well as metastases (Table 4.19). Both are uncommon. However, they can be a diagnostic pitfall and should be included in the differential diagnosis of unusual sinonasal tumors.

- Among those tumors involved by direct extension, primary nasopharyngeal tumors are a principal consideration, and others have been discussed above (see Tables 4.10 and 4.12).
- Most metastases to this region occur in the nasal cavity.
  - Renal cell carcinoma is by far the most common.
  - Hepatocellular, lung, and breast carcinomas have also been reported.

References: [113, 168–177]

## Case Presentations

### Case 1

#### Learning Objectives

1. To generate a differential diagnosis for a small round blue cell tumor
2. To become familiar with the histologic features of the tumor
3. To create a comprehensive immunohistochemical panel

**Case History**
A 55-year-old female complains of headaches. On imaging studies, a large left nasal cavity mass was identified. The mass involved the left maxillary sinus, sphenoid sinus, and bilateral medial orbits and showed intracranial extension through the anterior skull base.

**Gross Findings**
Excision of the mass revealed multiple white-tan to red soft tissue fragments.

**Histologic Findings** (Fig. 4.20a, b)
Uniform, small tumor cells arranged in nests. The neoplastic cells have scant cytoplasm, finely stippled nuclear chromatin, and inconspicuous nucleoli. The cytoplasm is pale with a fibrillary background. Rare mitoses are present and mild nuclear atypia. Necrosis is not identified.

**Differential Diagnosis**
- Olfactory neuroblastoma
- PNET/Ewing sarcoma
- Rhabdomyosarcoma
- Small cell neuroendocrine carcinoma

**Ancillary Studies** (Fig. 4.20c, d)
- Positive: NSE, CD56, synaptophysin, S100 (sustentacular)
- Negative: TTF-1, pan-cytokeratin, desmin
- EWSR1/FLI1 and EWSR1/ERG translocations strong positive

**Final Diagnosis** *Low-grade olfactory neuroblastoma (ONB)*

**Take-Home Messages**
1. Neuroendocrine morphology is classically nested with monotonous cells and nuclei with finely stippled ("salt and pepper") chromatin.

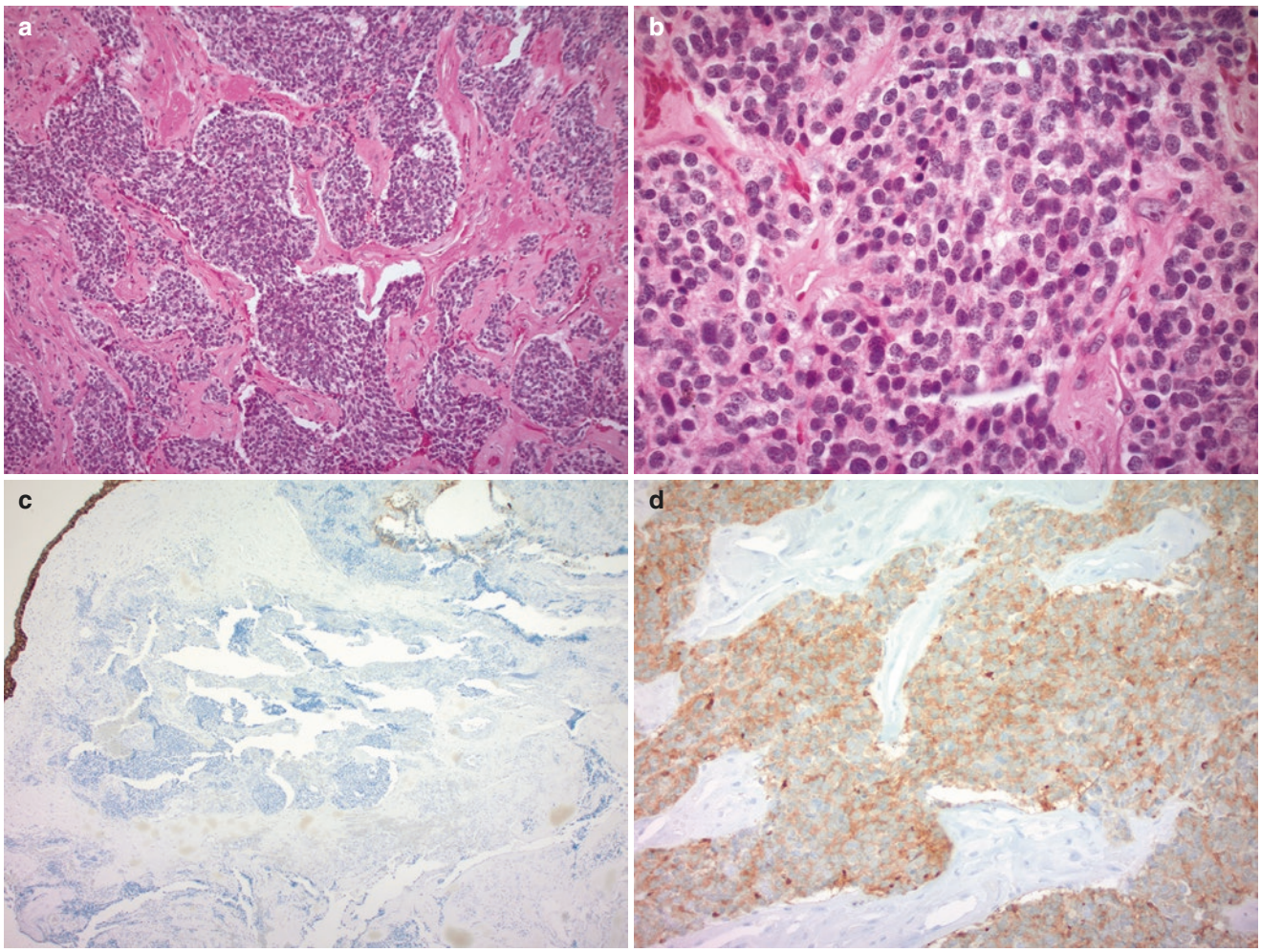


**Fig. 4.20** Case 1. (**a**) Nests of monotonous cells in a fibrous stroma. (**b**) The tumor cells have round to oval nuclei with a "salt and pepper" chromatin. A delicate, fine fibrillary background is characteristic in low-grade tumors. (**c**) Tumor cells are negative for keratin and (**d**) strongly positive for synaptophysin

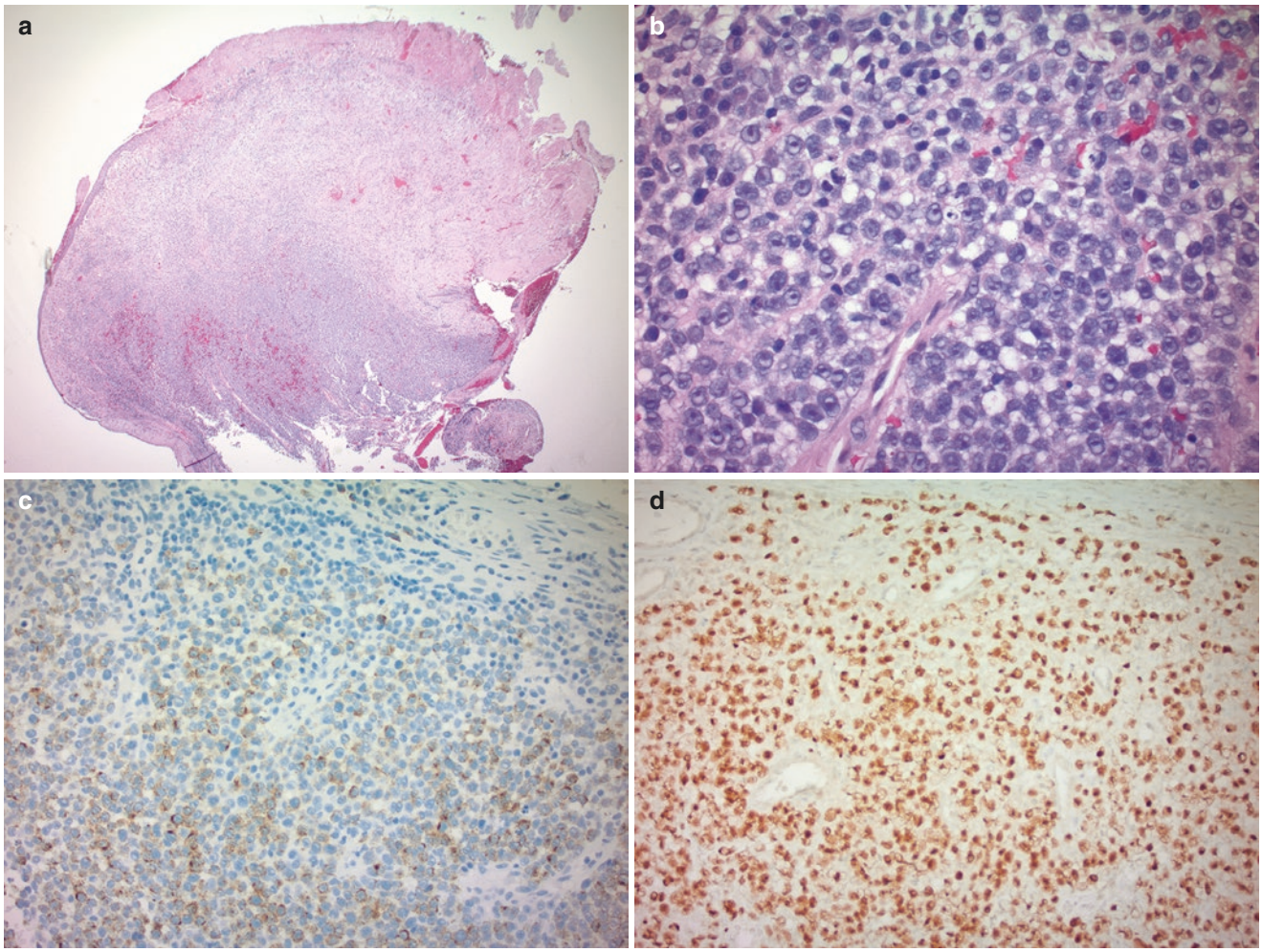


**Fig. 4.21** Case 2. (**a**) A nasal polyp with sheets of (**b**) slightly dyshesive, pleomorphic cells with a moderate amount of amphophilic cytoplasm, centrally located, vesicular nuclei, and prominent nucleoli. (**c**) The tumor cells are positive for HMB45 and (**d**) SOX10

2. The fibrillary matrix and lack of pleomorphism are characteristics of low-grade ONB.
3. Strong neuroendocrine (NE) marker expression excludes PNET and rhabdomyosarcoma. Both tumors may show weak, focal staining with NE markers.
4. Small cell carcinoma (SmCC) expresses keratin, typically in a dot-like, cytoplasmic pattern. SmCC is of a higher nuclear grade with necrosis and frequent mitoses.
5. Knowledge of the differential diagnosis and application of a thorough IHC panel is essential to rule out other tumors in the differential diagnosis.

References: [113, 125, 178]

## Case 2

### Learning Objectives

1. To become familiar with the histologic features of the tumor
2. To generate the differential diagnosis
3. To become familiar with the immunohistochemical features of the tumor

### Case History

An 80-year-old female presents with double vision, sixth nerve palsy, gait disorder, and epistaxis. MRI of the brain with and without contrast showed frontal sinus opacification and a rapidly progressive right, polypoid nasal mass concerning for an aggressive fungal infection.

### Gross Findings

Polypoid tissue fragment with solid homogeneous cut surface.

### Histologic Findings (Fig. 4.21a, b)

Sheets of tumor underlying the nasal mucosa. The tumor cells are slightly dyshesive with a moderate amount of amphophilic cytoplasm, vesicular nuclei, and prominent nucleoli.

**Differential Diagnosis**
- Sinonasal melanoma
- Olfactory neuroblastoma (ONB)
- Sinonasal undifferentiated carcinoma (SNUC)
- Clear cell sarcoma

**IHC and Other Ancillary Studies** (Fig. 4.21c, d)
- Positive: S100 (weak), HMB45, SOX10
- Negative: panCK, synaptophysin, CD45

**Final Diagnosis** *Sinonasal melanoma*

**Take-Home Messages**
1. Sinonasal melanomas are rare but among the most common malignant, non-epithelial tumors of this site.
2. Most sinonasal melanomas are polypoid and amelanotic with surface ulceration.
3. SN melanomas uniformly have a poor prognosis, so histologic features used in prognostication of skin melanomas are of little value. BRAF mutations are far less common when compared to skin melanomas.
4. This case's immunoprofile excludes SNUC (CK positive) and ONB (synaptophysin positive).
5. Clear cell sarcoma shares overlapping IHC features with melanoma but is unlikely in this location. In difficult cases, fluorescent in situ hybridization (FISH) analysis for the t(12;22)(q13;q12) translocation is diagnostic for clear cell sarcoma.

References: [111, 112, 114, 127, 179–182]

## Case 3

**Learning Objectives**
1. Become familiar with inflammatory nasal lesions and causes of eosinophilic mucin.
2. Develop a differential diagnosis of necrotizing sinonasal lesions.
3. Identify causes of vasculitis in the sinonasal tract.

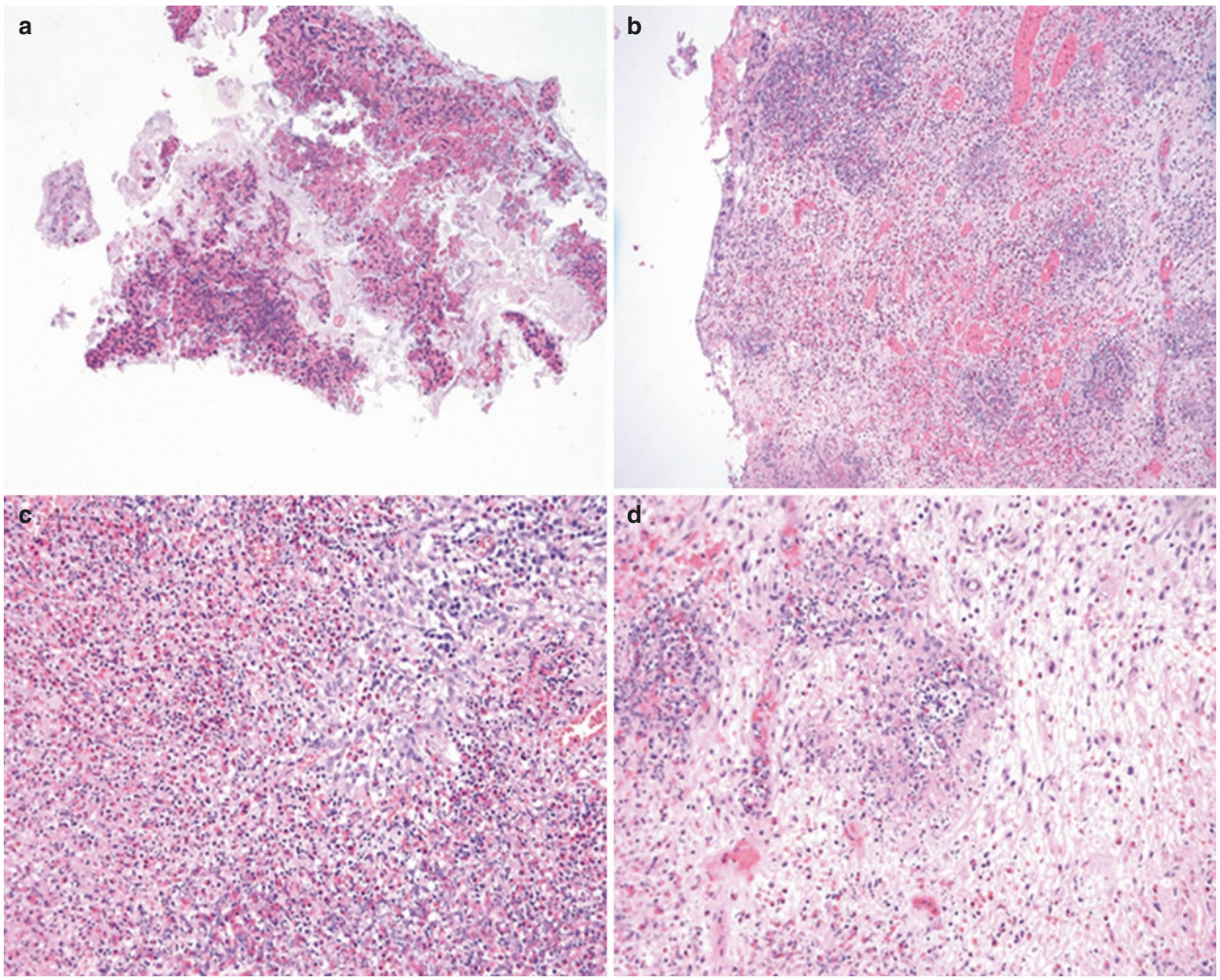


**Fig. 4.22** Case 3. (**a**) Allergic mucin with numerous aggregates of eosinophils. (**b**) Diffusely inflamed sinus tissue with eosinophilic abscesses and (**c**) a granulomatous inflammation. (**d**) Necrosis of small vessel walls with eosinophils and neutrophils in the lumen consistent with eosinophilic vasculitis

**Case History**

A 42-year-old male presents with a 10-month history of recalcitrant rhinosinusitis, nasal polyps, and chronic lung infections and "high levels" of eosinophils in his blood. He has had functional endoscopic sinonasal surgery (FESS) twice over the past year. The patient failed maximal medical therapy including intranasal and oral corticosteroids and antifungals. He was taken to the operating room for a third FESS.

**Gross Findings**

Multiple fragments of red-tan mucoid soft tissue measuring 5 × 5 × 3.5 cm in aggregate.

**Histologic Findings** (Fig. 4.22)

Respiratory mucosa with eosinophilic abscesses, granulomatous inflammation, and vasculitis. Allergic mucin is also present.

**Differential Diagnosis**

- Allergic fungal rhinosinusitis
- Granulomatosis polyangiitis
- Eosinophilic granulomatosis polyangiitis
- Cocaine-induced midline destructive lesion

**Ancillary Studies**

- Positive: serum p-ANCA
- Negative: GMS stain

**Final Diagnosis** *Eosinophilic granulomatosis polyangiitis (EGPA)*

**Take-Home Messages**

1. EGPA is one of the ANCA-associated vasculitides, a rare multisystemic disorder involving medium and small vessels characterized by a necrotizing vasculitis with tissue and blood eosinophilia and granulomatous inflammation.
2. Patients typically have allergic rhinosinusitis, polyposis, and a history of asthma. Lungs, skin, and kidneys are the most commonly involved sites.
3. Diagnosis relies on a defined set of clinical criteria, some of which include the presence of asthma, serum eosinophilia, and histologic or clinical evidence of vasculitis involving two or more extrapulmonary organs.
4. Fungal infection must be ruled out whenever allergic mucin is identified, and special stains should be ordered.
5. The most common immunofluorescence pattern on biopsy shows a perinuclear ANCA pattern against myeloperoxidase.
6. Vasculitis may be difficult to detect on mucosal biopsies, but the diagnosis can be suggested in the appropriate clinical context.

References: [36, 44, 52, 183–185]

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# Salivary Gland

5

Danielle Elliott Range

## List of Frequently Asked Questions

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1. *What are the basic histologic components of the salivary gland, and how are they characterized?*

   Many salivary gland (SG) tumors are biphasic, composed of at least two cell types, ductal and myoepithelial cells. An understanding of how the different components of normal salivary gland express various immunohistochemical markers will help inform the pathologist of a specific tumor type and aid in the correct diagnosis. Not all of the markers expressed in normal tissue are present in its neoplastic counterpart. In addition, among the normal SG components, there are different types of ducts, acini, and supporting cells including serous and mucinous acini, intercalated ducts, striated ducts, excretory ducts, and two types of supporting cells (myoepithelial and basal cells). Figure 5.1 depicts the normal acinar-ductal unit. Table 5.1 shows the immunohistochemical profile of the different components and their variations.

   Reference: [1]

2. *How has the terminology of salivary gland tumors changed and what are the newest entities described in this group?*

   A handful of old and new tumors were either reclassified or added to the 4th edition of the *World Health Organization (WHO) Classification of Head and Neck Tumors* published in 2017. Some novel entities have been excluded, pending further studies, but are worthy of discussion here (Table 5.2). The questions that follow in this chapter will use the newer terminology and include older terms for clarification, when needed.

   References: [2, 3]

3. *What are some of the unusual morphologic changes that are seen in pleomorphic adenomas and what is their significance?*

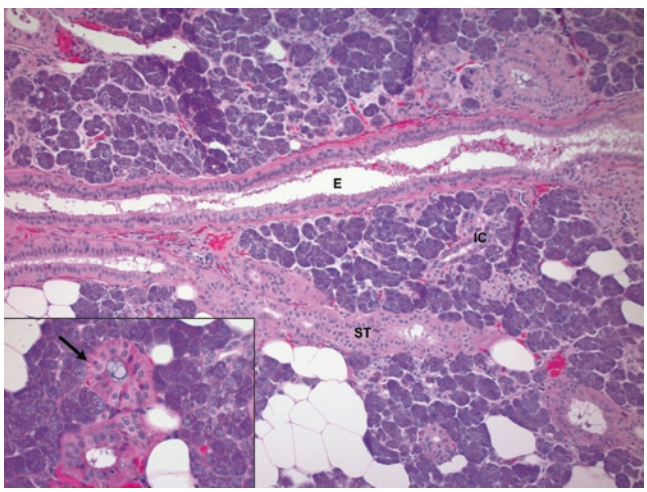


**Fig. 5.1** Normal parotid gland. Serous acini predominate. A large interlobular excretory duct (E) with a second layer of abluminal basal cells (arrow) gives rise to striated ducts (ST) with cuboidal cells and subnuclear striations (inset, arrow). Smaller intercalated ducts (IC) are found among the acini

**Table 5.1** Histology and immunoprofile of normal salivary gland cell types

| Cell type | Morphology | Positive stains | Negative stains |
|---|---|---|---|
| Myoepithelial cell | Abluminal cells that support acini and intercalated ducts<br>Spindled, elongated cells with oval nucleus | CK5/6<br>CK14<br>p63, p40<br>SMA<br>MSA<br>Calponin<br>Caldesmon<br>Sox-10 | CK7<br>LMWCK<br>weak, variable<br>S100 variable |
| Basal cell | Abluminal cells that support excretory ducts<br>Low cuboidal cells with central, round to oval nucleus | CK5/6<br>CK14<br>p63, p40<br>CK7<br>CK8/18<br>Sox-10 | Negative muscle markers:<br>SMA<br>Calponin<br>Caldesmon<br>S100<br>variable |
| Serous acini | Triangular cells with round, basally located nucleus<br>Basophilic, cytoplasmic, zymogen granules | GCDFP-15<br>CK8/18<br>Amylase<br>Sox-10<br>PAS<br>PAS-D<br>DOG-1<br>CD117 | Mucicarmine<br>Alcian blue<br>P63<br>CK7 |
| Mucous acini | Triangular cells with round, basally located nucleus<br>Pale, mucinous cytoplasm | Mucicarmine<br>PAS<br>PASD | CD117<br>CK7 |
| Intercalated duct luminal cells | Luminal cells<br>Cuboidal with scant cytoplasm, round nucleus | CK7<br>CK8/18<br>Cam5.2<br>CK19<br>CK14<br>Galectin 3<br>EMA<br>CEA<br>Sox-10<br>DOG-1<br>CD117 weak | S100 variable |
| Striated duct | Luminal, columnar cells<br>Central, round nucleus; and subnuclear, cytoplasmic striations | CK7<br>CK8/18<br>Cam5.2<br>CK19<br>CK14<br>Galectin 3<br>Sox-10<br>AMA, PTAH | SMA<br>Calponin<br>Caldesmon<br>S100 |
| Apocrine cells | Abundant, eosinophilic vacuolated cytoplasm, apical snouting | AR<br>GCDFP-15 | |
| Oncocytic cells | Abundant, eosinophilic granular, cytoplasm, central, round nucleus | AMA, PTAH | |

*CK* cytokeratin, *SMA* smooth muscle actin, *MSA* muscle-specific actin, *LMWCK* low molecular weight cytokeratin, *HMWCK* high molecular weight cytokeratin, *GCDFP* gross cystic disease fluid protein, *PAS(D)* periodic acid-Schiff (with diastase), *EMA* epithelial membrane antigen, *CEA* carcinoembryonic antigen, *AMA* anti-mitochondrial antibody, *PTAH* phosphotungstic acid hematoxylin, *AR* androgen receptors

**Table 5.2** Changes in WHO terminology for salivary gland tumors

| New/reclassified tumors | Previous or alternate name | Comments |
|---|---|---|
| Clear cell carcinoma (CCC) | Hyalinizing clear cell carcinoma<br>Clear cell carcinoma, not otherwise specified (NOS) | A more encompassing term was favored since not all CCC are hyalinizing |
| Secretory carcinoma | Mammary analogue secretory carcinoma (MASC) | A new entity with a specific ETV6-NTRK3 translocation |
| Polymorphous adenocarcinoma (PAC) | Polymorphous low-grade adenocarcinoma[a] (PMLG) | The "low-grade" designation was removed to allow for flexibility in grading |
| Intraductal carcinoma | Low-grade intraductal carcinoma[a]<br>Low-grade salivary duct carcinoma[a]<br>Low-grade cribriform cystadenocarcinoma[a] | A broad term used to encompass old and new lesions that are *noninvasive* (or microinvasive) intraductal carcinomas |
| Poorly differentiated carcinoma | Large cell carcinoma[a]<br>Now includes: large cell neuroendocrine carcinoma<br>Small cell neuroendocrine carcinoma<br>Undifferentiated carcinoma | Neuroendocrine carcinomas in this category may or may *not* have neuroendocrine differentiation |
| Ductal papillomas | Includes: Inverted ductal papilloma<br>Intraductal papilloma<br>Sialadenoma papilliferum | All three entities are papillomas of salivary duct origin |
| Adenocarcinoma, not otherwise specified | Includes: Mucinous adenocarcinoma<br>Cystadenocarcinoma | A diagnosis of exclusion for tumors that do not fit under any other named entity |
| Cribriform adenocarcinoma of (tongue) minor salivary gland | Remains in the PAC (PMLG) category despite some differences in clinical presentation and behavior | Shares PRKD genetic alterations similar to those of PAC<br>Shares some morphologic overlap with PAC |
| Metastasizing pleomorphic adenoma | Removed from the list of malignant tumors | Discussed in the section on pleomorphic adenomas, given their identical histologic appearance |

[a]Indicates previous terminology

Conventional pleomorphic adenomas have an admixture of myoepithelial and ductal cells with varying amounts of chondromyxoid stroma. Metaplastic changes can display both epithelial and stromal differentiation.

- The most well-described epithelial change in PA is squamous metaplasia. The squamous cells show abundant, eosinophilic cytoplasm, and bland nuclear features, with or without keratin pearl formation (Fig. 5.2).
- Cystic change within the ducts and associated keratin is referred to as adnexal-like differentiation.
- On small biopsy material, mucoepidermoid carcinoma (MEC) enters the differential diagnosis. However, keratinization is not a feature of MEC and is rarely seen, even in its high-grade form.

Most stromal metaplasias seen in PA are due to the pluripotent differentiation of the myoepithelial cell.

- Fatty metaplasia is not an uncommon finding, and it usually comprises less than 20% of the tumor but may be as much as 80%. It is seen almost exclusively in the major salivary glands.
- Ultrastructural studies show myoepithelial cells with abundant intracellular lipid. Consequently, these fatty areas express cytokeratins and myoepithelial markers.
  - Sebaceous metaplasia is commonly seen alongside fatty metaplasia.

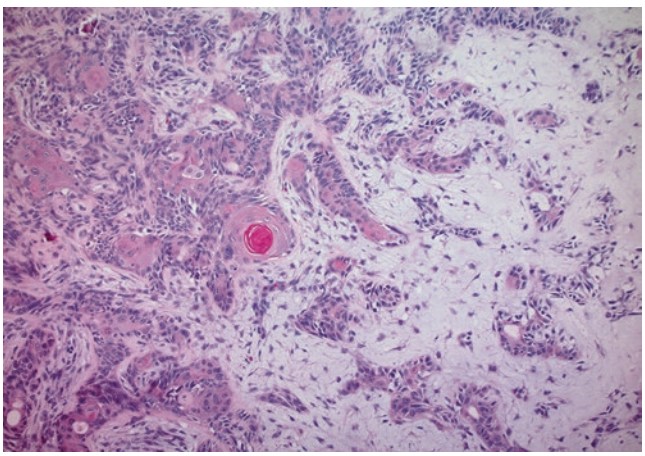

**Fig. 5.2** Pleomorphic adenoma with squamous metaplasia. Chondromyxoid stroma (right) contains nests of hyperchromatic, small, angulated, myoepithelial cells surrounding eosinophilic ductal cells with squamous metaplasia and keratin pearl formation

- Other mesenchymal changes include bony metaplasia and schwannian change.
  - Such areas will demonstrate myoepithelial differentiation by immunohistochemistry.

Various case series and reports have described intravascular tumor in pleomorphic adenomas.

- Epithelium and stroma can be seen in small, thin-walled vessels and large, muscular vessels. The proposed mechanism is artifactual tumor spillage into the vasculature as a result of biopsy or surgical manipulation.
- None of the reported cases have been associated with tumor metastasis or aggressive behavior. The phenomenon is observed most commonly in major salivary glands and is characterized by:
  - An absence of platelet meshwork
  - Involvement of vessels at the tumor periphery
  - Involvement of more than one vessel

References: [4–13]

4. *What is the biologic behavior of "benign" metastasizing pleomorphic adenoma and are there any risk factors for its development?*
   - Metastasizing pleomorphic adenoma (MPA) is a rare entity with less than 100 cases reported in the English literature.
   - The old terminology of *benign* metastasizing PA has fallen out of favor, as estimated mortality rates are 20% and disease-free survival approaches 50%.
   - The latency period between diagnosis and metastasis averages 15 years (range: 3–51 years).
   - Knight et al. reported metastases most commonly in the bone (37%), lung (34%), and cervical lymph nodes (20%). There are also reports of MPA to the kidney, skin, and brain.
   - There are no definitive histopathologic features to distinguish MPA from conventional PA (Fig. 5.3). The morphology of the metastases is identical to the primary tumor and shows no cytologic atypia or malignant transformation. A few factors are associated with increased risk:
     - Repeated surgical manipulation – up to 80% are associated with at least one, though typically multiple, recurrences at the primary site. Recurrent tumors may show multiple nodules (Fig. 5.4).
     - Metastasis occurs only after resection of the primary tumor, raising the possibility of tumor spillage into the vasculature as a possible mechanism.

   References: [14–19]
5. *What are the malignant forms of pleomorphic adenoma and how are they diagnosed?*

   Up to 15% of untreated PA will undergo malignant transformation. The malignant forms of PA are carcinoma ex pleomorphic adenoma (CEXPA) and carcinosarcoma. CEXPA is a rare tumor primarily seen in the parotid gland with a minority of cases presenting in the submandibular gland and the palate. Patients present with rapid growth of a long-standing, preexisting mass. Regardless of histologic subtype, CEXPA is a high-grade tumor.
   - The type of carcinoma which arises in a CEXPA should always be specified and usually takes the form of adenocarcinoma, not otherwise specified (NOS) or salivary duct carcinoma (SDC).
   - Evidence of PA must be present either by histologic evaluation or clinical documentation of a previous PA at the same site. Extensive hyalinization or fibrosis in the tumor only suggests a previous PA (Fig. 5.5).
   - CEXPA is broadly divided into three categories: intracapsular, minimally invasive, and widely invasive.
     - Intracapsular carcinoma exhibits overt, cytologically malignant features (i.e., atypical mitoses, pleomorphism, necrosis) within the capsule of the PA. It can look like anything from ductal carcinoma in situ to an infiltrative carcinoma.
   - Random atypia or areas that resemble cytologically low-grade carcinomas (e.g., mucoepidermoid or

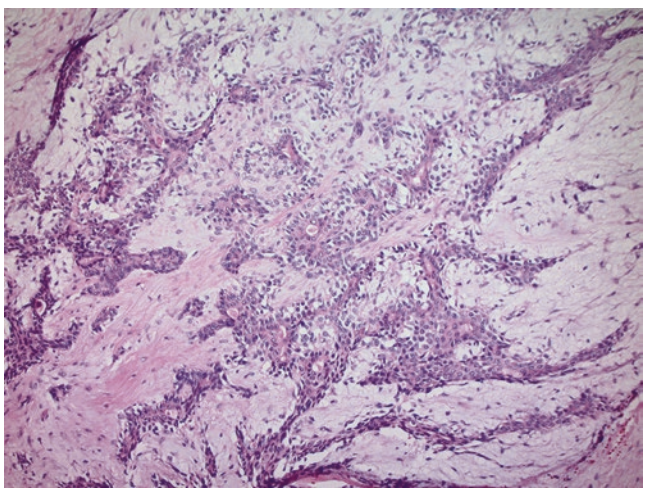

**Fig. 5.3** Pleomorphic adenoma

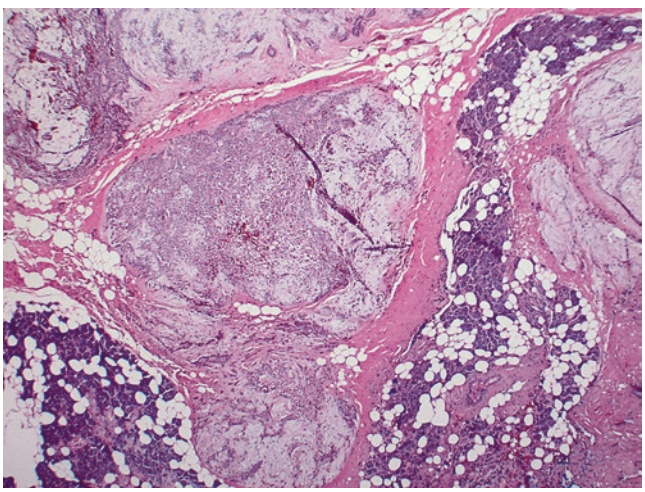

**Fig. 5.4** Recurrent pleomorphic adenoma. Multiple nodules of predominantly chondromyxoid stroma are scattered within normal parotid gland parenchyma

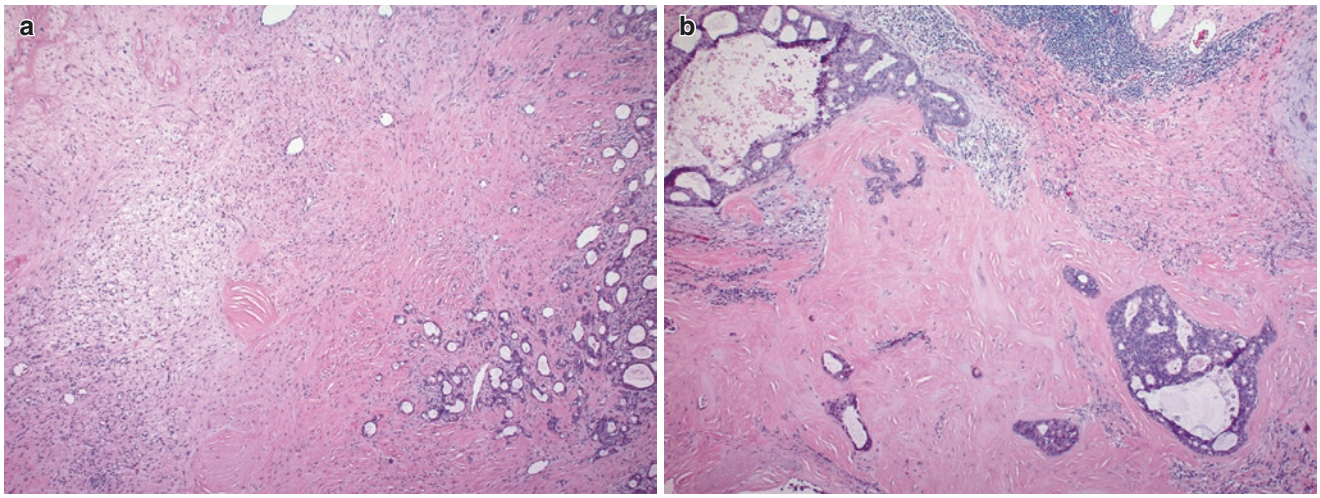


**Fig. 5.5** Carcinoma ex pleomorphic adenoma. (**a**) Residual tubules of pleomorphic adenoma are seen at the periphery of a large, hyalinized, fibrotic nodule. (**b**) Salivary duct carcinoma arising in a pleomorphic adenoma shows cribriform glands with punched out lumens, Roman arches, and comedo necrosis

adenoid cystic carcinoma) are not sufficient for a diagnosis of intracapsular carcinoma.
  - Minimally invasive CEXPA shows invasion of the PA capsule. By definition, the distance of invasion beyond the capsule must be less than 1.5 mm.
  - Widely invasive CEXPA shows invasion ≥1.5 mm beyond the PA border with an associated mortality rate of 35–65%.
- Tumors with less than 1.5 mm of invasion show few or no recurrences, no distant metastases or tumor-associated deaths. Several studies that proposed a cut-off of 4–6 mm show similar outcomes.
- The proportion of carcinoma, type of carcinoma, tumor size, grade, and extent of invasion all have prognostic significance and should be reported.

Carcinosarcoma is a biphasic tumor composed of malignant epithelial and mesenchymal components. It may arise de novo or from a preexisting PA (up to 30%). They account for less than 1% of all SG malignancies with less than 100 reported cases.

- Over 70% occur in the parotid gland; minor SG sites include palate and tongue.
- There is a male predominance and mean age at diagnosis is in the sixth decade.
- The carcinomatous component is usually a poorly differentiated adenocarcinoma, NOS or SDC.
- The sarcomatous portion is usually a high-grade chondrosarcoma. Osteosarcoma, fibrosarcoma, and unspecified spindle sarcoma are also seen.
- Carcinosarcomas have a poor prognosis with distant metastases and subsequent death in 60% of patients.
- Histologic grade and distance of invasion beyond the capsule of a preexisting PA strongly correlate with clinical behavior.

References: [13, 19–27]

6. *What are the grading systems for mucoepidermoid carcinoma and their correlation with clinical outcomes? Are there any independent histopathologic features that correlate with clinical outcomes?*
   - Mucoepidermoid carcinoma (MEC) is the most common malignancy of the salivary glands in adults and children.
   - MEC is characterized by a variably solid and cystic tumor with three cell types (Fig. 5.6):
     - Intermediate cell: most common cell type ranges from a small basaloid cell to a large cell with a moderate amount of eosinophilic cytoplasm, small, dark to slightly vesicular nucleus.
     - Squamous/epidermoid cell: large, polygonal cell with abundant eosinophilic cytoplasm scattered singly and in small nests.
     - Mucous cells: large cell with clear, mucinous cytoplasm and eccentric, dark nucleus.
   - Grading of MEC relies on several histomorphologic features. There are three popular grading systems, all with a three-tiered approach (Table 5.3).
     - Despite this lack of standardization, tumor grade significantly correlates with survival in each system, and it is an important determinant of therapy.
     - High-grade tumors are usually treated with surgery, radiation, and neck dissection.
     - The Brandwein system tends to bundle low and intermediate tumors together and upgrades individual tumors. The AFIP system does the opposite, generally downgrading tumors and bundling intermediate and high-grade tumors.

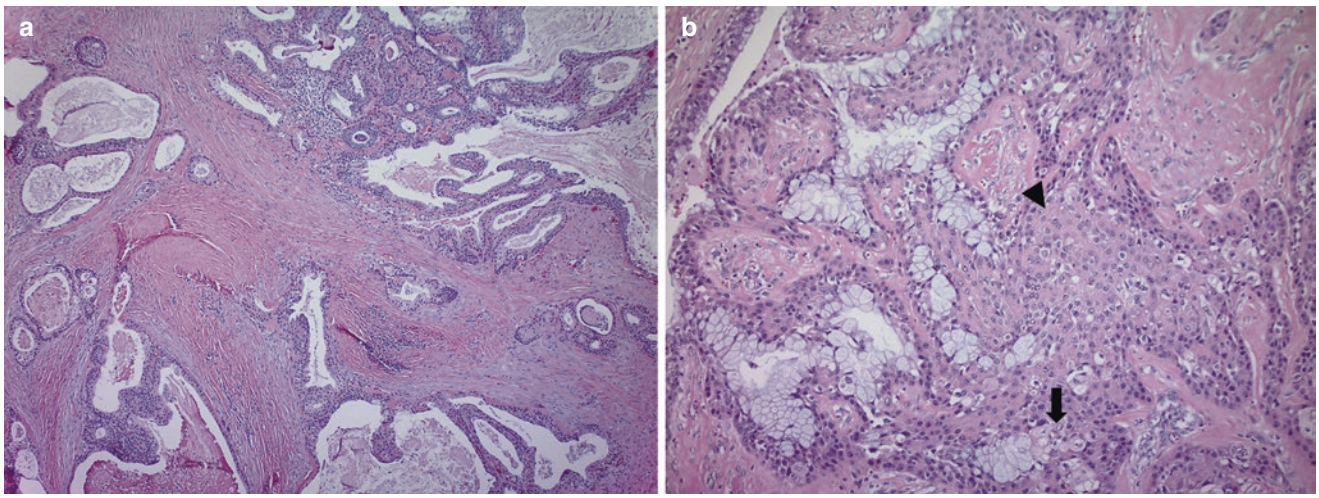


**Fig. 5.6** Mucoepidermoid carcinoma. (**a**) Predominantly cystic tumor in a fibrotic stroma with smaller daughter cyst. (**b**) Sheets of eosinophilic intermediate cells (arrowhead) show minimal atypia. Rare squamous cells (arrow) and numerous mucous cells are present

**Table 5.3** Comparison of grading systems for mucoepidermoid carcinoma

| **Modified Healy** | **Brandwein** | | **AFIP** | |
|---|---|---|---|---|
| | Feature | Points | Feature | Points |
| *Low-grade*: Micro- and macrocysts<br>Mucus to squamoid cells 1:1<br>Minimal to moderate amount of intermediate cells<br>Daughter cysts form from large cysts<br>Minimal atypia<br>Rare mitoses<br>Circumscribed invasion<br>Extravasated mucin pools with stromal reaction | Less than 25% cystic | 2 | Less than 20% cystic | 2 |
| | Perineural invasion | 3 | Perineural invasion | 2 |
| | Necrosis | 3 | Necrosis | 3 |
| *Intermediate grade*: No macrocysts<br>Few microcysts<br>Solid cellular nests<br>Moderate pleomorphism<br>Few mitoses<br>Uncircumscribed invasion<br>Fibrosis between cell nests<br>Chronic inflammation at periphery | >4 mitoses/10 hpf | 3 | ≥4 mitoses/10 hpf | 3 |
| | Pronounced atypia | 2 | Anaplasia | 4 |
| | Bone invasion | 3 | | |
| | Lymphovascular invasion | 3 | | |
| | Infiltrative border | 2 | | |
| *High-grade*: No cysts, solid growth<br>Considerable pleomorphism<br>Frequent mitoses<br>Soft tissue, perineural, or lymphovascular invasion<br>Desmoplastic stroma<br>Chronic inflammation less prominent | *Low-grade* | 0 | 0–4 points | |
| | *Intermediate grade* | 2–3 | 5–6 | |
| | *High-grade* | 4+ | 7–14 | |

*hpf* high-power field

  - 70–80% of MEC will be low or intermediate grade (LG, IG).
  - Population-based studies show no statistically significant difference in overall or disease-free survival between LG and IG tumors.
- Regardless of the grading system, a high tumor grade is an independent predictor of decreased survival. Other independent predictors of a worse prognosis include:
  - Advanced age
  - Tumor size
  - Positive lymph node metastases
  - Positive surgical margins
- 40–80% of LG and IG MECs are positive for the fusion product between the Mastermind-like 2 gene (MAML2) and the CREB-regulated transcription coactivator gene (CRTC), resulting in the t(11; 19)(q21; p13) translocation.
  - Several smaller studies have shown that the (MAML2) gene rearrangement partnered with

either CRTC1(MECT1) or CRTC3 conveys a favorable prognosis.
  - The specificity of the MAML2 rearrangements approaches 100% for MEC and may aid in the diagnosis of high-grade tumors.

References: [28–38]

7. *What are the three types of adenoid cystic carcinoma and how do they relate to tumor grade?*
   - Adenoid cystic carcinoma (AdCC) has a classic biphasic cellular composition of myoepithelial cells and ductal cells.
     - The predominant cells are small, uniform myoepithelial cells with scant, pale cytoplasm and bland, hyperchromatic, round to angulated nuclei. Ductal cells are low, cuboidal with regular, round nuclei, and a more dispersed chromatin.
     - Perineural invasion (PNI) is frequent.
   - AdCC has three growth patterns (in order of frequency):

1. Cribriform: nests of basaloid cells with sieve-like, punched out spaces containing pale, basophilic glycosaminoglycans or eosinophilic basement membrane material. Small ducts are scattered throughout the stroma and within the basaloid nests (Fig. 5.7).
2. Tubular: small duct proliferation with surrounding myoepithelial cells and dense, hyaline stroma.
3. Solid: large, solid nests and lobules of basaloid cells with minimal stroma. Nuclei are slightly larger than other types and more vesicular.

   - Histologic grading is based on type:
     - Low-grade: tubular, no solid component
     - Intermediate grade: cribriform (with or without minor solid component)
     - High-grade: at least 30% solid type
   - A higher percentage of solid type correlates with worse prognosis.
   - Some authors contend that any amount of a solid component will impact prognosis. As a result, this feature should be reported in clinical cases.
   - The MYB-NIFB translocation (t(6;9)) is present in approximately 30% of cases but has no impact on behavior.
     - Eighty percent of AdCC (including fusion negative cases) will express MYB by immunohistochemistry (IHC).
   - AdCC is a locally aggressive tumor characterized by a protracted clinical course of recurrences, late metastases, and death. Regardless of grade, most patients are treated with radiation therapy for local control. Lymph node metastases are seen in about 20% of patients. While 5-year survival rates approach 80%, 15-year survival rates are less than 20%.

References: [39–44]

8. *What are the histologic features of acinic cell carcinoma?*

Acinic cell carcinoma (AcCC) represents approximately 10% of all salivary gland carcinomas. It most commonly occurs in the parotid gland (85–90%) with a slight female predominance. AcCC is grossly well-circumscribed, non-infiltrative and may be lobulated.

- Morphologic subtypes include solid, microcystic/cystic, follicular, and papillo-cystic (Fig. 5.8). None of the morphologic variants correlate with clinical behavior.
- The non-acinar cells in AcCC are of intercalated duct origin and seen in the papillary, microcystic, and follicular types. These subtypes generally express CK7.

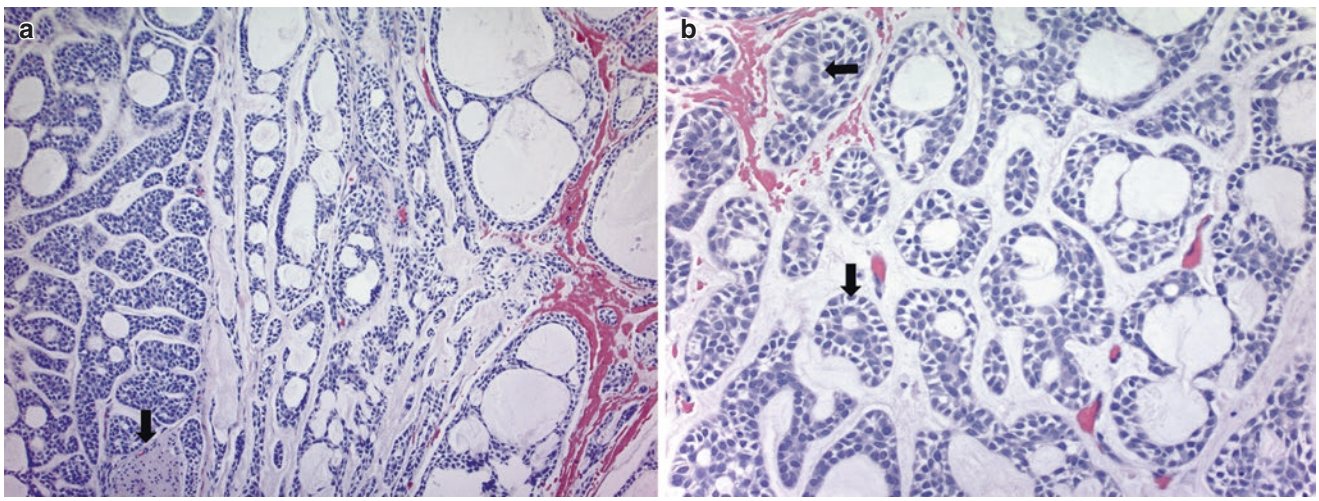


**Fig. 5.7** Adenoid cystic carcinoma. (**a**) Areas of solid ACC have basaloid myoepithelial cells and demonstrate perineural invasion (arrow). Cribriform regions with lightly basophilic stroma are seen on the right. (**b**) Higher magnification shows the hyperchromatic, angulated myoepithelial cells, focally surrounding ductal structures (arrows)

  - The cells have a moderate amount of eosinophilic cytoplasm with variably sized, intracytoplasmic vacuoles that may coalesce to form lumina (Fig. 5.9a).
  - Cells show minimal atypia and may form sheets with small cystic spaces or large, thyroid-like, follicular spaces.
- The eosinophilic, luminal material reacts with PAS and may show weak mucicarmine staining.
- The solid type comprises sheets of acinar cells with granular, basophilic cytoplasm and intracytoplasmic, zymogen granules. Nuclei range from small, dark, dot-like to round with fine chromatin and conspicuous nucleoli (Fig. 5.9b). This subtype generally lacks duct differentiation and is negative for CK7.
- Cells may have a hobnail-type appearance; this should not be mistaken for apocrine-type, apical snouting.
- Strong cytoplasmic and canalicular staining for DOG-1 is a characteristic.
- AcCC is sometimes associated with a prominent lymphoid stroma.
- A small subset of cases occurs in minor salivary glands (5%), mainly the lip and buccal mucosa. Many of these, as well as zymogen granule-poor types, harbor the ETV6-NTRK3 translocation and have been reclassified as secretory carcinomas; see question 9.

References: [45–49]

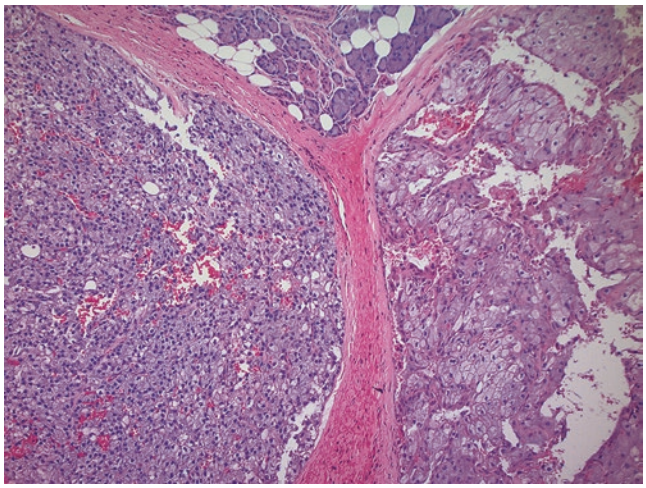

**Fig. 5.8** Acinic cell carcinoma. Acinar cells are arranged in sheets and contain basophilic, granular cytoplasm (left) as well as finely reticulated, pale cytoplasm (right) with small, round, dark nuclei. In contrast, the normal parotid gland (top) shows small acini in a normal lobular architecture with intervening ducts

9. *What is mammary analogue secretory carcinoma and how is it characterized?*

Mammary analogue secretory carcinoma is a recently described tumor derived from intercalated duct epithelium that resembles secretory carcinoma of the breast. The 4th edition of the *WHO Classification of Head and Neck Tumors* uses the term secretory carcinoma (SC). It is primarily a tumor of the major salivary glands (80%). Patients are typically middle-aged with a slight male predominance.

- SC is circumscribed, unencapsulated tumors with invasive growth. The cells are arranged in tubular, papillary, microcystic, and solid growth patterns (Fig. 5.10). Fibrous septa separate the tumor lobules. The luminal pink, bubbly (colloid-like) material is positive for mucicarmine and PAS stains with and without diastase.
- The tumor cells are cuboidal with small, bland vesicular nuclei with conspicuous, central nucleoli, mild atypia, and vacuolated or granular, eosinophilic cyto-

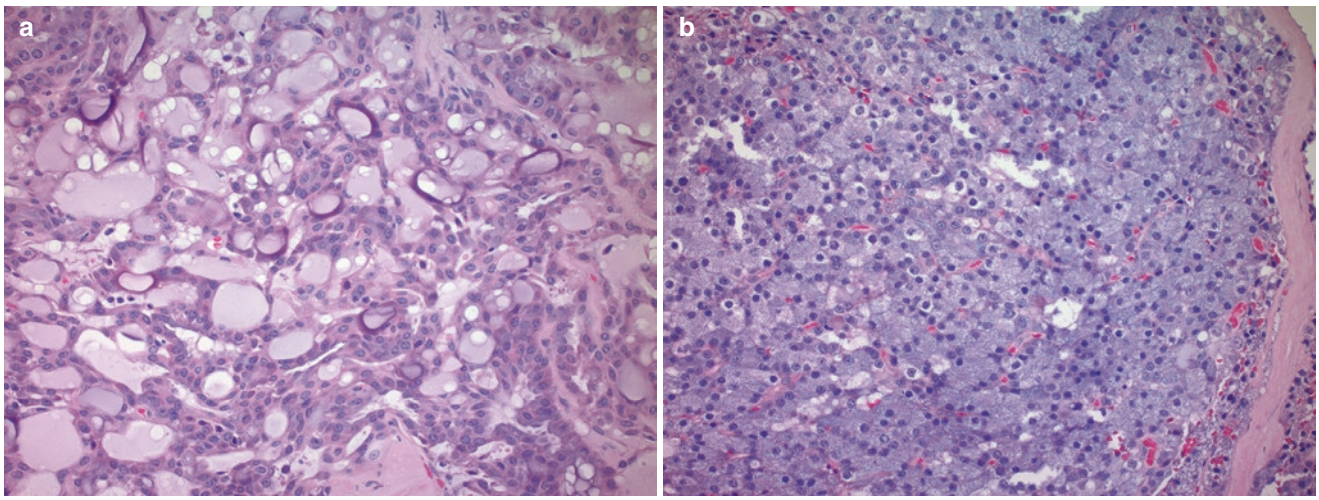


**Fig. 5.9** Acinic cell carcinoma. (**a**) Microcystic pattern, with numerous small cysts, lined by cuboidal, intercalated duct-type cells. (**b**) Solid type with the "blue dot" appearance of small nuclei in acinar cells with deeply basophilic granules

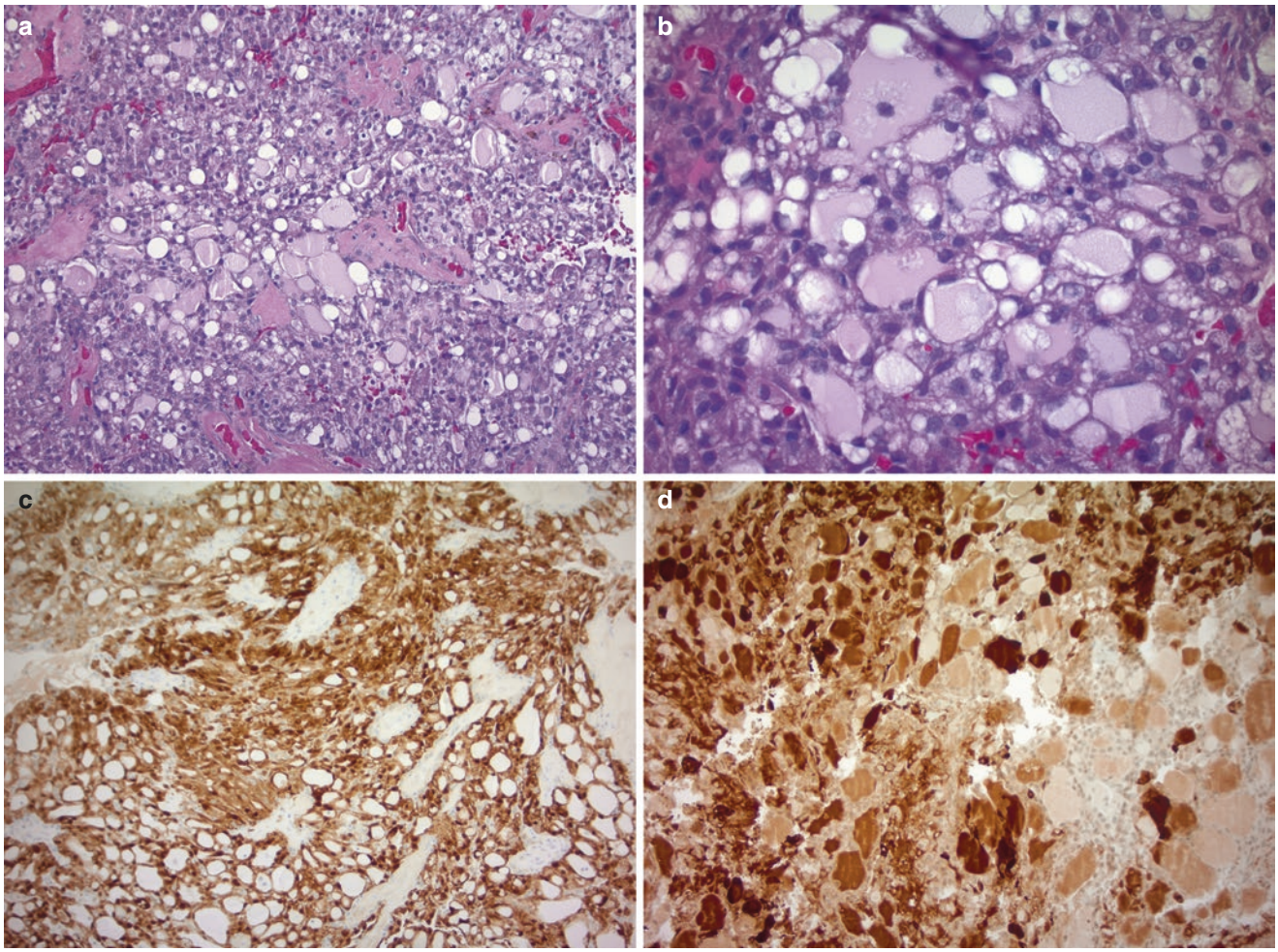


**Fig. 5.10** Secretory carcinoma. (**a**) Microcystic pattern with variably sized spaces and pale eosinophilic secretions. (**b**) Tumor cytoplasm is finely vacuolated and lacks basophilic zymogen granules. (**c**) The tumor is strongly positive for S100 and (**d**) mammaglobin

plasm. Mitoses, necrosis, and lymphovascular invasion are rare.

- SC is characterized by the ETV6-NTRK3, t(12;15)(p13;q25) translocation, identical to that seen in mammary secretory carcinoma. Other translocation partners include t(12;XX).
- The primary differential diagnostic consideration with SC is acinic cell carcinoma. Table 5.4 summarizes the differences between SC and AcCC.
  - A subset of zymogen granule-poor AcCC and those in minor SG have been retrospectively reclassified as SC based on molecular findings.
  - The clinical significance of this distinction is unclear given the limited number of cases. However, SC may have a slightly higher rate of lymph node metastases (20%).
- SC can undergo high-grade transformation. High-grade tumors express p53 and membranous beta-catenin.

References: [46, 49–57]

10. *What are the clues to the diagnosis of polymorphous adenocarcinoma (polymorphous low-grade adenocarcinoma) and which entities are in the differential diagnosis?*

Polymorphous adenocarcinoma (PAC) is a monotypic tumor comprising cells of terminal/intercalated duct origin. It is classically described as cytologically uniform but architecturally diverse. It shows a relatively even distribution among intraoral and major salivary gland sites. There is twofold female predominance with a mean age of 60 years old.

- PAC is the second most common intraoral salivary gland carcinoma after adenoid cystic carcinoma.
- The palate is the most common location (approximately 60%).
- The different growth patterns include solid, lobular, papillary, ductal, and tubular; cribriform and papillary growth are less common.
- PAC is usually unencapsulated with a more solid, lobular center and small nests and cords of single cells radiating toward the tumor periphery in an infiltrative

**Table 5.4** Contrasting features between secretory carcinoma and acinic cell carcinoma

| | Secretory carcinoma | Acinic cell carcinoma |
|---|---|---|
| Gender predominance | Male | Female |
| Location | Minor and major SG | 90% parotid |
| Predominant growth pattern | Solid, tubular<br>Papillae common | Solid, microcystic<br>Papillae rare |
| Infiltrative growth | Yes | No |
| Cell morphology | Monotonous<br>Eosinophilic, vacuolated, granular | Varied<br>Eosinophilic to basophilic, granular, clear, oncocytic |
| Hobnail cells | Yes | No |
| PAS+ cytoplasmic granules | No | Yes |
| DOG-1 IHC | Negative | Positive |
| S100 IHC | Positive | Negative |
| Mammaglobin IHC | Positive | Negative |

pattern. This arrangement creates the classic, concentric, targetoid appearance (Figs. 5.11 and 5.12).

- The cells are small to intermediate in size with bland, oval nuclei, delicate nuclear membranes and pale chromatin.
- Perineural invasion is common and necrosis is rare.
- Mutations in PRKD1 E710D are present in up to 70% of cases.
- Overall 5- and 10-year survival rates are 91% and 73%, respectively. Distant metastases and deaths due to disease are rare.
- Locoregional recurrences, including cervical lymph node metastases, approach 30% and can have long latency periods in excess of 15 years. For this reason, and because of reports of occasional high-grade transformation, the "low-grade" moniker has been removed from the name in the 4th edition of WHO classification system.

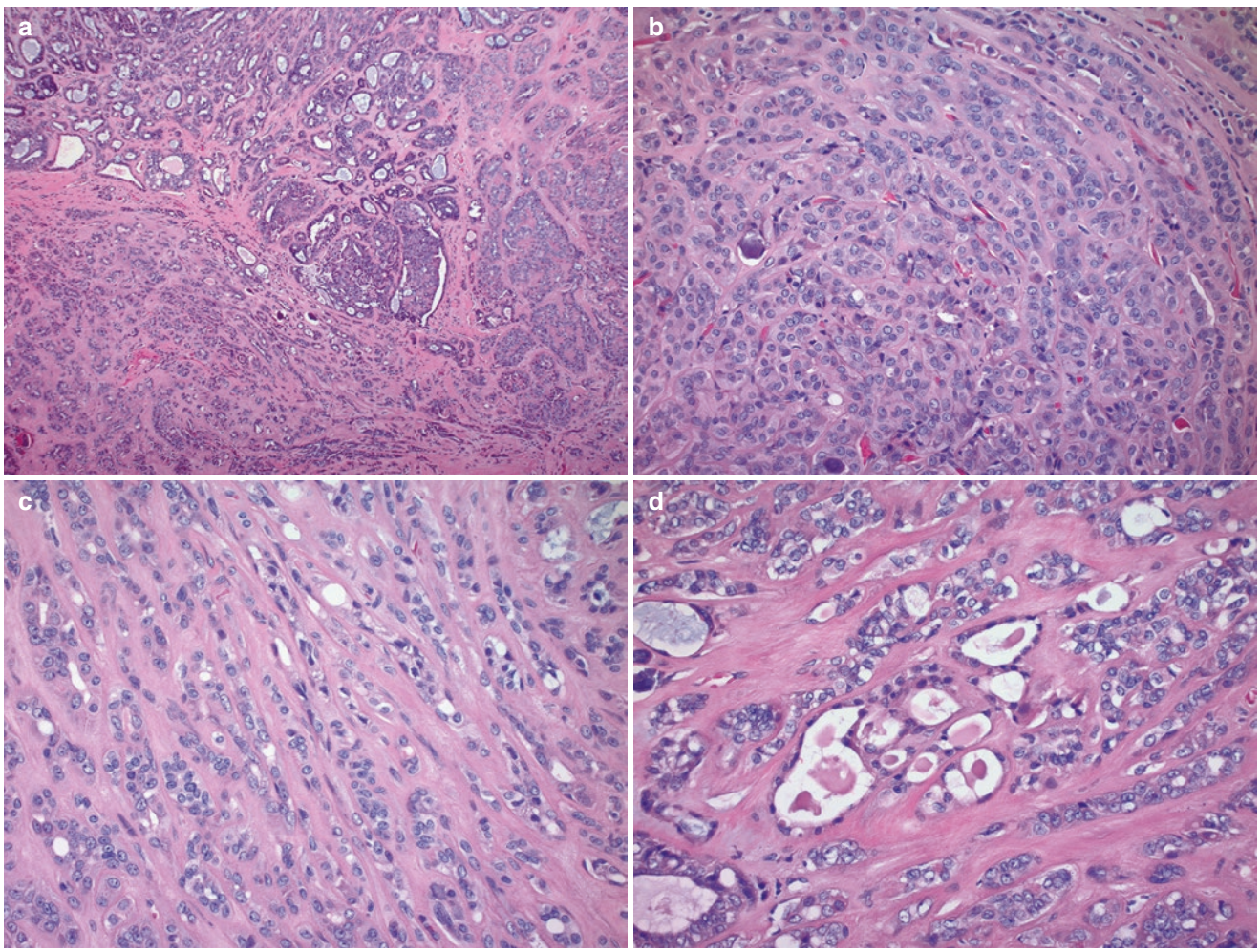


**Fig. 5.11** Polymorphous adenocarcinoma. (**a**) Low magnification shows a variegated architecture with papillary structures toward the center and small tubules (top), single cells (bottom left), and lobules (right) at the periphery. (**b**) A tumor lobule shows a concentric targetoid arrangement and nuclear monotony with oval, bland, pale nuclei. (**c**) Tumor cells are arranged in single files and (**d**) tubules

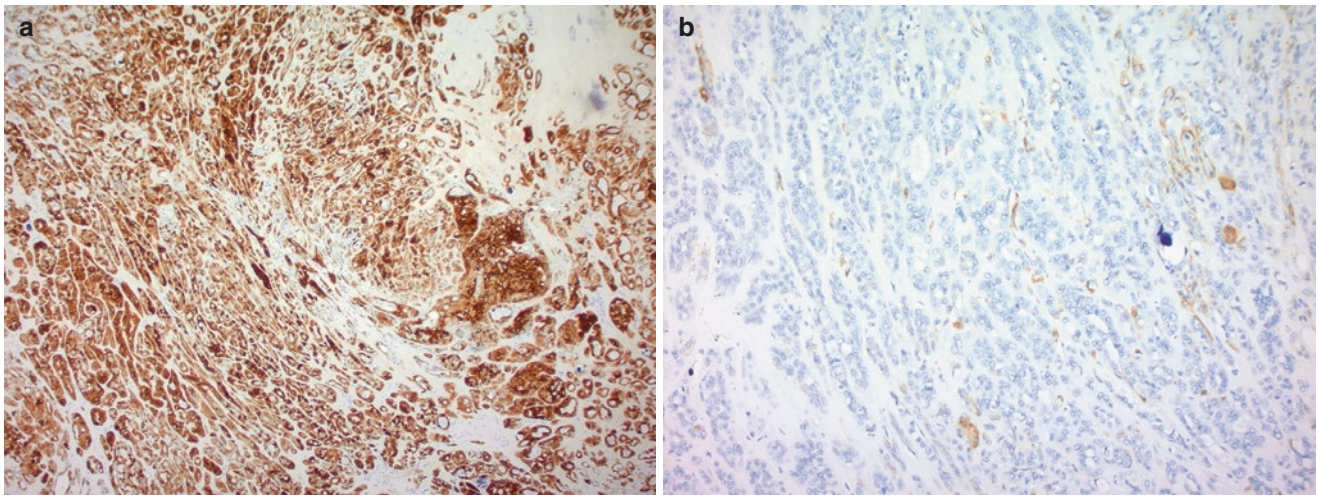


**Fig. 5.12** Polymorphous adenocarcinoma. (**a**) S100 is strongly and diffusely positive. (**b**) SMA shows rare, scattered positive cells

**Table 5.5** Tumors in the differential diagnosis of polymorphous adenocarcinoma

| | Polymorphous adenocarcinoma | Adenoid cystic carcinoma | Pleomorphic adenoma | Cribriform adenocarcinoma of SG |
|---|---|---|---|---|
| Biphasic | No | Yes | Yes | Yes |
| Predominant cell | Ductal<br>Monotonous, oval, fine to vesicular, pale chromatin | Myoepithelial<br>Basaloid, small, hyperchromatic, angulated | Variable cell types<br>Small dark myoepithelial cells, cuboidal ductal cells, ±squamous cells | Ductal<br>PTC-like nuclei, oval, overlapping, irregular membranes, fine, pale chromatin |
| Cytoplasm | Appreciable, eosinophilic | Scant, pale | | Abundant, clear to eosinophilic |
| Patterns | Classic single file, cell growth<br>Variable: tubular, lobular, rarely cribriform, or papillary | Cribriform, tubular, solid | Variable sheets and nests of myoepithelial cells, scattered duct proliferation | Fibrous septa, lined by basal cells, retract from tumor nodules, creating glomeruloid effect<br>Solid, cribriform, papillary |
| Stroma | Not prominent, variable<br>Collagenous, mucoid, hyaline | Prominent in areas<br>Hyaline or basophilic | Chondromyxoid | Collagenous, vague palisading of small, dark nuclei at edges of nodules |
| PNI | Frequent | Frequent | None | Not prominent |
| Myoepithelial markers | Negative | Positive | Positive | Positive at edges of tumor nodules |
| Ductal markers | Diffusely positive, LMWCK | Focal positive | Positive | Diffusely positive, LMWCK |
| p63/p40 | Positive/Negative | Positive/Positive | Positive/Positive | Positive/na |
| S100 IHC | Strong, diffuse | Weak | Variable | Strong, diffuse |
| Molecular | PRKD1 E710D mutation | NIFB-MYB | PLAG1, HMGA2 | PRKD1-3 translocation |

*SG* salivary gland, *PTC* papillary thyroid carcinoma, *PNI* perineural invasion, *LMWCK* low molecular weight cytokeratins, *na* data not available

The major differential diagnoses with PAC arise primarily because the diagnosis is made on limited biopsy samples typically from the oral cavity (Table 5.5). Its polymorphous architecture has many mimics that are greatly reduced on excision specimens.

- Cribriform adenocarcinoma of (minor) salivary gland (CASG) shows significant morphologic overlap with PAC but a distinct clinical picture. Less than 100 cases have been reported in the literature. It occurs primarily in the minor salivary glands, and patients typically present with cervical lymph node metastases. However, the tumor has an excellent prognosis with no reported distant metastasis or deaths due to disease.
- CASG (Fig. 5.13) is not currently classified by the WHO but is probably best regarded as a cribriform variant of PAC. A subset harbor translocations of PRKD1-3 with ARID1A and DDX3X.

References: [2, 58–66]

11. *What are the morphologic subtypes of basal cell adenomas, their clinical relevance, and differential diagnosis?*

Basal cell adenomas are rare, accounting for 1–3% of all salivary gland tumors. They present primarily in the parotid gland, with a minority of cases in intraoral sites (upper lip) and submandibular gland. There is a slight female predominance with a wide age range and a peak incidence in the seventh decade.

- BCA is a well-circumscribed, encapsulated tumor composed of bland, basaloid cells that show some degree of nuclear palisading. Mitoses are rare, and necrosis is absent.

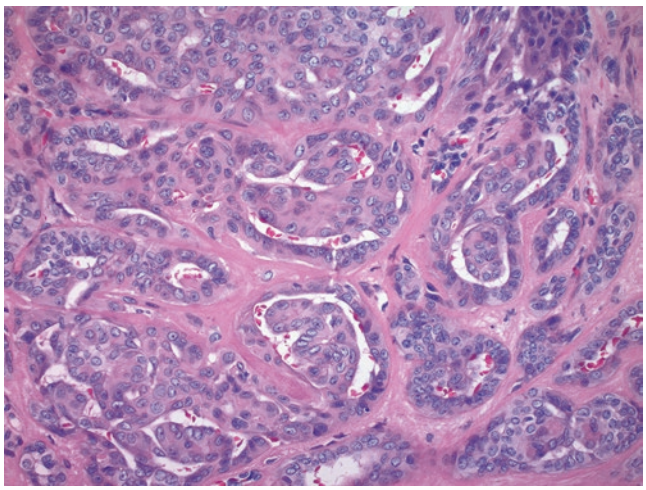

**Fig. 5.13** Cribriform adenocarcinoma of the salivary gland. Tumor cell aggregates retract from basal cells at the stromal interface and form glomeruloid structures. Nuclei are oval, pale, and grooved reminiscent of papillary thyroid carcinoma

- There are four morphologic types (Table 5.6) of BCA; most tumors will show at least two types (Fig. 5.14).
- The two main cell types are abluminal with varying amounts of ductal cells:
  - Myoepithelial cells: small, dark cells with round to oval, hyperchromatic nuclei and scant cytoplasm.
    - Muscle markers: positive
    - Basal markers: positive (p63, CK5/6, CK14)
  - Basal cells: larger, abluminal cells with oval, more pale nuclei and more abundant, eosinophilic cytoplasm. They typically align at the epithelial-stromal interface and demonstrate palisading.
    - Muscle markers: negative
    - Basal markers: positive (p63, CK5/6, and CK14)

Basal cell adenocarcinoma (BCAC) poses the most significant diagnostic challenge with BCA. BCAC only differs from BCA by demonstrating infiltrative growth, including capsular, vascular or perineural invasion. Increased mitotic activity, pleomorphism, and necrosis may be seen but are not prominent features.

- Some authors suggest that a BCA with mitoses in excess of three per ten high-power fields should be carefully examined and completely submitted for histologic evaluation to exclude BCAC.
- The solid variant is the most common type of BCAC, and palate is the most common intraoral site.
- The differential diagnosis of BCAC depends on type and location. Immunohistochemical stains and morphologic features can help make the correct diagnosis.

**Table 5.6** Clinicopathologic features of the morphologic types of basal cell adenoma

| | Tubulo-trabecular | Solid | Membranous | Cribriform |
|---|---|---|---|---|
| Morphology | Interlacing network of tumor cords of varying thickness<br>Tubules lined by duct epithelium and surrounded by abluminal cells | Large, irregularly shaped sheets and nodules separated by stroma<br>±Squamous eddies | Solid nests and nodules rimmed by dense, eosinophilic stroma<br>Multinodular growth with "jigsaw" puzzle arrangement<br>±Squamous eddies | Cribriform nests of variable size<br>Nests have light cells in the center, dark cells at the periphery |
| Stroma | Cellular, collagenous<br>S100 IHC positive | Collagenous | Hyalinized, basement membrane material | Homogeneous pale blue/gray or pink |
| Molecular | CTNNB1 mutations<br>β-catenin IHC positive | None | Cyclin-D1 mutations<br>β-catenin IHC negative | None |
| Comments | DDX: canalicular adenoma – exclusive to the lip, edematous stroma, uniform, 2-cell thick cords | DDX: basaloid squamous cell carcinoma – abrupt keratin, necrosis | May be multifocal<br>Up to 25% recur<br>Associated with Brooke-Spiegler syndrome | DDX: adenoid cystic carcinoma – absence of palisading and only one abluminal cell type |

*DDX* differential diagnosis

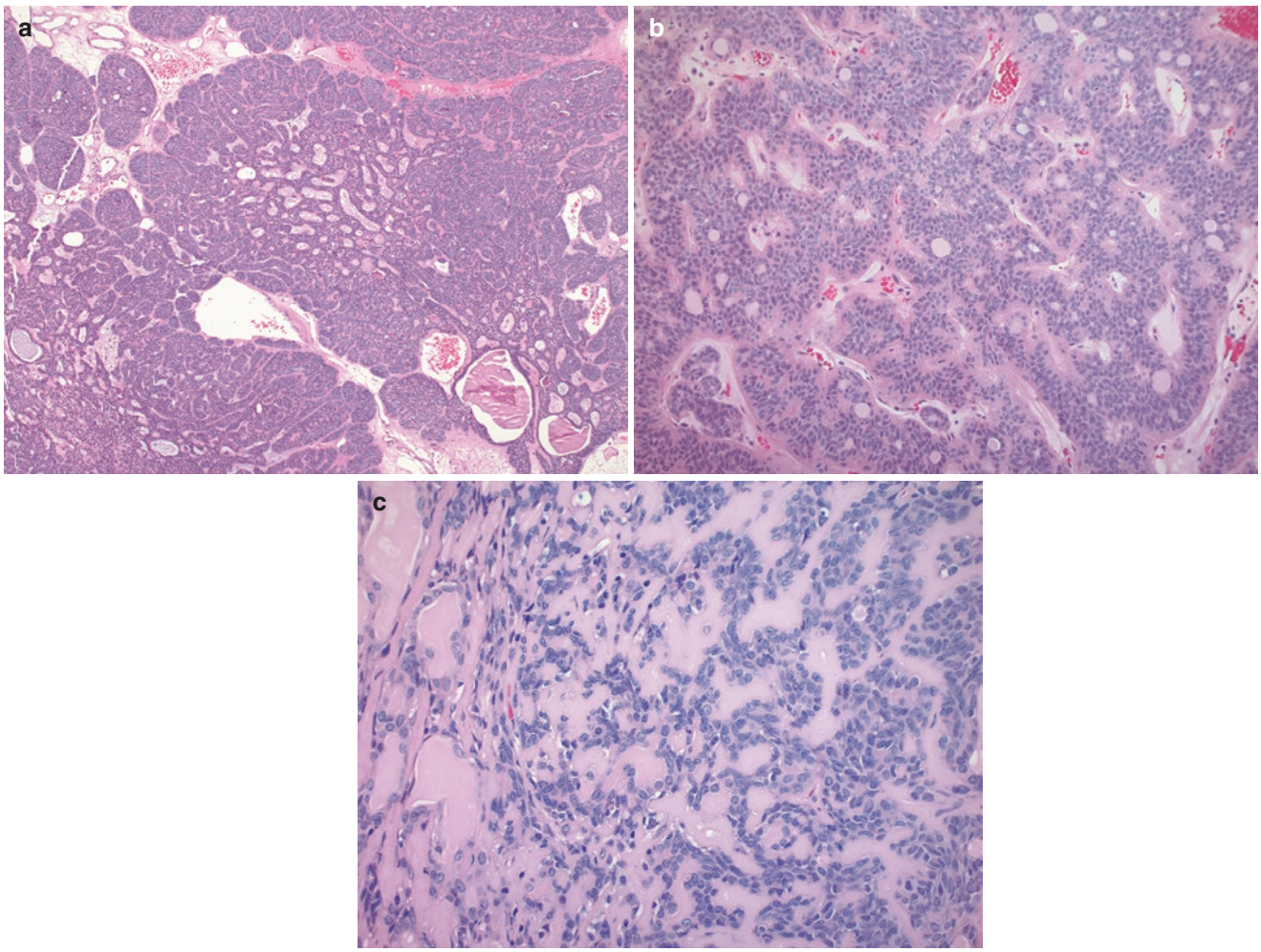


**Fig. 5.14** Basal cell adenoma. (**a**) Solid type with tumor nests arranged in lobules. (**b**) Tubulo-trabecular pattern with ribbons of tumor cells and scattered tubular lumens. (**c**) Membranous type, cells are surrounded by hyalinized, eosinophilic basement membrane material

  - Adenoid cystic carcinoma
  - Basaloid squamous cell carcinoma
  - Basal cell carcinoma

References: [67–72]

12. *What are the criteria used to diagnose myoepithelial tumors, their subtypes, and the differential diagnoses?*

Myoepithelial tumors are rare tumors accounting for less than 2% of all salivary gland neoplasms. The parotid gland is the most common site (40–60%) with up to 20% of cases presenting in minor salivary gland, usually palate. Myoepitheliomas and myoepithelial carcinomas (MyEC) present as a slow-growing, painless masses.

- Myoepithelial tumors are encapsulated and composed almost exclusively of myoepithelial cells. Some authors do not accept any ductal elements, while others will allow for as much as 10% duct formation. Given the morphologic overlap with so many SG tumors, we prefer the former, more stringent criteria.
- There are five different cell types: epithelioid, spindled (Fig. 5.15), plasmacytoid or hyaline (Fig. 5.16), clear cell, and mucinous. Tumor variants generally comprise at least 75% of one cell type, but a mixed pattern is the rule.
  - The cell type is not clinically significant, but awareness of the different morphologies and their mimics is important in making an accurate diagnosis (Table 5.7).
  - The stroma can be positive for Alcian blue but usually negative for mucicarmine.
- The diagnosis of myoepithelial tumors requires demonstration of myoepithelial lineage by immunohistochemistry or ultrastructural analysis.
- Myoepithelial tumors co-express keratins and muscle markers to varying degrees:

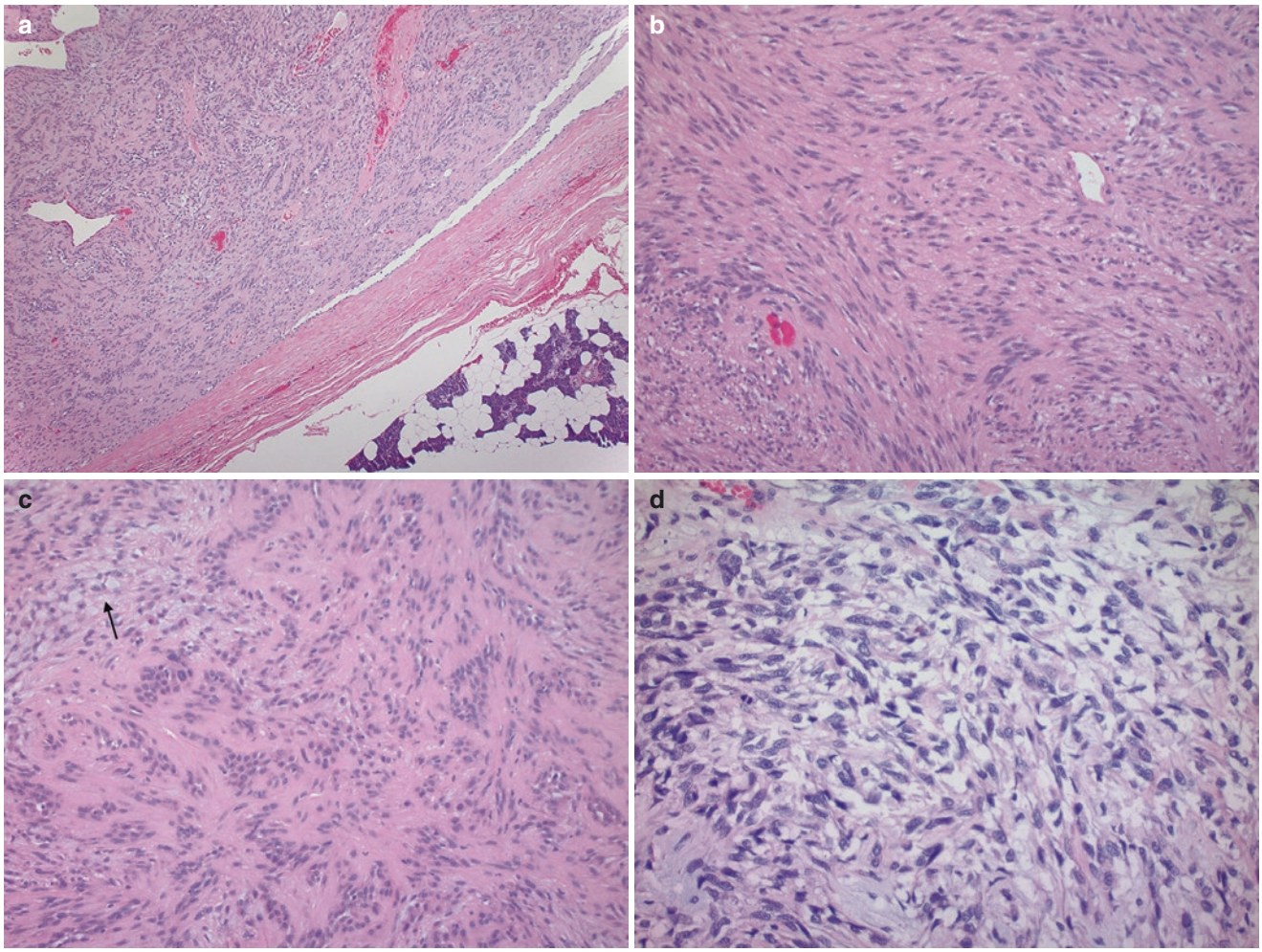


**Fig. 5.15** Spindled myoepithelial tumors. (**a**–**c**) Myoepithelioma. A well-circumscribed spindle cell tumor composed of bland spindle cells arranged in intersecting fascicles with vague palisading similar to a schwannoma. Foci of tumor cell cords (**c** arrow) in a mucoid stroma offer a clue to the diagnosis. (**d**) Spindled myoepithelial carcinoma, in contrast, shows increased nuclear atypia and mitoses

  - Keratins: AE1/3, 34BetaE12, Cam5.2, CK14
  - Muscle markers: calponin, smooth muscle actin, SMA, MSA, calponin
  - Other positive markers: vimentin, S100, p63, GFAP
  - Negative markers: CK7
- A few notable exceptions to the classic immunoprofile:
  - Spindle variant is negative for pan-cytokeratin.
  - Mucinous variant expresses CK7, mucicarmine, with variable p63 and calponin.
  - Plasmacytoid variant may only weakly express muscle markers.
- Myoepithelial carcinoma (MyEC) is distinguished from myoepitheliomas by:
  - An infiltrative border, multinodular growth
  - Frequent or atypical mitoses (see Fig. 5.15d)
  - Tumor nodules with a hypercellular periphery and a necrotic center (see Fig. 5.16c, d)
- Histologic parameters such as grade, cell type, mitotic rate, the presence of necrosis, nerve or vascular invasion do not consistently correlate with prognosis.
- Clinically, MyEC has high metastatic rates, averaging 40–50% and frequent recurrences. Common sites of metastases are the lungs and cervical lymph nodes.

References: [1, 73–80]

13. *What is the differential diagnosis of oncocytic lesions of salivary gland?*

The three principal oncocytic lesions of the salivary gland are oncocytoma (Fig. 5.17), nodular oncocytic hyperplasia (or oncocytosis), and oncocytic carcinoma (Fig. 5.18). Among these, less than 10% represent oncocytic carcinomas. Table 5.8 summarizes the features of each.

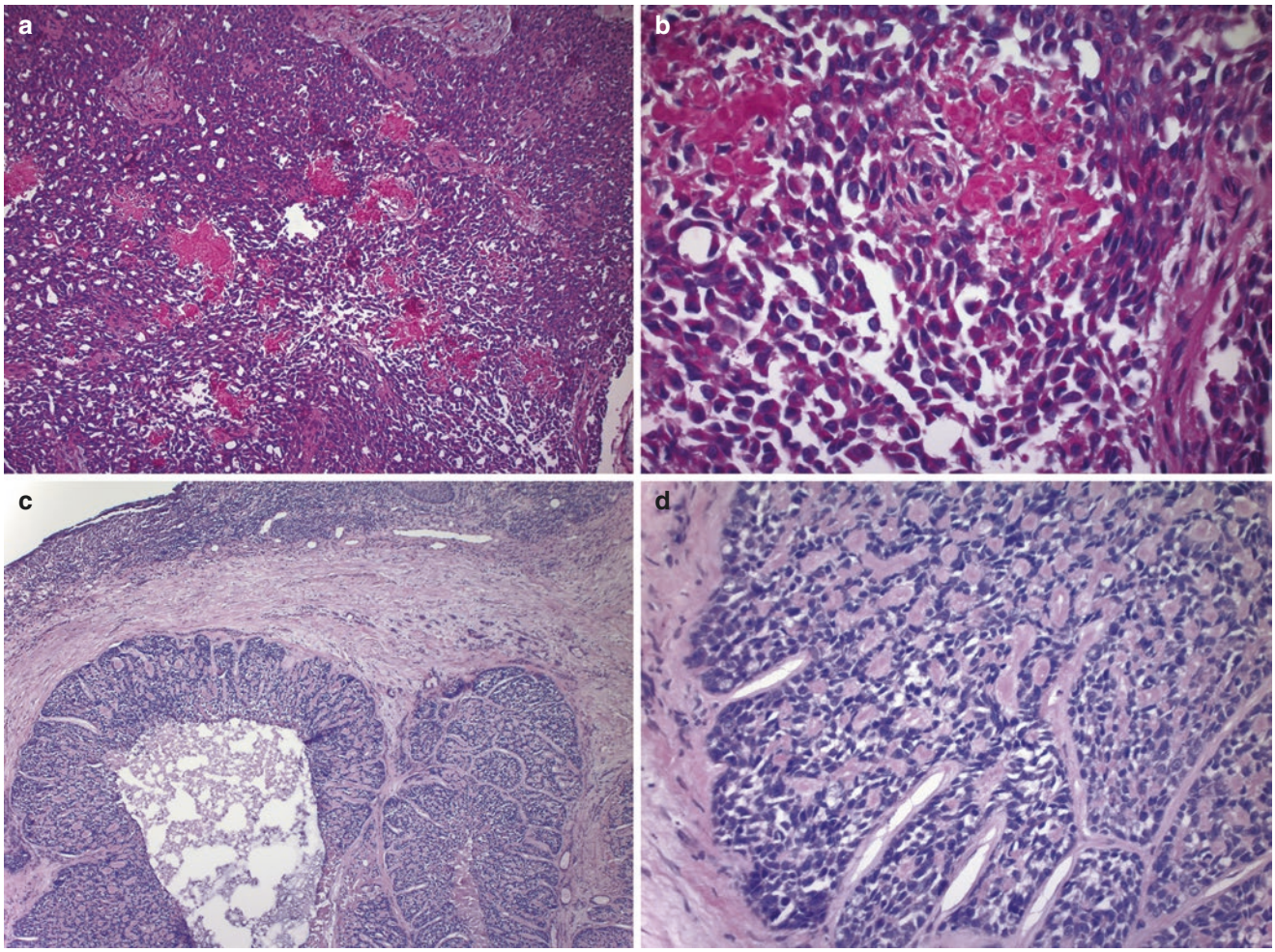


**Fig. 5.16** Hyaline type myoepithelial tumors. (**a**, **b**) Myoepithelioma. Sheets of monotonous tumor cells with brightly eosinophilic, plasmacytoid cytoplasm and tufts of hyaline, basement membrane material (**b** center). (**c**, **d**) Myoepithelial carcinoma. Submucosal tumor lobules with necrotic centers and tumor cells surrounded by hyaline, basement material

- All three lesions occur in older patients (sixth to seventh decades) with no gender preference.
- Care should be taken to distinguish the clear cell variant of oncocytoma from other primary *and* secondary clear cell tumors (see question 14).
- The infiltrative growth pattern of oncocytic carcinoma is a key feature in the diagnosis, as pleomorphism and atypia may be focal.

Oncocytic change occurs in a variety of salivary gland entities; a few tumors are notable for having oncocytic variants. These variants are generally defined as having at least 50% oncocytic change and should be considered in the differential diagnosis of oncocytic tumors.

- The oncocytic variant of epithelial-myoepithelial carcinoma (EMCA) shows the classic biphasic pattern of outer myoepithelial cells and inner ductal cells. When both ductal and myoepithelial cells are oncocytic, immunohistochemical stains may be necessary to appreciate the biphasic pattern.
  - Seethala et al. noted that oncocytic EMCA has a tendency toward papillary growth and frequently demonstrates sebaceous differentiation.
  - The immunoprofile is similar to that of the usual type of EMCA: p63 and muscle markers will highlight the myoepithelial layer, and various keratins will stain the ductal component.
  - In oncocytomas, p63 only stains cells at the periphery of the tumor nodules.
- The oncocytic variant of mucoepidermoid carcinoma (oncMEC) is a rare tumor with only a few cases described in the literature.
  - The oncocytes are arranged in sheets and nests in a fibrotic stroma.
  - The majority of cases are low to intermediate grade.

**Table 5.7** Variants of myoepithelial tumors, their features, and tumors in the differential diagnosis

| Myoepithelial variant and morphology | | Tumors in differential diagnosis | |
|---|---|---|---|
| Epithelioid | Nests, cords, pseudoglandular spaces polygonal cells, moderate amount of eosinophilic cytoplasm, indistinct cell borders<br>Central nucleus<br>Myxoid matrix | Polymorphous adenocarcinoma | EMA+, CEA+, DOG-1+<br>Muscle markers– |
| | | Adenocarcinoma, NOS | EMA+, CEA+, CK7+<br>Muscle markers– |
| Clear cell<br>PAS+<br>PASD– | Polygonal cells with abundant clear/pale, glycogen-rich cytoplasm<br>Small, raisinoid nuclei<br>Microcystic spaces | Squamous carcinoma | p63+, CK5/6+<br>Muscle markers– |
| | | EMCA | EMA+, CEA+ |
| | | Renal cell carcinoma | Pax-8+, RCC antigen+<br>Muscle markers– |
| | | Clear cell carcinoma | Muscle markers–, S100– |
| | | Oncocytoma | AMA+, PTAH+<br>Muscle markers–, p63– |
| | | Mucoepidermoid carcinoma | EMA+, CK7+<br>Muscle markers– |
| Spindle<br>Cam5.2–<br>CK– | Fascicular or storiform growth<br>Elongated, spindled cytoplasm<br>Short, oval, to elongated nuclei | Neural tumors | Muscle markers– |
| | | Leiomyosarcoma | Muscle markers+<br>CK–, p63– |
| | | Fibrosarcoma | CK–, muscle markers– |
| Plasmacytoid<br>Muscle markers+/weak | Round, dyshesive cells with dense eosinophilic cytoplasm<br>Eccentric, dark nucleus<br>Hyalinized or mucoid stroma | Plasmacytoma | EMA+, CD138+, kappa+, lambda+<br>CK–, muscle markers– |
| | | Melanoma | HMB-45+, Mart-1+<br>Muscle markers–, CK– |
| | | Medullary thyroid carcinoma | TTF1+, Pax-8+<br>Muscle markers– |
| | | Rhabdomyosarcoma | CK–, p63–<br>Desmin+, MyoD1+, myoglobin+ |
| Mucinous<br>CK7+<br>E-cadherin+<br>Mucicarmine+ | Signet ring cells with intracellular mucin, eosinophilic cytoplasm<br>Eccentric nucleus | Secretory carcinoma (MASC) | Mammaglobin+, EMA+<br>Muscle markers–/wk+ |
| | | Metastatic adenocarcinoma | Site of origin markers+: TTF-1, GATA-3, Pax-8<br>Muscle markers– |

*NOS* not otherwise specified, *RCC* renal cell carcinoma, *wk* weak, *TTF* thyroid transcription factor, muscle markers, SMA, MSA, calponin, caldesmon

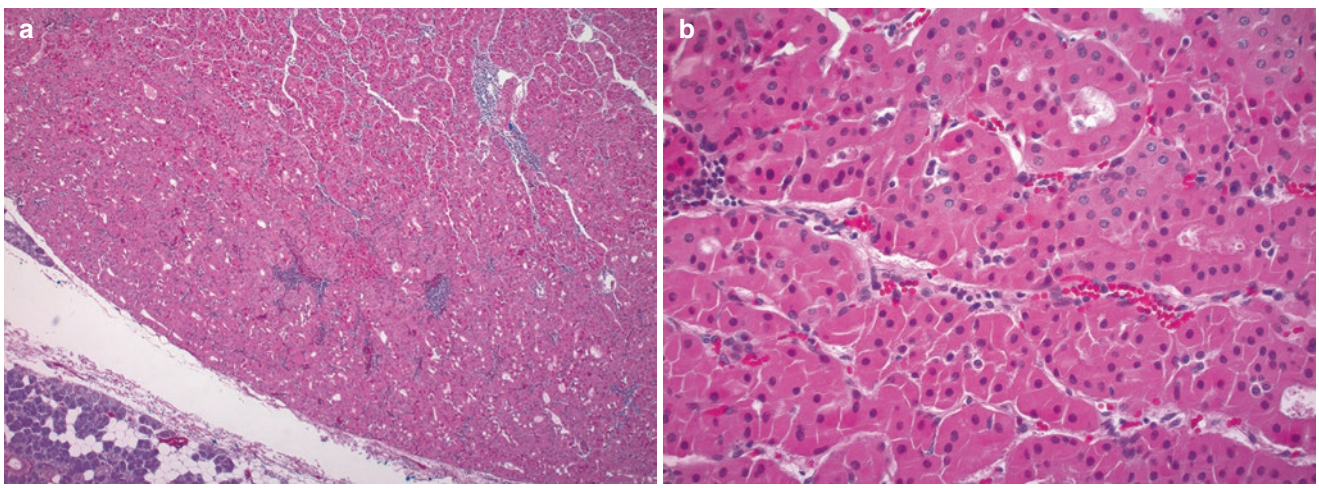


**Fig. 5.17** Oncocytoma. (**a**) A well-circumscribed, solid tumor. (**b**) Cells with abundant, granular, eosinophilic cytoplasm are arranged in trabeculae with scattered duct lumens

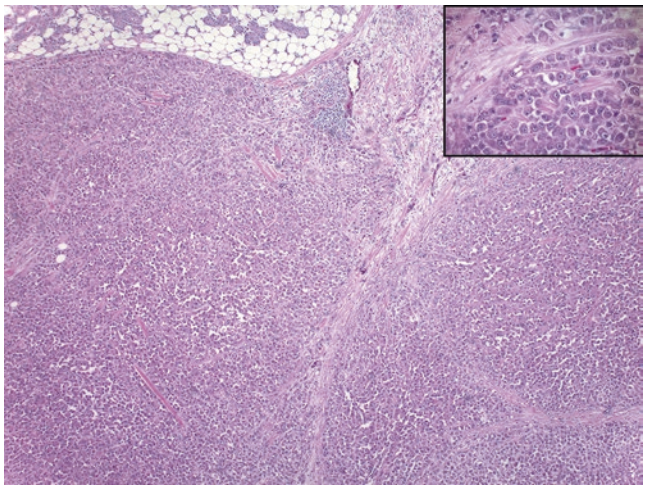

**Fig. 5.18** Oncocytic carcinoma. Sheets of atypical tumor cells with a high N-C ratio, granular pink cytoplasm, and nuclear pleomorphism

**Table 5.8** Pathologic features of oncocytic salivary gland lesions

| | Oncocytoma | Oncocytic carcinoma | Oncocytosis |
|---|---|---|---|
| Site | Parotid (85%) | Parotid | Parotid |
| Well-circumscribed | Yes | No, infiltrative | Yes |
| Encapsulated | Yes, at least partial | No | No |
| Atypia | No | Yes, may be focal | No |
| Nodular | Single nodule | Single nodule | Multiple nodules |
| Multifocal | No | No | Yes |
| Necrosis/ Mitoses | No/No | Some/Yes | No/No |

  - The tumors are mostly solid; conventional areas of MEC may be scarce, and mucous cells may be difficult to find without special stains.
  - The Warthin tumor-like variant of MEC typically shows disorganized, multilayered, oncocytic epithelium lining cysts and papillae with a dense lymphoid stroma and occasional mucus cells.
  - Awareness of both of these variants is essential in avoiding an incorrect diagnosis but conveys no prognostic value. Both variants stain strongly and diffusely with p63 and harbor MAML2 gene rearrangements.

References: [69, 81–90]

14. *What is the differential diagnosis of clear cell tumors of the salivary gland?*

Clear cell carcinoma is a rare, low-grade tumor of primarily minor salivary gland, with 80% occurring in intraoral sites (tongue and palate). Immunohistochemical stains and electron microscopy support a squamous origin.

- CCC is characterized by small nests, cords, and single files of clear cells separated by a dense, eosinophilic, hyaline stroma. The cells are small with a high nuclear to cytoplasmic ratio, bland nuclei, and clear to pale pink cytoplasm. Necrosis and mitoses are rare (Fig. 5.19).
- CCC rarely shows a predominance of optically clear cells.
- A myxoid, fibrocellular stroma may be present in lieu of the hyalinized stroma.
- CCC harbors the EWSR1-AFT1 rearrangement in 80–90% of cases. The same alteration is seen in clear cell odontogenic carcinomas, a postulated, intraosseous relative of CCC.
- Perineural invasion is frequent (40–50%).
- Increased mitotic activity or necrosis should raise concern for high-grade transformation.
- Metastatic rates to regional lymph nodes are estimated at 25%. However, CCC are considered low-risk tumors with metastases to distant sites and subsequent deaths at less than 4%.

Areas of clear cell change can be seen in a wide variety of benign and malignant salivary gland tumors. A few SG tumors such as epithelial-myoepithelial carcinoma (Fig. 5.20) and mucoepidermoid carcinoma (Fig. 5.21) are notable for their clear cell variants. The list in Table 5.9 is not comprehensive, and metastatic lesions, like squamous cell carcinoma and renal cell carcinoma, should also be considered.

References: [73, 91–98]

15. *What are the different ductal carcinomas and how are they distinguished?*

Salivary duct carcinoma (SDC) is a high-grade tumor of salivary duct origin. It is a disease of the elderly with a marked male predominance. As many as 60% occur in the parotid gland, though submandibular and minor salivary glands can also be involved. Up to 10% of cases arise in a carcinoma ex pleomorphic adenoma.

- SDC resembles high-grade ductal carcinoma in situ of the breast. It comprises large ducts/cysts lined by pleomorphic cells with coarse chromatin, prominent nucleoli, and moderate to abundant eosinophilic cytoplasm. The cells are arranged in a cribriform pattern with Roman-bridge architecture and comedo necrosis. Apical snouting, typical of apocrine differentiation, is characteristic (Fig. 5.22).
- Distinction from squamous cell carcinoma and high-grade transformation of other salivary gland carcinomas is critical, as the latter are more aggressive. Immunohistochemical stains and careful sampling to exclude a preexisting low-grade component are useful in arriving at the correct diagnosis.

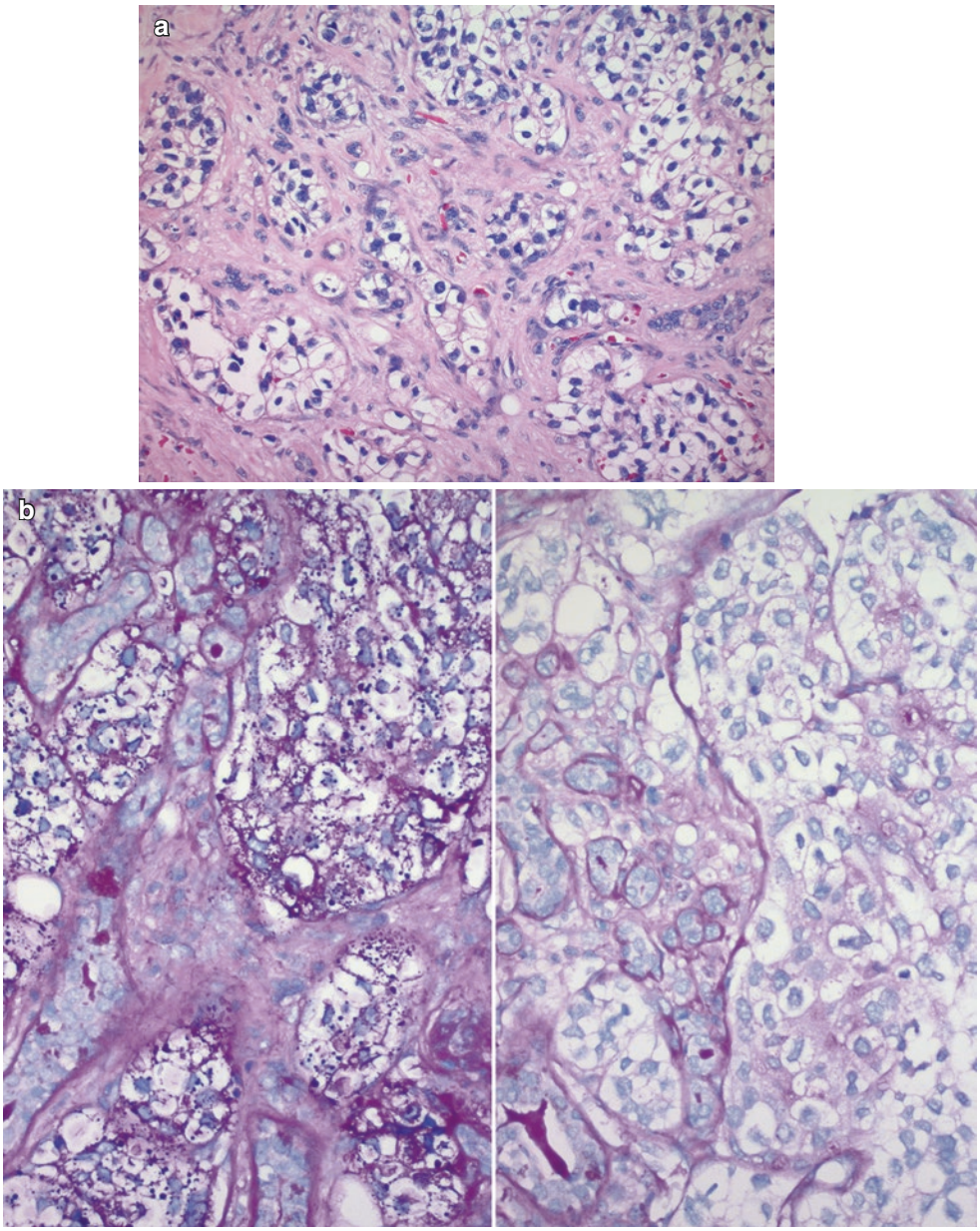


**Fig. 5.19** Clear cell carcinoma. (**a**) Infiltrative nests of polygonal cells with clear cytoplasm, distinct cell borders, and atypical nuclei in a fibrous stroma. (**b**) Intracytoplasmic glycogen is (left) PAS-positive and (right) diastase sensitive

- Regardless of gender, SDC expresses androgen receptors (AR), a marker of apocrine change. Williams et al. contend that AR-negative SDC is sufficiently rare enough to question the diagnosis.
- SDC has a poor prognosis with high rates of lymph node metastasis (50–70%), distant metastases (50%), and local recurrences (40–50%). Five-year survival ranges from 23% to 64%.

Intraductal carcinoma (IDC) is an in situ, ductal proliferation that resembles atypical ductal hyperplasia or low-grade ductal carcinoma in situ of the breast. IDC is rare, shows a slight female predominance, and overwhelmingly occurs in the parotid gland.

- IDC is predominantly cystic with round smooth contours and a micropapillary, solid, or cribriform architecture. The cribriform lesions can show irregular or slit-like spaces with larger cells at the periphery and small, dark cells crowded toward the lumen center.
- The cells have a moderate to abundant amount of eosinophilic cytoplasm that may have vacuoles, apical snouts, or PASD-positive globules. The nuclei are bland with a finely dispersed chromatin and variable nucleolar prominence.
- The sine qua non of the diagnosis is the demonstration of a myoepithelial layer surrounding the cysts and ducts.

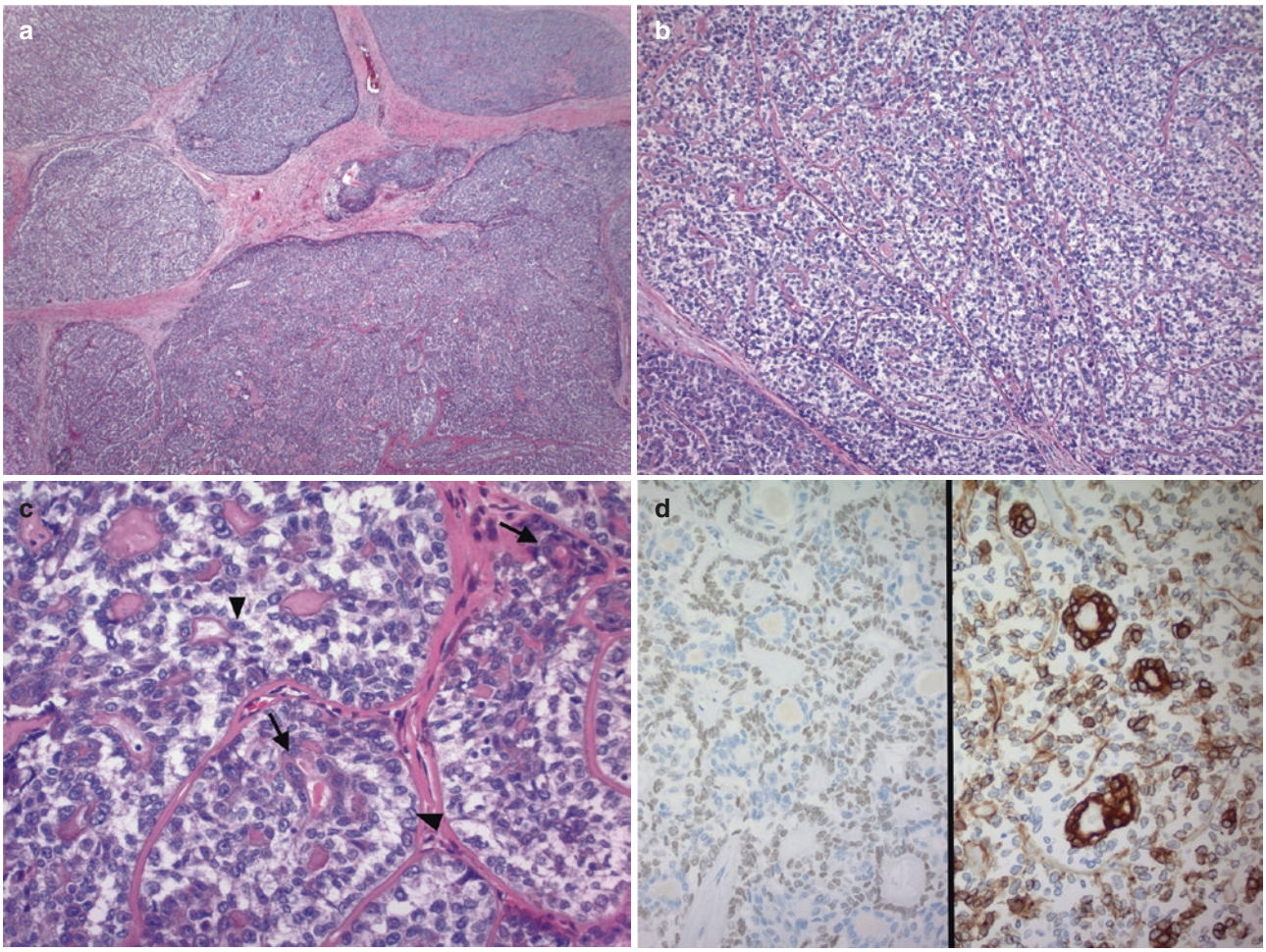


**Fig. 5.20** Epithelial-myoepithelial carcinoma. (**a**) Large, irregular tumor lobules in a fibrous stroma. (**b**) Areas of clear cell change separated by thin, fibrous bands. (**c**) Higher magnification shows a distinct two cell population of cuboidal, pink luminal cells (arrows) and clear, abluminal myoepithelial cells (arrowhead). (**d**) Immunohistochemistry for (left) p63 highlights myoepithelium and (right) pan-cytokeratin strongly stains ductal cells

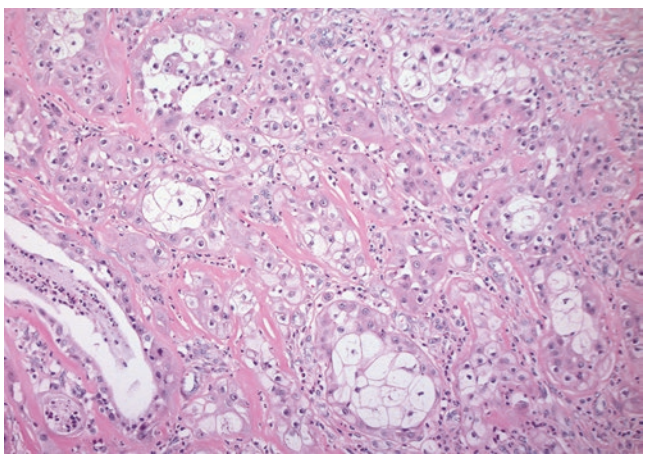

**Fig. 5.21** Mucoepidermoid carcinoma. Clear cells can be seen but are usually not the predominant or only cell type

- Intermediate- and high-grade cytology occurs in 13–17% of cases. Tumors show increased mitotic activity and pleomorphism; rare foci of necrosis may be present.
- Foci of limited stromal invasion can be seen in 20–23% of cases. Even with this finding, IDC has an excellent prognosis.
  - Cases with limited invasion should be diagnosed as "IDC with focal invasion."
  - Thorough sampling should be done to assess the amount or presence of invasion.
- Rare local recurrences are attributed to incomplete excision, and no reports of distant metastases or death due to disease have been described. Table 5.10 compares SDC to low- and high-grade IDC.

References: [3, 99–108]

**Table 5.9** Characteristics of clear cell carcinomas of salivary gland

| | Clear cell carcinoma | Epithelial-myoepithelial carcinoma | Myoepithelial carcinoma | Oncocytic carcinoma | Mucoepidermoid carcinoma |
|---|---|---|---|---|---|
| Location | 80% intraoral<br><10% in parotid | 60% parotid<br>Sinonasal > palate | 80% parotid | 70–80% parotid<br>Rare in minor SG | Major and minor salivary gland |
| Ducts | None<br>±Entrapped ducts | Prominent | None | None, microcysts | Large ducts, cysts |
| Myoepithelium | None | Present | Present | None | None |
| Papillae | None | Present | None | None | Papillary infoldings |
| Morphology | Infiltrative<br>Small nests, thin cords<br>Polygonal cells<br>Slightly irregular, eccentric nuclei | Circumscribed, encapsulated<br>Large, solid nests | Multinodular, infiltrative<br>Sheets of clear cells<br>Raisinoid nuclei | Foci of classic oncocytes with granular, pink cytoplasm | Three cell types: squamous, intermediate, and mucous cells |
| Stroma | Hyaline, collagenous | Hyaline, not prominent | Hyaline, myxoid | Not prominent | Extravasated mucin |
| PNI | Frequent | Occasional | Occasional | Frequent | Rare |
| Necrosis | Rare | Not typical | Present | Occasional | Rare |
| Mitoses | Rare | Present, low | Present | Present | Rare |
| Positive stains | p63, CK7, 34βE12, CK14, PAS | M: p63, S100, calponin, SMA, PAS<br>D: Cam5.2, AE1/3 | p63, S100, calponin, vimentin, GFAP, PAS | PTAH, AMA, CK7, PAS± | p63 diffuse, strong CK7, PAS |
| Negative stains | S100, calponin, SMA, vimentin, GFAP, PASD | PASD | CK7, PASD | S100, calponin, SMA, PASD | PASD |

*SG* salivary gland, *PNI* perineural invasion, *M* myoepithelium, *D* ducts, *PTAH* phosphotungstic acid hematoxylin

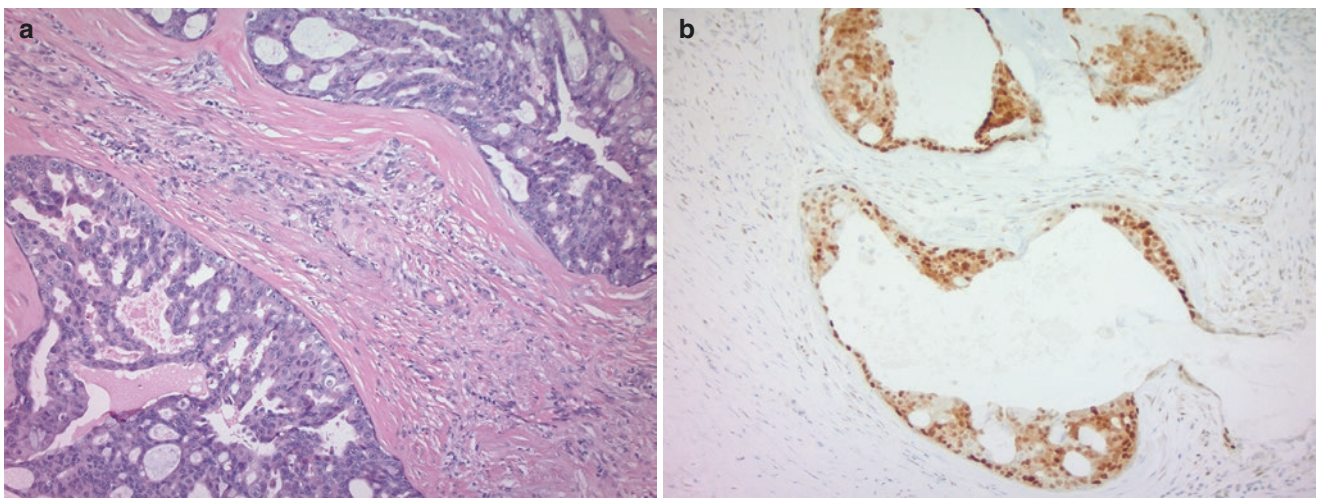


**Fig. 5.22** Salivary duct carcinoma. (**a**) Cribriform, large ducts are (**b**) positive for androgen receptors

16. *Are there specific histologic features for the diagnosis of adenocarcinoma, not otherwise specified?*

By definition, adenocarcinoma, not otherwise specified (ACA, NOS) is a glandular carcinoma that does not meet histologic criteria for any other SG carcinoma; it is a diagnosis of exclusion. All cases show an infiltrative glandular or ductal proliferation; more specific histologic features are not established. Table 5.11 summarizes the clinicopathologic features of ACA, NOS.

- Tumors comprise cuboidal or columnar cells of different subtypes, including mucinous and oncocytic. The 2017 WHO classification includes mucinous and intestinal types of adenocarcinoma in the ACA, NOS category (see question 2).
- The growth patterns are numerous, including cribriform and solid architectures, papillae, nest, cords, and tubules.
- ACA, NOS are generally aggressive tumors, though low-grade tumors have a better prognosis.

**Table 5.10** Histologic features of ductal carcinomas of salivary gland

| | IDC, low-grade | IDC, high-grade | SDC |
|---|---|---|---|
| Myoepithelial layer | Present | Present | Absent |
| Invasion | None/focal | None/focal | Y, extensive |
| Micropapillary | Yes | Yes | Very rare |
| Cystic | Yes | Yes | Yes |
| Cytoplasmic lipofuscin | Present | Present | Absent |
| Necrosis | No | Focal | Yes, extensive |
| Cytology | Low-grade | High-grade | High-grade |
| Luminal spaces | Slit-like to round | Slit-like to round | Round, rigid |
| Mitotic activity | Rare | Scattered | Frequent |
| Androgen receptor IHC | Negative | Positive | Positive |
| S100 IHC | Positive, diffuse | Positive/focal positive | Negative |
| Her2/neu IHC | Variable | Variable/ negative | Positive |

*IDC* intraductal carcinoma, *SDC* salivary duct carcinoma

**Table 5.11** Clinicopathologic features of adenocarcinoma, NOS

| | |
|---|---|
| Mean age, gender | 60 years, M > F |
| Incidence of SG carcinoma | 10–15% |
| Major SG | 40–60% (submandibular gland <10%) |
| Minor SG | 30–40% (palate, buccal) |
| 5-year, 10-year overall survival | 60%, 40% |
| High-grade: Low-grade | 2–3:1 |

- High-grade tumors show frequent mitoses, pleomorphism, and necrosis.

References: [109–111]

17. *What is high-grade transformation, how is it different from dedifferentiation, and which salivary gland tumors can undergo such changes?*

Dedifferentiation of any tumor is characterized by the sharp demarcation of a well-differentiated tumor from a high-grade component that shows none of the histomorphologic features of the original. When salivary gland carcinomas undergo "dedifferentiation," the high-grade component is typically a poorly differentiated adenocarcinoma or an undifferentiated carcinoma. Because the high-grade component is recognized as being similar to the lower-grade component and there may be a transition from the low-grade area, the term dedifferentiation is not wholly accurate. In such a setting, high-grade transformation (i.e., from a low-grade adenocarcinoma to a higher-grade carcinoma) is the preferred term.

- Tumors with high-grade transformation (HGT) characteristically show:
  - Marked nuclear pleomorphism
  - High mitotic activity
  - Necrosis
- The percentage of tumor that is needed for the HGT designation has not been defined for any of the tumor types. Despite the lack of standardization, all reported cases, regardless of tumor type, are associated with clinical progression.
- Table 5.12 summarizes the features and diagnostic considerations of transformed SG carcinomas. HGT

**Table 5.12** Features and staining of tumors with high-grade transformation

| | HGT features | Comments | Stains |
|---|---|---|---|
| Acinic cell carcinoma | Solid nests<br>Pleomorphic, vesicular nuclei<br>Abundant cytoplasm<br>Comedo necrosis | May resemble SDC<br>Metastases will have LG and HG components<br>LVI, PNI | (m)β-catenin+<br>AR–, Her2/neu–, p53– |
| Adenoid cystic carcinoma (AdCC) | Solid, irregular, confluent nests and large sheets<br>Pleomorphic cells, large vesicular nuclei, prominent nucleoli<br>Comedo necrosis, micropapillae<br>Variable loss of myoepithelial differentiation<br>Abrupt transition from LG component | In contrast, solid AdCC: admixed with tubular and cribriform types<br>Slightly enlarged cells with angulated, dark nuclei<br>Gradual transition from solid to tubular areas<br>Metastases have HG component only | p53+ (50% of cells), Her2/neu+, CD117+ (LG, HG), MYB-NIFB+ |
| Epithelial-myoepithelial carcinoma | Loss of biphasic pattern<br>Gradual transition to myoepithelial anaplasia or abrupt transition to HGT<br>Clear, spindle, and squamoid features | Abrupt and gradual HGT have same prognosis<br>LN metastases, DM, death | Loss of myoepithelial markers |
| Polymorphous adenocarcinoma | Solid growth, pleomorphism, necrosis<br>Loss of myoepithelial markers | Association with XRT<br>History of multiple recurrences over long periods<br>Disease progression, no reported DM or deaths | S100+<br>AR±<br>Muscle markers– |
| Secretory carcinoma | Solid growth, pleomorphism, necrosis | LN metastases, DM, death | p53+<br>ETV6 rearrangements+ |

*SDC* salivary duct carcinoma, *LG* low-grade, *HG* high-grade, *LVI* lymphovascular invasion, *PNI* perineural invasion, *m* membranous, *AR* androgen receptors, *AdCC* adenoid cystic carcinoma, *LN* lymph node, *DM* distant metastases, *XRT* radiation therapy

is very rare, and most of the information is based on only a handful of reported cases for each tumor.

References: [54, 112–119]

18. *What are the principal papillary tumors of the salivary gland and their differential diagnosis?*

There are four main entities in the group of papillary tumors of the salivary gland: inverted ductal papillomas (InvDP), intraductal papillomas (IDP), sialadenoma papilliferum (SAP), and papillary cystadenoma lymphomatosum (Warthin tumor).

The ductal papillomas occur within the salivary duct system, at the intersection of the excretory duct and surface epithelium. So, their primary location is in the minor salivary glands. The lip, usually upper, is the most common site, followed by the buccal mucosa, palate, floor of mouth, and tongue. The ductal papillomas include inverted ductal papillomas (InvDP)and intraductal papillomas (IDP). Both are rare entities described in small series and case reports. Table 5.13 summarizes the different papillary lesions and the most common entities in the differential diagnosis.

- Inverted ductal papillomas (IDP) are well-circumscribed tumors with endophytic growth and pushing borders.
  - The junction of the tumor and the surface epithelium may show a dilated, pore-like orifice.
  - The papillae are broad and lined by basaloid cells that show epidermoid differentiation with squamous, transitional or mucous-type, columnar epithelium.
  - Mitoses are infrequent, and cellular atypia is minimal.
- Intraductal papillomas show an exophytic growth of complex, branching papillae that protrude into a well-circumscribed, unicystic cavity.
- Sialadenoma papilliferum extends from the mucosal surface and presents as a slow-growing, papillary, verrucoid mass:
  - Unencapsulated, biphasic tumor composed of complex papillae.
  - The base shows an endophytic proliferation of ducts with varying amounts of ectasia.
- Cystadenomas are a diagnostic consideration for IDP. Cystadenomas are typically well-circumscribed, multicystic tumors of major and minor salivary gland.
  - Thin, fibrous bands separate the cysts which are lined by an oncocytic, cuboidal to columnar epithelium; mucous and squamous cells may also be present.
  - Papillary growth may be focal or predominate.
- Warthin tumor (WT) is the second most common tumor of salivary gland, after pleomorphic adenoma. It occurs exclusively in the parotid gland and rarely in the peri-parotid lymph nodes. WT have a slight male predominance and may be multifocal and bilateral.
  - The tumor comprises papillae with fibrovascular cores containing a dense lymphoid stroma (Fig. 5.23).

**Table 5.13** Differential diagnosis of papillary tumors of salivary gland

| | Inverted ductal papilloma | Intraductal papilloma | Sialoadenoma papilliferum | Warthin tumor | Mucoepidermoid carcinoma | Cystadenoma |
|---|---|---|---|---|---|---|
| Site | Minor SG | Minor SG | Minor SG | Parotid ±multifocal, bilateral | Major and minor SG | Major and minor SG |
| Growth pattern | Endophytic | Exophytic | Exophytic, verrucoid | Exophytic | Multicystic, multinodular | Multiloculated cysts |
| Surface involvement | No, pore-like opening | No | Yes | No | No | No |
| Encapsulated | Yes | Yes | No | No, well-circumscribed | No, infiltrative | Yes |
| Papillae | Yes, broad, bulbous | Yes, delicate, complex | Yes, delicate | Yes, lymphoid stroma | No | Yes, focal or predominant |
| Cystic | Yes | Yes, unilocular | Yes, single cyst | Yes | Yes, multiple | Yes, multiloculated cyst |
| Cells | Basaloid cells with squamous, transitional or mucous differentiation | Cuboidal/ columnar ductal cells, ±Mucus cells | Stratified squamous-lined papillae Underlying ductal proliferation ±Associated chronic inflammation | Bi-layered oncocytes | Squamous, mucus, epidermoid | Oncocytic cuboidal/ columnar ±Squamous and mucous cells |

  - A characteristic bilayer of inner columnar and outer cuboidal oncocytes lines the papillae which protrude into cystic spaces. The cells are cytologically bland and may show squamous, sebaceous, or mucous cell metaplasia.

References: [120–126]

19. *Does primary squamous cell carcinoma of salivary gland exist and how is it diagnosed?*

Primary squamous cell carcinoma (SCC) of the salivary gland is exceedingly rare and occurs in the parotid gland. Case reports involving the submandibular gland have been difficult to confirm. Many historical cases likely represent salivary duct carcinomas or metastatic squamous cell carcinomas from the skin. Most reports do not give detailed information about the clinicopathologic features, raising questions about the rigor of the diagnosis. It is essentially a diagnosis of exclusion; adherence to strict criteria is essential.

- Primary SCC of the parotid is thought to arise from squamous metaplasia involving Stensen's duct.
- One should suspect a primary SCC of the salivary gland in the following settings:
  - No history of previous skin carcinoma.
  - SCC is not solely confined to intraparotid lymph nodes.
  - Keratinization is present.
  - Other head and neck primary sites have been excluded.
  - History of radiation to the parotid.
  - Duct obstruction or elongated mass (i.e., growing along/in the main duct)
  - The presence of squamous dysplasia or arising from a large duct origin

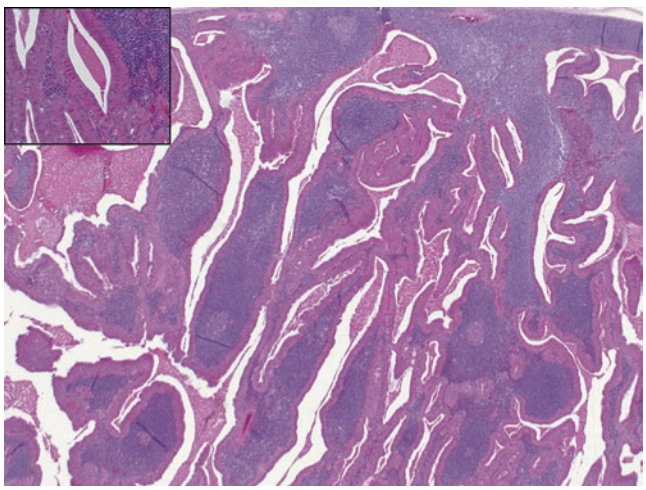

**Fig. 5.23** Warthin tumor. A papillary and cystic neoplasm with a lymphoid stroma and eosinophilic cyst debris composed of (inset) a bilayer of oncocytic cells

- The handful of cases that are most plausible have a few features in common:
  - Patients are predominantly male, between 50 and 70 years old.
  - Variable smoking history.
  - Facial nerve paralysis and regional lymph node involvement at presentation.
- Other salivary gland carcinomas with squamous differentiation or metaplasia, especially those that may undergo high-grade transformation, must be excluded.
  - High-grade mucoepidermoid carcinoma (MEC) is a common mimic of SCC.
  - MEC should not show keratinization, and mucicarmine staining helps to identify mucous cells.

References: [127–130]

20. *What are the common metastases to salivary gland?*

Nonlymphoid metastases to the salivary glands account for about 15% of all malignant SG tumors. The majority of metastases to salivary gland are from the head and neck sites (80–90%), most commonly involve the parotid gland (90–95%), and are squamous cell carcinomas (40–60%).

- The most common metastases are listed in order of frequency:
  - Head and neck cutaneous squamous cell carcinoma (30–65%)

**Table 5.14** Metastatic tumors to salivary gland and their differential diagnosis

| Primary site | Secondary tumor | Primary SG tumor in differential diagnosis |
|---|---|---|
| Regional: Head and neck | Cutaneous SCC | HG mucoepidermoid carcinoma<br>Salivary duct carcinoma<br>Primary SCC |
| | Cutaneous melanoma | Myoepithelial carcinoma<br>Undifferentiated carcinoma |
| | Mucosal SCC (larynx, pharynx) | Lymphoepithelial carcinoma<br>Large cell undifferentiated carcinoma |
| | Merkel cell carcinoma | Primary neuroendocrine carcinoma |
| Distant: Infraclavicular | Lung | Adenocarcinoma, NOS<br>Large cell undifferentiated carcinoma<br>Primary neuroendocrine carcinoma |
| | Breast | Salivary duct carcinoma<br>Secretory carcinoma<br>Adenocarcinoma, NOS |
| | Kidney | Clear cell carcinoma<br>Oncocytoma/oncocytic carcinoma |

  - Head and neck cutaneous melanomas (20–30%)
  - Infraclavicular sites (10–15%)
- Metastases to intra- and peri-parotid lymph nodes occur via lymphatic spread.
- Metastases to submandibular gland are typically intraparenchymal and spread hematogenously.
- The most common distant sites are the lung, breast, and kidney, accounting for over 90% of distant secondary tumors.
  - Melanomas and tumors from distant sites are more likely to present as occult primaries.
  - Latency periods of up to several years may exist between initial diagnosis and the SG metastases.
- Primary SG tumors must be excluded with a thorough clinical history and examination. Ancillary studies can aid in this distinction, but there is some overlap in the immunoprofile and histomorphology of primary and secondary tumors (Table 5.14).

References: [131–138]

21. *Which primary tumors of salivary gland are identical to their counterparts at other sites?*

Some rare primary salivary gland carcinomas exist which are best known as primary tumors at other anatomic sites (e.g., small cell lung carcinoma). Due to their rarity in SG, all of these tumors should be distinguished from metastases, and this is best done by relying on clinical history. Primary SG lymphoepithelial carcinoma, squamous cell carcinoma, and sebaceous carcinoma are histomorphologically indistinguishable from their counterparts in other locations (Table 5.15).

- SG is the second most common site (after larynx) for neuroendocrine tumors of the head and neck.
- Under the current 4th edition of the WHO, poorly differentiated NEC and undifferentiated carcinomas all fall under the moniker of poorly differentiated carcinoma, *regardless* of NE marker expression:
  - Poorly differentiated NEC is divided into small cell and large cell types:
- The most common subtype in the SG is the small cell type.
- Behavior does not appear to differ much between the small and large cell NEC, though the number of cases are limited.
- PD NEC of salivary gland may stain for CK20, and this helps to distinguish it from primary lung tumors.
  - Undifferentiated carcinomas are composed of large cells that show no light microscopic evidence of glandular or squamous differentiation:
- Some are known to have ultrastructural evidence of neuroendocrine differentiation but don't usually demonstrate such features by immunohistochemistry.

References: [139–143]

**Table 5.15** Primary carcinomas of salivary gland with identical counterparts from other locations

| | Primary salivary gland tumor | | Differential diagnosis | |
|---|---|---|---|---|
| Poorly differentiated carcinoma (WHO 4th ed.) | Small cell NEC | CK20±, CK7∓, TTF1∓ | Small cell carcinoma of lung | TTF-1+ CK7∓ CK20– |
| | Large cell NEC | CK20±, CK7∓, TTF1∓ | Merkel cell carcinoma | CK20+ CK7– |
| | | | Large cell NEC of lung | TTF-1+ CK20– |
| | Undifferentiated carcinoma | | Sinonasal undifferentiated carcinoma Nasopharyngeal carcinoma | |
| Others | Lymphoepithelial carcinoma | | Sinonasal undifferentiated carcinoma Nasopharyngeal carcinoma | |
| | Squamous cell carcinoma | | Lung, mucosal HN, and skin SCC | |
| | Sebaceous carcinoma | | Sebaceous carcinoma, skin | |

*NEC* neuroendocrine carcinoma, *HN* head and neck, *SmCC* small cell carcinoma

22. *Which clinicopathologic features predict behavior in salivary gland carcinomas and how does tumor type relate to behavior?*

Factors effecting clinical behavior and prognosis in SG carcinomas are similar to other carcinomas. Table 5.16 lists the clinical and pathologic factors that predict survival in SG carcinomas.

  - As discussed earlier, tumor grade correlates with survival. But only a handful of SG carcinomas are routinely graded and include:
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Adenocarcinoma, NOS
  - For the remainder of SG carcinomas, specific tumor types have an implied histologic grade. But unlike grade, tumor type inconsistently correlates with survival.
  - The relationship between grade, histologic type, and behavior among the more common SG carcinomas is summarized in Table 5.17.
- Broadly, low- to intermediate-risk and high-risk tumors have a 5-year survival of ≥80% and ≤50%, respectively.
- The aggressive local behavior of adenoid cystic carcinoma, regardless of grade, is considered high risk.

References: [38, 144–149]

**Table 5.16** Factors impacting survival in salivary gland carcinomas

| Clinical | Pathologic |
|---|---|
| Stage<br>Nodal status<br>Symptoms of nerve involvement<br>Age | Grade<br>Perineural invasion<br>Margin status |

**Table 5.17** Clinical behavior of salivary gland carcinomas by histologic type

| Low/intermediate-risk | High-risk |
|---|---|
| Low-grade mucoepidermoid carcinoma<br>Low-grade adenocarcinoma, NOS<br>Carcinoma ex pleomorphic adenoma[a]<br>Low-grade salivary duct (intraductal) carcinoma<br>Acinic cell carcinoma<br>Epithelial-myoepithelial carcinoma<br>Myoepithelial carcinoma<br>Basal cell adenocarcinoma<br>Secretory carcinoma<br>Cystadenocarcinoma<br>Clear cell carcinoma<br>Polymorphous (low-grade) adenocarcinoma | High-grade mucoepidermoid carcinoma<br>High-grade adenocarcinoma, NOS<br>Carcinoma ex pleomorphic adenoma[a]<br>Salivary duct carcinoma<br>Adenoid cystic carcinoma<br>Small cell carcinoma<br>Squamous cell carcinoma<br>Sebaceous carcinoma |

[a]Depends on amount of capsular invasion

23. *What is the distribution of salivary gland tumors in the minor salivary glands?*

Diagnosing minor SG tumors is a particular challenge because the readily accessible location encourages acquisition of small biopsies which create diagnostic difficulties. Knowing the frequency of tumors by site (Table 5.18) and other clinicopathologic features can be helpful.

- The common biphasic tumors of minor SG were discussed earlier (see Table 5.5).
- The squamoid lesions of minor SG are compared in Table 5.19.
- Common among most minor SG tumors:
  - Unencapsulated.
  - Mucosal involvement does not equate with malignancy.
- A few clinical correlates are worth noting:
  - There is at least a slight female predominance for minor SG tumors in the United States, regardless of type or site.
  - Cystadenomas are the most common benign lower lip tumor.
  - The most common site for canalicular adenomas is the upper lip.
  - There is a higher risk of malignancy for any tumor occurring in minor SG when compared to major SG.
  - The percentage of benign versus malignant tumors in minor SG varies among authors.
- In the largest series, benign tumors are slightly more common in minor SG (51–61%).

**Table 5.18** Most common findings in minor salivary gland tumors

| | Most common | Second most common |
|---|---|---|
| Overall site (frequency) | Palate (55%) | Buccal (15%) |
| Site of benign tumors | Palate | Buccal |
| Site of malignant tumors | Palate | Buccal |
| Tumor (all) | Pleomorphic adenoma | Mucoepidermoid carcinoma |
| Benign tumor | Pleomorphic adenoma | Cystadenoma |
| Malignant tumor | Mucoepidermoid carcinoma | Polymorphous adenocarcinoma = adenoid cystic carcinoma |

**Table 5.19** Differential diagnosis of squamoid lesions of minor salivary gland

| Lesion | Clinical | Morphology |
|---|---|---|
| Mucoepidermoid carcinoma | Painless, submucosal mass | Usually cystic in minor SG location<br>Multiple layers of cells line cysts, plaque-like solid aggregates of intermediate, or squamous cells also line cystic spaces<br>None/very rare keratinization<br>Bland, minimal cytologic atypia |
| Mucocele | Trauma history, ±pain | Paucicellular, no epithelial lining<br>Lower lip, not palate like other tumors<br>Mixed inflammatory reaction<br>"denuded" cyst, no epithelial lining<br>Pushing borders |
| Squamous cell carcinoma | Mucosal lesion | In situ carcinoma or dysplasia<br>Keratinizing, atypical cells<br>Irregular infiltrative growth |
| Necrotizing sialometaplasia | Painful, short clinical course | Apparent infiltrative growth but organized, follows normal ductal-lobular distribution<br>"Infiltrative nests" appear rounded, not irregular<br>Ulcerative or necrotic salivary tissue |

- On average, benign and malignant tumors represent approximately 55% and 45% of minor SG tumors, respectively.

References: [150–155]

24. *What are the most common salivary gland tumors in children?*
    - There are some unique characteristics of salivary gland tumors in children when compared to adults. Table 5.20 highlights notable findings between the two groups.
    - Several authors eliminate vasoformative tumors (hemangiomas and lymphangiomas) from their study design, as many of these lesions will not undergo surgery. But when these lesions are taken into consideration, their incidence exceeds that of pleomorphic adenoma.

    References: [156–165]
25. *What are the most common benign (nonlymphoid) mesenchymal tumors of salivary gland and their characteristics?*
    - Lymphomas of salivary gland account for almost 8% of all SG tumors and will be addressed separately in Chap. 10. Here we discuss the common nonlymphoid mesenchymal tumors of SG.
    - Hemangiomas are by far the most common benign mesenchymal tumor of SG.
      - Hemangiomas occur in children and represent the most common salivary gland tumor in children under 1 year old.
      - The tumors comprise thin-walled, nonmuscular, vascular spaces lined by bland endothelial cells. Mitoses may be frequent, but atypia is absent.
      - Most lesions undergo involution by age 10, obviating the need for surgery.
    - Lipomas represent about 20% of benign mesenchymal tumors of SG. They occur primarily in the major SG of adults (>85% parotid) with an average age of 55 years and a male predominance.
      - Lipomas of SG are histologically identical to those of soft tissue, composed of encapsulated, mature fatty tissue. They should be devoid of salivary gland structures, except for rare residual acini or ducts at the tumor periphery.
      - Variants of lipomas (e.g., spindled lipoma, angiolipoma) are seen less commonly in SG but do occur. Table 5.21 lists the morphologic features which distinguish the benign lipomatous tumors.
      - Several SG tumors may show fatty metaplasia, most especially pleomorphic adenomas and myoepitheliomas.
    - Peripheral nerve sheath tumors (Table 5.22) are ranked among the top three benign mesenchymal lesions, after vascular and fatty tumors.
      - Schwannomas are more common than neurofibromas.
      - As much as 35% of neurofibromas in SG are associated with neurofibromatosis type 1.

    References: [6, 166–170]
26. *What are the most common primary malignant mesenchymal tumors of salivary gland?*
    - Primary sarcomas of the salivary gland are rare, representing approximately 0.5% of all salivary gland tumors and 2% of malignant salivary gland tumors.

**Table 5.20** Comparison of salivary gland tumors in children and adults

| Most common finding | Children | Adults |
|---|---|---|
| Age at diagnosis | Second decade | Fifth decade |
| Site of all tumors | Parotid 65%<br>Minor SG 25% | Parotid |
| Minor SG site | Palate | Palate |
| Benign tumor | Hemangioma, lymphangioma | Pleomorphic adenoma |
| Benign epithelial tumor | Pleomorphic adenoma | Pleomorphic adenoma |
| Malignant tumor | Mucoepidermoid CA | Mucoepidermoid CA |
| Malignancy rate among SG tumors | 30% for all tumors<br>50–60% for epithelial tumors | 15–25% |
| Mesenchymal tumor | Hemangioma | Lipoma |
| Mesenchymal malignancy | Rhabdomyosarcoma | Variable[a] |
| Overall 5-year survival | 95% | 60% |

[a]See question 27

**Table 5.21** Clinicopathologic features of fatty tumors of salivary gland

| | Lipoma | Sialolipoma | Lipoadenoma |
|---|---|---|---|
| Clinical | Adult, male | Adult, rarely children | Adult, rarely children |
| Site | Parotid | Parotid > oral > submandibular | Parotid > oral > submandibular |
| Encapsulated | Yes | Yes | Vaguely lobular |
| Fat predominates | Yes, mature fat only | Yes | No |
| Epithelium | None | Normal salivary elements evenly distributed in fat | Predominantly epithelium with interspersed fat<br>Amount of fat varies widely |
| Sebaceous metaplasia | None | Frequent, associated periductal fibrosis, and chronic inflammation | Frequent, associated periductal fibrosis, and chronic inflammation |
| Oncocytes | Absent | Absent/rare | Present in oncocytic variant |

**Table 5.22** Comparison of schwannomas and neurofibromas

| | Schwannoma | Neurofibroma |
|---|---|---|
| Clinical | NF type 2, bilateral Carney complex | NF type 1, multiple |
| Encapsulated | Yes | No, infiltrative |
| Nuclei | Short spindled nuclei | Short, spindled, wavy hyperchromatic |
| Morphology | Antoni A hypercellular areas Antoni B hypocellular, edematous, myxoid areas Verocay bodies – nuclear palisading around an eosinophilic center | Haphazardly arranged cells in an edematous stroma with scattered collagen bundles |
| Stroma | Collagenous, myxoid, cystic | Myxoid |
| Thick-walled vessels | Present | Absent |
| Atypia | Yes, degenerative | No/rare |
| Immunoprofile | Strong, diffuse S100 Strong, diffuse Sox-10 | Weak, variable S100 and Sox-10 |

*NF* neurofibromatosis

- Approximately 80% occur in the parotid gland. There is male predominance, and the average age is 40 years old.
- Patients present with a painless mass that may show rapid growth and eventual tenderness.
- Luna et al. outlined four criteria used to classify a sarcoma as primary to salivary gland:
  1. The patient must not have a history of a similar sarcoma at any other site.
  2. Metastatic disease to the salivary gland must be excluded.
  3. Gross and microscopic examination must establish the salivary gland, and not adjacent soft tissues, as the primary site.
  4. Carcinosarcoma must be excluded.
- Cockerill et al. reported 17 primary sarcomas of salivary gland along with a literature review of an additional 170 cases. The most common tumor types (Table 5.23) are listed in order of frequency.
- Salivary gland sarcomas, as a group, carry a poor prognosis related to tumor size, type, and histologic grade. The behavior of individual tumor types, when compared to their soft tissue counterparts, is variable.
  - SG sarcomas have high rates of recurrence (30–35%), distant metastases (25–40%), and mortality (28–40%).
  - The lung is the most frequent metastatic site.
- An accurate diagnosis is critical, given the prognostic implications. Carcinosarcoma and myoepithelial carcinoma should be excluded.

References: [169, 171–176]

**Table 5.23** Frequency of sarcomas in salivary gland

| Sarcoma type | Number of cases |
|---|---|
| Rhabdomyosarcoma (all types) | 33 |
| Liposarcoma (all types) | 19 |
| Hemangiopericytoma/malignant SFT | 18 |
| Malignant peripheral nerve sheath tumor (all types) | 17 |
| Malignant fibrous histiocytoma | 17 |
| Angiosarcoma (including Kaposi's sarcoma $n = 2$) | 15 |
| Leiomyosarcoma | 11 |
| Synovial sarcoma | 10 |

*SFT* solitary fibrous tumor, Based on findings from reference [171]

**Table 5.24** Comparison of lymphoepithelial cysts relative to HIV status

| | LE cysts (HIV-negative) | HIV-related LE cyst |
|---|---|---|
| Age, gender | 50–70 years old, male | 25–50 years old, male |
| Site | Parotid, unilateral | Parotid, bilateral |
| Clinical | Usually asymptomatic, occasionally painful | Lymphadenopathy, LE cyst may precede HIV diagnosis |
| Cyst type | Unilocular | Multilocular |
| Cyst lining | Stratified squamous | Stratified squamous |
| Cyst wall | Dense lymphoid tissue | Dense lymphoid tissue |
| Lymphoid tissue | Germinal center formation | Germinal centers with follicle lysis Irregular follicles, neutrophils, plasma cells, macrophages |
| LE lesions | Absent | Present |

27. *What is the differential diagnosis of benign cystic lesions of the salivary gland?*

Lymphoepithelial (LE) cysts are squamous-lined lesions with an associated dense, lymphoid population. They occur almost exclusively in the parotid gland with rare cases reported in the floor of mouth. The demographics vary depending on the presence of HIV (human immunodeficiency virus) infection. Table 5.24 compares LE cysts in HIV-positive and HIV-negative patients. Surgical excision is the treatment of choice.

- The differential diagnosis of LE cyst includes a cystic metastatic squamous cell carcinoma to intra- or periparotid lymph nodes.
  - The more common metastatic squamous cell carcinoma to this area is from the skin, and it is typically not cystic.
  - The epithelium of LE cysts lacks the atypia and keratinization seen in squamous cell carcinoma.

The remaining, nonneoplastic cystic lesions are all related to duct obstruction or trauma. They typically

**Table 5.25** Clinicopathologic features of common salivary gland cysts

| | Mucocele | Mucus retention cyst | Salivary duct cyst |
|---|---|---|---|
| Age (years) | Younger than 30, children | Peak incidence 70, all ages | Older than 30, usually 50–80 |
| Etiology | Trauma | Obstruction | Obstruction, mucus stasis |
| Site | Lower lip (80%), FOM, cheek | Major and minor SG | Parotid (80%), submandibular, FOM |
| Cyst lining | No epithelium lining | Attenuated duct lining | Attenuated or metaplastic duct lining |
| Cyst contents | Mucin, macrophages, and inflammation | Mucin | Mucin and mucus plugs are generally absent |
| Comments | Older lesions may show only granulation tissue, muciphages, and scant mucin | May be inflamed if duct wall is disrupted | Cyst wall may be inflamed or has salivary lobules Unilocular |

*FOM* floor of mouth

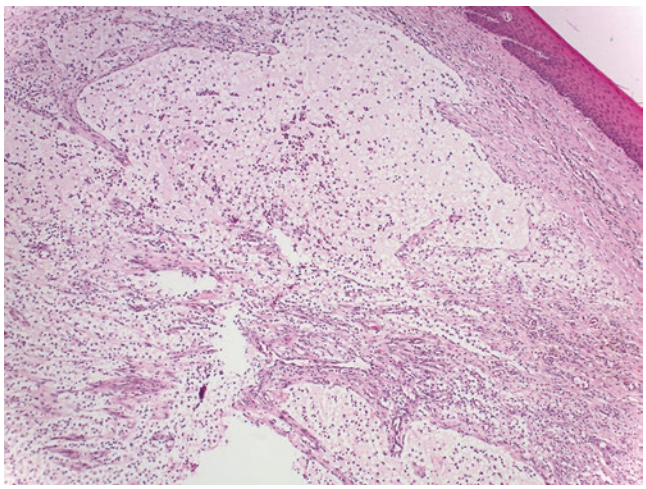

**Fig. 5.24** Mucocele. The submucosa of the lower lip squamous epithelium contains a pseudocyst filled with proteinaceous fluid and inflammatory cells. A true epithelial lining is absent

present as a compressible, painless mass. Table 5.25 compares the primary nonneoplastic cysts of salivary gland.

- Mucoceles are the most common nonneoplastic lesion of the salivary gland. They lack epithelium and are, therefore, not true cysts (Fig. 5.24). They are essentially a cystic space created by extravasated mucin into the submucosa.
  - Large mucoceles of the floor of mouth are called ranulas.
- Mucus retention cysts and salivary duct cysts represent true cysts, lined by an attenuated or metaplastic epithelium.

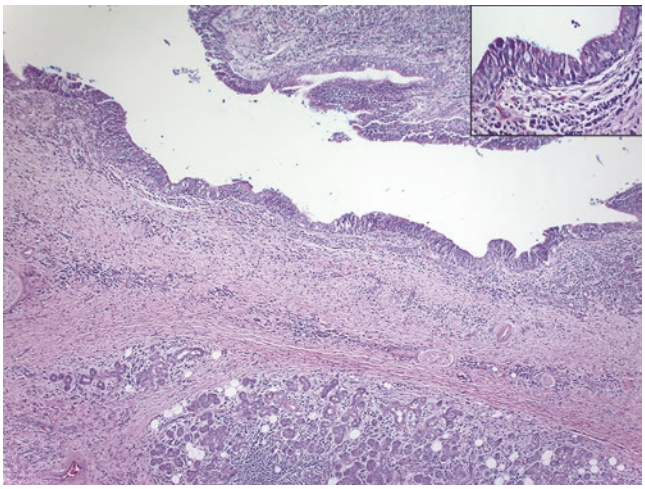

**Fig. 5.25** Salivary duct cyst. Chronic sialadenitis with salivary duct cyst lined by (inset) ductal epithelium with focal goblet cell metaplasia

  - The pathogenesis is related to intermittent, partial duct obstruction or mucus stasis with subsequent dilatation.
  - Salivary duct cysts (Fig. 5.25) may show oncocytic, squamous, or mucinous metaplasia raising concern for mucoepidermoid carcinoma or cystadenoma.
    - Unlike MEC, the cyst is generally unilocular and the lining is typically attenuated or lined by a single-cell layer.
    - Cystadenomas are typically multicystic.

References: [1, 177–181]

28. *What are the major inflammatory lesions of the salivary gland?*
    - Lymphoepithelial sialadenitis (LESA) is characterized by an extensive lymphoid infiltrate primarily involving the parotid gland. Bilateral disease and isolated submandibular disease are very uncommon.
      - LESA has a strong female predilection and is associated with, but not exclusive to Sjögren syndrome.
      - A diagnosis of Sjögren syndrome requires confirmation of various clinical and laboratory findings. Focal lymphocytic sialadenitis is usually diagnosed on a labial biopsy and requires one or more aggregates of ≥50 lymphocytes with minimal plasma cells (focus score ≥1).
      - The hallmark of LESA is the lymphoepithelial lesion: proliferative, slightly spindled duct epithelium infiltrated by slightly enlarged lymphocytes.
      - Extranodal marginal zone B-cell lymphoma of SGs is typically preceded by LESA.
    - Chronic sclerosing sialadenitis (CSS, Kuttner tumor) is an inflammatory process that most commonly affects the submandibular gland.

**Table 5.26** Clinicopathologic features of inflammatory lesions of salivary gland

| | Chronic sclerosing sialadenitis | Obstructive chronic sialadenitis | LESA | Necrotizing sialometaplasia |
|---|---|---|---|---|
| Age (years), sex | 50–60, M | 50, M | 40–50, F | 40–60, M |
| Site<br>Bilaterality | Submandibular<br>25% | Submandibular<br>No | Parotid<br>Yes | Palate, minor SG<br>No |
| Clinical presentation | Mass, painless | Intermittent, prandial pain, swelling | Dry mouth, pain, swelling | Pain, swelling, mucosal ulceration |
| Follicular HP/Florid follicular HP | Yes/Yes | Yes/No | Yes/Yes | No/No |
| Cellular fibrosis with inflammation | Yes, storiform | No | No | No |
| Sheets of plasma cells | Yes | Rare | Rare | No |
| Other inflammation | Eosinophils | Neutrophils, granulomatous | No | Neutrophils, necrosis |
| Obliterative phlebitis | Yes | No | No | No |
| Lymphoepithelial lesions | Rare | No | Yes | No |
| Dilated ducts, periductal inflammation | Focal | Yes | No<br>Duct proliferation | No<br>Extensive squamous metaplasia |
| IgG4 plasma cells per hpf (percent of total IgG) | 100–200 (70%) | 10–20 (<5%) | 1–20 (<5%) | None |
| Clinical associations | Other organ involvement<br>Allergic disorders | Sialoliths | Sjögren syndrome<br>MALT lymphoma | Trauma, ischemia<br>Bulimia |
| Other findings | Elevated serum IgG4 | Rule out infection in granulomatous cases | Anti-Ro/SSA, anti-La/SSB antibodies<br>Labial biopsy with focus score ≥1 | Overlying pseudoepitheliomatous hyperplasia<br>Extensive squamous metaplasia |

*LESA* lymphoepithelial sialadenitis, *HP* hyperplasia, *hpf* high-power field

  - Recent studies show that most cases of CSS are a manifestation of IgG4-related diseases, an inflammatory disorder resulting in tumor-like, fibroinflammatory lesions in multiple organs (e.g., pancreas, SG, orbit, kidneys, lung).
  - CSS-/IgG4-related sialadenitis must be clinically distinguished from obstructive chronic sialadenitis given the far-reaching clinical implications and its therapeutic response to corticosteroids.
- A subset of cases previously labeled as CSS is best classified as an obstructive chronic sialadenitis and is likely related to sialolithiasis. Table 5.26 highlights the salient features of the different types of sialadenitis.

References: [182–188]

29. *What are the common lymphomas of salivary gland?*

Lymphomas of salivary gland account for almost 8% of all salivary gland tumors. Here we highlight salient features of hematolymphoid lesions in the SG, but the reader is referred to Chap. 10 for a more detailed discussion.

- Salivary gland accounts for 5% of all extranodal lymphomas.
- Eighty percent of SG lymphomas occur in the parotid.
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is the most common lymphoma of salivary gland, followed by follicular lymphoma and diffuse large B-cell lymphoma.
  - Lymphoepithelial sialadenitis (LESA) is a precursor of MALT and is associated with Sjögren syndrome (see question 28).
- A subset of follicular lymphomas occur primarily in intraparotid LNs and is, therefore, not always of an extranodal origin.

References: [189–194]

30. *Which nonneoplastic lesion of salivary gland may represent a premalignant process?*

Sclerosing polycystic adenosis (SPA) is a rare fibroproliferative lesion of SG with only a handful of cases reported in the literature. It occurs predominantly in the parotid gland with a wide age range. Average age at presentation is in the fourth decade, and there is a slight female predominance. Patients usually present with a painless, slow-growing mass and occasional minor nerve pain and tingling.

- SPA is well-circumscribed with a pseudocapsule; prominent, cystically dilated ducts in a dense, scle-

rotic stroma; and variable amounts of chronic inflammation.
- Cystic spaces are lined by apocrine, clear, or oncocytic-like cells. Attenuated or denuded epithelium is replaced by foamy histiocytes. Large, serous acinar cells with abundant eosinophilic cytoplasm and PAS-D-positive granules are distinctive. The granules may coalesce to form intracytoplasmic globules.
- The intraductal proliferations in SPA may be exuberant with cribriform architecture and atypia. An associated myoepithelial layer expresses p63 but may be negative for muscle markers.
- Atypical SPA is clonal and some regard it as neoplastic with a low malignant potential.
  - High-grade atypia should be regarded as an intraductal carcinoma. The significance of mild to moderate cytologic atypia is unclear.
- Densely fibrotic areas may resemble radial scars of the breast and should not be mistaken for carcinoma. The normal lobular architecture should be maintained.
- Recurrence rates approach 20% and may occur over several years. A single report of an associated invasive carcinoma exists.

References: [195–202]

## Case Presentations

### Case 1

**Learning Objectives**

1. To become familiar with the morphologic features of a salivary gland adenocarcinoma
2. To develop a differential diagnosis for a parotid gland adenocarcinoma

**Case History**

A 68-year-old female presents with a firm, painless, preauricular mass.

**Gross Findings**

Poorly circumscribed 2.0 cm mass of the parotid gland with attached skin. The cut surface is solid, tan-white, and homogeneous. Extra-glandular extension is present into adjacent skin.

**Histologic Findings** (Fig. 5.26)

Large sheets and lobules of tumor are composed of back-to-back glands with foci of cribriform architecture. Tumor cells are columnar with oval nuclei, fine chromatin, and absent nucleoli. Focal single-cell necrosis is present, but geographic and comedo necroses are absent.

**Differential Diagnosis**

- Metastatic adenocarcinoma
- Adenocarcinoma, not otherwise specified
- Neuroendocrine carcinoma, large cell type
- Salivary duct carcinoma

**IHC and Other Ancillary Studies (Not Shown)**

- Positive: pan-cytokeratin, strong CK7, weak, focal CK20
- Negative: TTF-1, CDX2, synaptophysin, chromogranin, p63, CK5/6

**Final Diagnosis** *High-grade adenocarcinoma, not otherwise specified (NOS)*

**Follow-Up** 4 months later the patient had disease progression with lung and lymph node metastases while receiving chemotherapy.

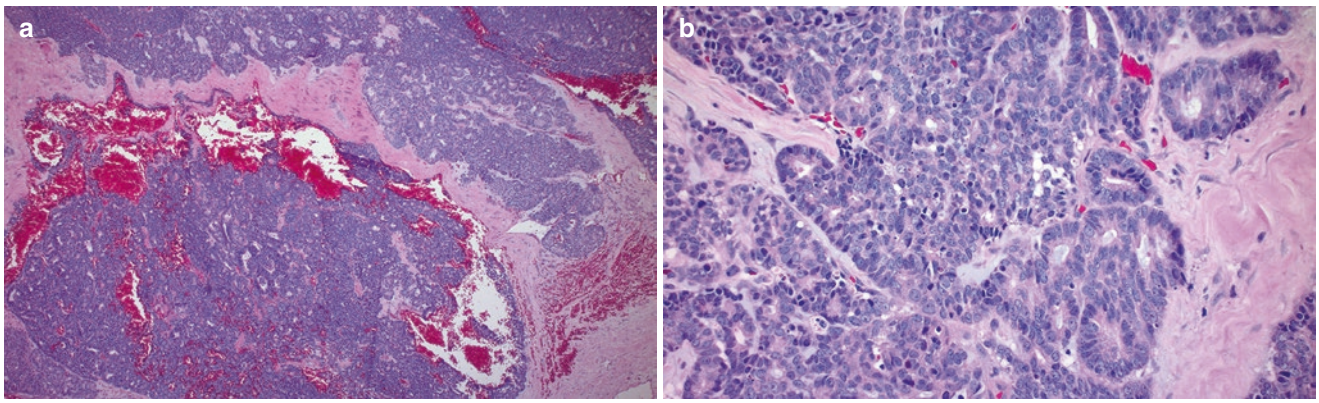


**Fig. 5.26** Adenocarcinoma, NOS. (**a**) Infiltrative lobules of tumor (**b**) are composed of complex glands with cigar-shaped nuclei, luminal mucin, and single-cell necrosis

**Take-Home Messages**

1. Adenocarcinoma, NOS must demonstrate glandular or duct differentiation. By definition, it cannot meet criteria for the diagnosis of any named carcinoma of salivary gland. It is a diagnosis of exclusion. Metastases from other sites should be excluded clinically and by immunohistochemistry.
2. Intestinal-type of adenocarcinoma, NOS has a similar appearance to this case and may express CK20 or CDX2. A primary gastrointestinal carcinoma should be excluded clinically but is highly unlikely to present as an unknown primary with parotid metastasis and strong CK7 expression.
3. Large cell neuroendocrine carcinoma will not show such clear glandular differentiation. Salivary duct carcinoma has a high nuclear grade, more cribriform structures, and comedo necrosis.

References: [109, 110, 203]

## Case 2

**Learning Objectives**

1. To generate a differential diagnosis of squamous malignancies of the parotid
2. To become familiar with the grading of salivary gland carcinomas

**Case History**

A 58-year-old female presents with a firm, painless, posterior auricular mass.

**Gross Findings**

A 1.8 cm solid, tan-white circumscribed, but invasive mass in the parotid gland. Areas of necrosis are identified on sectioning. Cysts are not present.

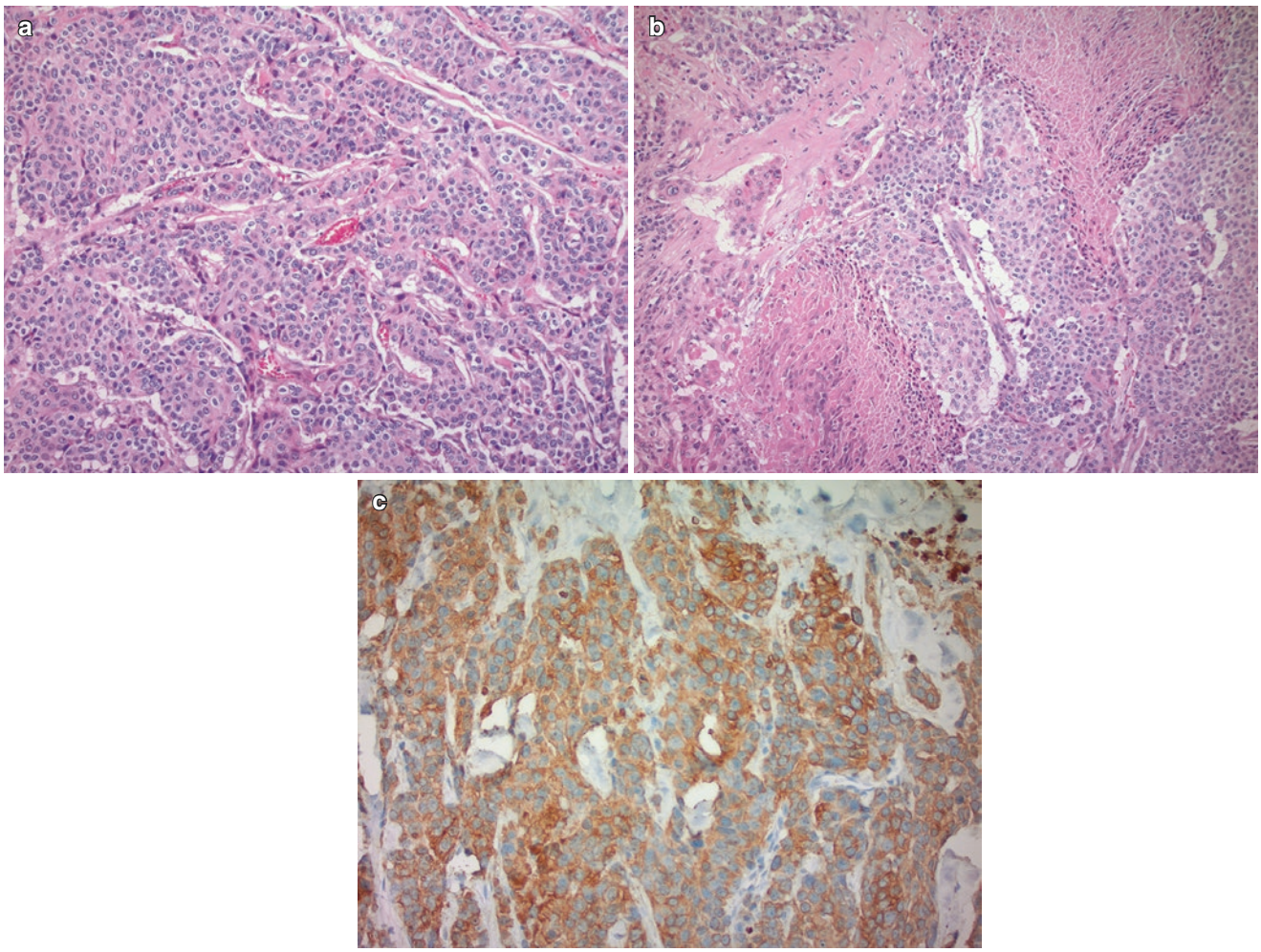


**Fig. 5.27** Mucoepidermoid carcinoma, high-grade. (**a**) Solid nodules of intermediate cells with (**b**) foci of infiltrative nests, extensive necrosis, and LVI (upper left). (**c**) Tumor cells are strongly positive for CK5/6

**Histologic Findings** (Fig. 5.27a, b)
Nodules of tumor cells with areas of necrosis and a rounded, infiltrative border. The tumor cells are relatively monotonous with mild to moderate nuclear atypia and a moderate amount of eosinophilic cytoplasm. Mucus cells are not identified. Foci of lymphovascular invasion (LVI) are present. Rare clear cells and squamous cells are seen. Perineural invasion (PNI) and extra-glandular extension are present (not shown). Three peri-parotid lymph nodes are positive for carcinoma.

**Differential Diagnosis**
- Squamous cell carcinoma
- Oncocytic carcinoma
- Mucoepidermoid carcinoma

**IHC and Other Ancillary Studies**
- Positive: CK5/6 (Fig. 5.27c), p63 strongly positive

**Final Diagnosis** *High-grade mucoepidermoid carcinoma*

**Take-Home Messages**
1. The three principal grading systems for mucoepidermoid carcinoma (MEC) all show correlation with patient outcomes. The most important features are solid growth, pleomorphism, necrosis, mitoses, and perineural invasion. This case is difficult to grade because, despite lymphovascular invasion (LVI) and extensive necrosis, the cytologic features are relatively bland (e.g., minimal pleomorphism and mitotic activity). Application of the three main grading systems for this MEC yielded the following results:
   (a) Modified Healy: high-grade (HG) – solid growth, lymphovascular invasion, PNI, soft tissue extension. Using a "best fit" approach, this tumor would qualify as high-grade despite the absence of pleomorphism and frequent mitoses.
   (b) Brandwein: 13 pts, HG: less than 25% cystic (2 pts), necrosis (3 pts), PNI (3 pts), lymphovascular invasion (3 pts), and infiltrative border (2 pts).
   (c) AFIP, 7 pts; HG, less than 20% cystic (2 pts); necrosis (3 pts); and PNI (2 pts).
2. The tumor shows a predominance of intermediate cells with scattered clear and squamous cells. This varied population helps to exclude oncocytic carcinoma
3. The absence of keratin and a known squamous cell carcinoma of a head and neck site make this diagnosis highly unlikely.

References: [32, 37, 38, 204]

## Case 3

**Learning Objective**
1. To generate a differential diagnosis of squamous malignancies of the parotid

**Case History**
An 80-year-old male complains of a firm mass in the preauricular region. Physical exam reveals marked actinic changes of the skin on his face and head. He reports having several "small cancers burned off of his face" over the years.

**Gross Findings**
A large 2.6 cm, circumscribed mass is present in the parotid gland with two to three similar appearing, smaller masses in other areas of the gland. The largest is tan-white and firm and associated with a caseous, white material.

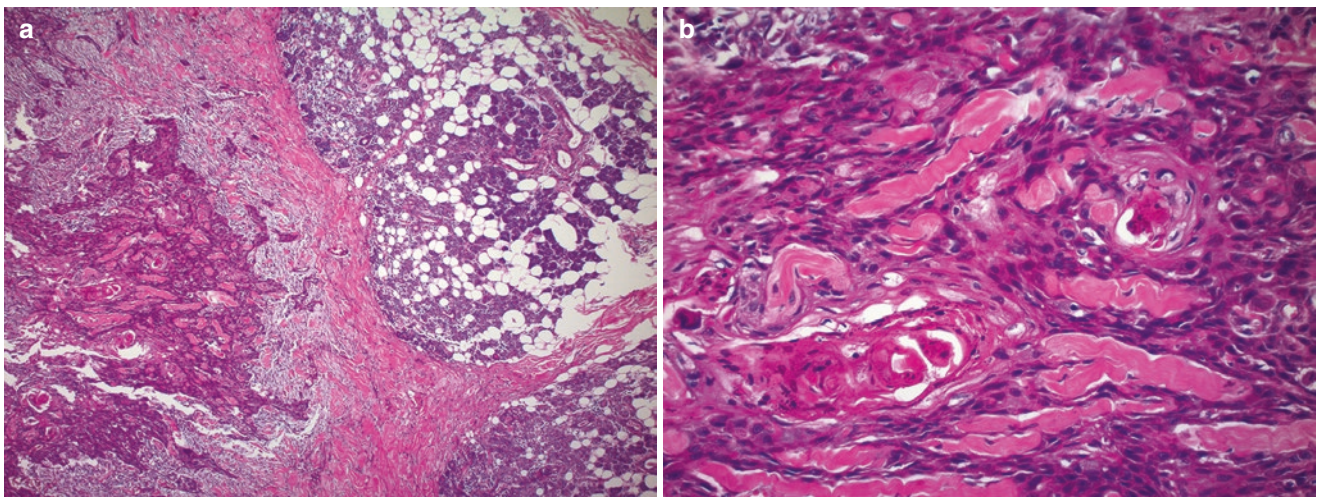


**Fig. 5.28** Metastatic squamous cell carcinoma. (**a**) Infiltrative sheets of squamous cell carcinoma involving parotid gland parenchyma. (**b**) High magnification shows keratinizing tumor cells with keratin pearls

**Histologic Findings** (Fig. 5.28)
A circumscribed, partially encapsulated, but infiltrative mass is present. The tumor shows nests of polygonal cells with abundant eosinophilic cytoplasm, hyperchromatic nuclei with coarse chromatin, and occasional pleomorphism. Keratin pearls are easily identified. Additional intraparotid lymph nodes show similar tumor cells.

**Differential Diagnosis**
- Primary squamous cell carcinoma (SCC)
- Metastatic squamous cell carcinoma
- High-grade mucoepidermoid carcinoma

**IHC and Other Ancillary Studies**
None

**Final Diagnosis** *Metastatic squamous cell carcinoma of the skin*

**Take-Home Messages**
1. There are no markers to definitively distinguish the source of a squamous cell carcinoma, especially if it is a keratinizing carcinoma.
2. Squamous cell carcinoma of the major salivary gland should be considered a metastasis until proven otherwise. A primary SCC at this site is exceedingly rare and should adhere to specific criteria, previously discussed in question 19.
3. High-grade mucoepidermoid carcinomas are rarely keratinizing and should only be focal. This patient's history of multiple skin "cancers" and multiple intraparotid lymph node metastases supports a diagnosis of metastatic SCC from the skin. This is one of the most common metastases to the parotid gland.

References: [127, 129, 133, 205]

## Case 4

**Learning Objectives**
1. To understand the criteria used to subclassify neuroendocrine carcinomas of the salivary gland (SG)
2. To develop a differential diagnosis for neuroendocrine carcinomas of SG

**Case History**
A 57-year-old male present with a mass at the angle of his mandible and cervical lymphadenopathy.

**Gross Findings**
A large, fleshy, necrotic tumor mass diffusely infiltrates the parotid parenchyma. Several peri-parotid lymph nodes also show tumor involvement.

**Histologic Findings** (Fig. 5.29a–c)
The tumor comprises large sheets of cells with extensive areas of necrosis. The cells are small to intermediate sized with scant to more appreciable, pale cytoplasm. The nuclei range from oval to slightly spindled with a fine, stippled chromatin, and an absence of nucleoli. There are frequent mitoses and single-cell necrosis. LVI and PNI are present (not shown).

**Differential Diagnosis**
- Metastatic small cell carcinoma
- Primary small cell carcinoma
- Large cell neuroendocrine carcinoma
- Metastatic Merkel cell carcinoma

**IHC and Other Ancillary Studies** (Fig. 5.29d–f)
- Positive: pan-cytokeratin (dot-like), CK5/6 (dot-like), synaptophysin, neuron-specific enolase (NSE)
- Negative: CK7, CK20, TTF-1, CD45
- Merkel cell oncoprotein serum antibody is negative

**Final Diagnosis** *Primary neuroendocrine carcinoma (NEC), small cell type (small cell carcinoma)*

**Follow-Up** A neck dissection was performed and yielded 6 positive lymph nodes out of 18 throughout levels 2 through 5.

**Take-Home Messages**
1. Primary small cell carcinomas, though well-defined, fall under the category of poorly differentiated carcinomas. This is primarily because they are all undifferentiated (e.g., no glandular or squamous differentiation) and may show variable or *no* neuroendocrine differentiation at all. The presence of two neuroendocrine markers, epithelial differentiation, and typical morphology support a diagnosis of small cell carcinoma.
2. NSE and CD56 alone are non-specific for neuroendocrine differentiation. The addition of synaptophysin or chromogranin expression is required for a diagnosis of NEC.
3. Small cell carcinomas can show a range of cell size. This patient's tumor has cells that are at the upper limit of size for small cell carcinomas (30 μ). Large cell NEC tends to have more pleomorphism; larger, polygonal cells; rosette formation with palisading; and prominent nucleoli. The distinction in head and neck sites does not appear to be clinically relevant as outcomes are equally dismal in both groups.
4. Merkel cell carcinomas are usually positive for CK20, but primary NEC of the parotid can also express CK20. Co-expression with CK7 and a negative CK20 excludes Merkel cell carcinoma. Salivary NECs may even express

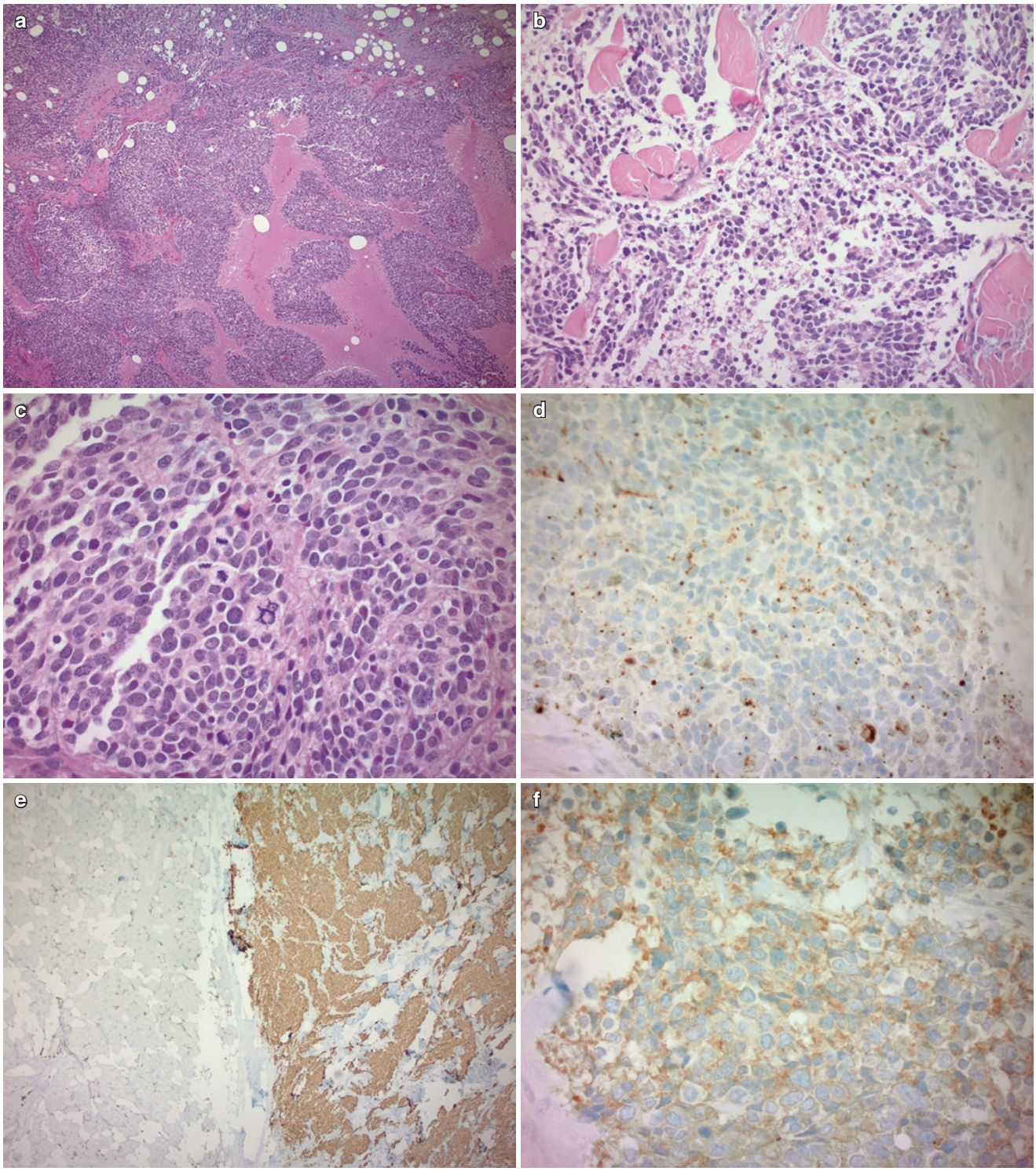


**Fig. 5.29** Small cell carcinoma. (**a**) Large areas of necrosis alternate with ribbons of carcinoma. (**b**) The tumor cells show slight spindling and single-cell necrosis. (**c**) Tumor nuclei have a finely stippled chromatin and frequent mitoses. Cell size is at the upper limit for small cell carcinoma, but the absence of nucleoli and pleomorphism do not favor a large cell NEC. (**d**) Pan-cytokeratin shows a dot-like, cytoplasmic staining pattern. (**e**) CD56 is strongly positive. (**f**) Synaptophysin is diffusely positive with focal granular staining

TTF-1, so clinical history is essential in arriving at the correct diagnosis.

References: [139–143, 206–208]

## Case 5

### Learning Objectives

1. To understand the classification of poorly differentiated carcinomas of the salivary gland
2. To generate a differential diagnosis of poorly differentiated carcinomas

### Case History

An 81-year-old female complains of a right cheek mass. CT scan shows a right cheek mass with duct dilatation and possible duct derivation versus involvement.

### Gross Findings

A 1.7 cm firm, tan-gray tumor mass is present in the buccal submucosal. The tumor is infiltrative with a tan-white cut surface. The overlying mucosa shows no gross lesions. Chest and neck CT scans are negative for metastatic disease.

### Histologic Findings (Fig. 5.30a, b)

The tumor is composed of sheets of small- to intermediate-sized cells with scant, pale cytoplasm. The cells are arranged in cords and trabeculae. Glands, tubules, ducts, and squamous features are not identified. The nuclei are round with prominent, central nucleoli. Mitotic activity is brisk. Perineural invasion is present. Necrosis is not identified.

### Differential Diagnosis

- Primitive neuroectodermal tumor
- Undifferentiated carcinoma
- Lymphoma
- Melanoma

### IHC and Other Ancillary Studies (Fig. 5.30c, d)

- Positive: pan-cytokeratin (strong), CK7, CD56 (weak, focal)

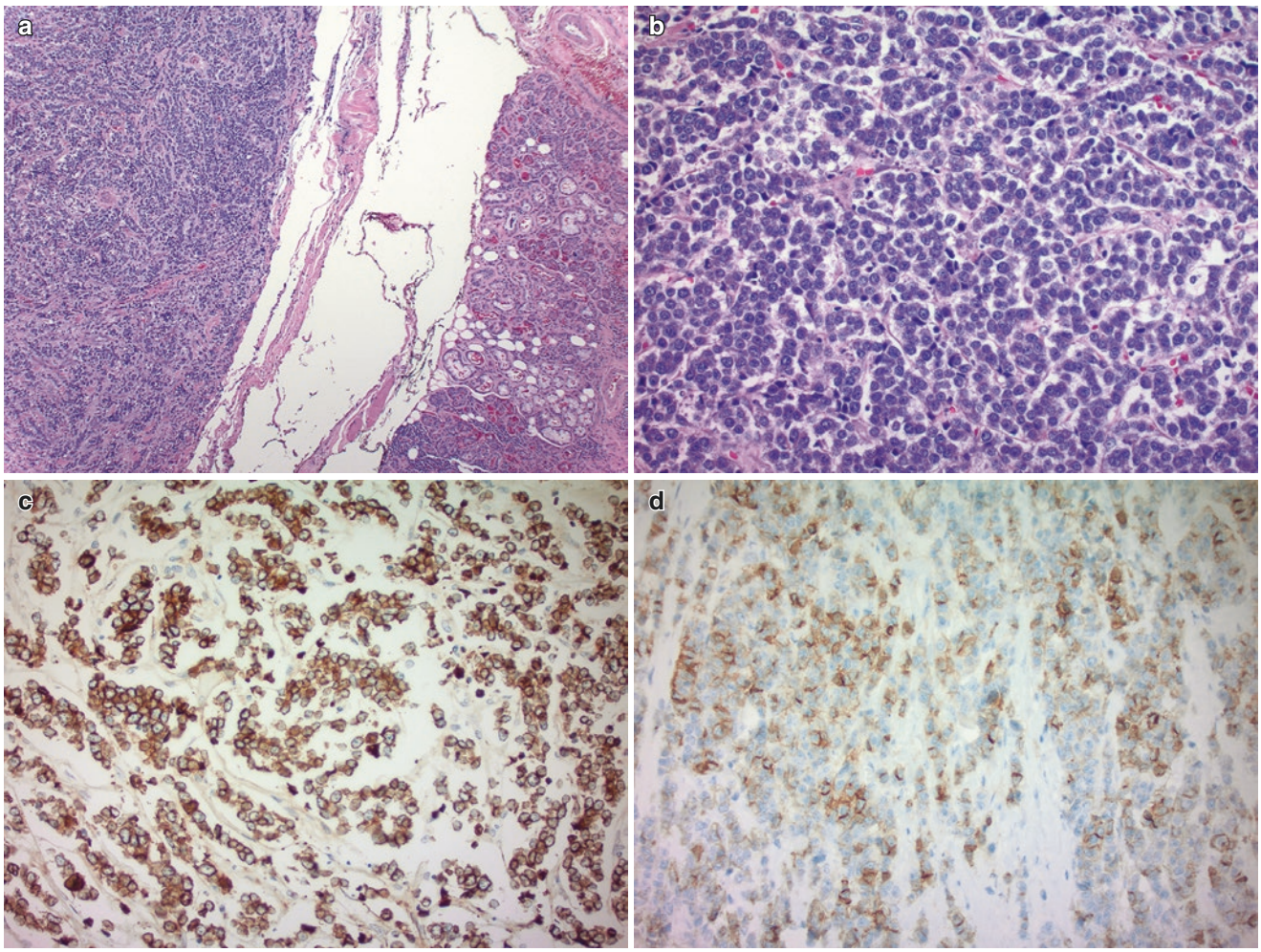


**Fig. 5.30** Poorly differentiated carcinoma. (**a**) Sheets of tumor cells adjacent to minor salivary gland of the cheek. (**b**) The tumor shows a vaguely organoid pattern. The cells are small, with a high N-C ratio, scant pale to basophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Frequent mitoses and single-cell necrosis are present. (**c**) CK7 immunohistochemistry is strongly positive. (**d**) CD56 shows focal staining

- Negative: synaptophysin, chromogranin, androgen receptors

**Final Diagnosis** *Poorly differentiated carcinoma*

**Follow-Up** 5 months later, the patient presents with a new neck mass in level 2. PET (positron emission tomography) scan shows liver and bone metastases.

**Take-Home Messages**

1. According to the WHO classification, poorly differentiated carcinomas include undifferentiated carcinomas like this case. By definition, undifferentiated carcinomas show no evidence of squamous or glandular differentiation. They may or may not demonstrate neuroendocrine features. The CD56 expression and morphologic features of this case are not sufficient for a diagnosis of NEC.
2. Lymphoma and melanoma are easily excluded with IHC stains.
3. As with all the tumors in this category, metastatic carcinomas must be excluded.

References: [2, 209]

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# Jaw and Bones of the Head and Face

6

Sasha Jane Betz and Ricardo J. Padilla

## Frequently Asked Questions

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45. What salivary gland neoplasms may occur within the jaws?

1. *What are the clinical and histologic features of proliferative periostitis?*

Proliferative periostitis (Garre's osteomyelitis, periostitis ossificans, nonsuppurative ossifying periostitis) is an inflammatory response of the bone and periosteum commonly seen in the tibia and posterior mandible. In the jaw, this reaction is usually identified in children and adolescents in response to a carious tooth. Other causes include pericoronitis and recent tooth extraction.

The radiographic feature most commonly associated with this condition is an "onionskin" appearance of parallel layers of trabeculae overlying the cortex. Presentations may vary to include fine spiculations perpendicular to the cortex, resulting in a "sunburst" pattern similar to an osteosarcoma. The radiographic and clinical presentations of swelling and/or pain may elicit concern and biopsy.

Histologically, deposition of immature woven bone overlies the dense lamellar bone of the cortex. The trabeculae parallel each other and demonstrate prominent osteoblastic rimming. The associated loose connective tissue harbors a mild chronic inflammatory cell infiltrate. Histologic mimickers may include fibrous dysplasia or an osteosarcoma. Fibrous dysplasia shows hypercellular connective tissue with a "ginger root" pattern of trabeculation in contrast to the parallel arrangement of trabeculae identified in proliferative periostitis (Fig. 6.1). An osteosarcoma will show irregular patterns of osteoid formation and atypical cells.

References: [1–4]

2. *What are the histologic and immunohistochemical features of melanocytic neuroectodermal tumor of infancy (MNTI)?*

Melanocytic neuroectodermal tumor of infancy (MNTI) arises from cells of the neural crest and most often occurs in the first 6 months of life. Less than 10% of these tumors occur after the first year of age. The presentation of a rapidly expansile, pigmented mass of the maxilla is characteristic. Despite an aggressive presentation, the vast majority of MNTI cases are benign. The malignancy rate is less than 10%.

MNTI is histologically characterized by a biphenotypic cell population. Nests or cords of large, epithelioid cells with abundant cytoplasm surround small, round, neuroblast-like cells with scant cytoplasm. Melanin is identifiable within the larger cells. The neoplastic cells lie within a densely collagenous stroma (Fig. 6.2). The

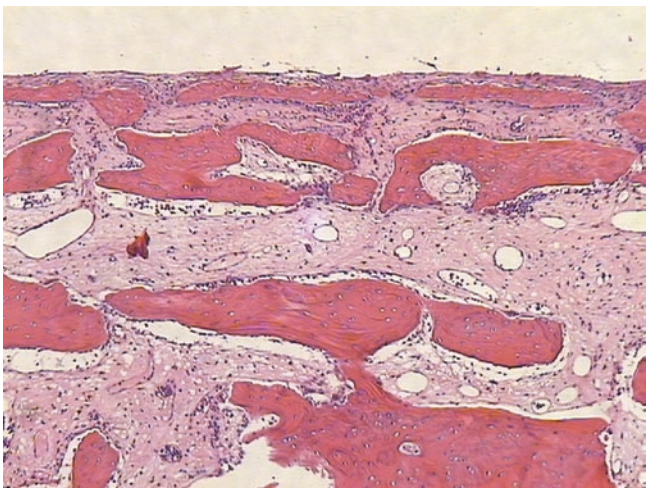

**Fig. 6.1** Proliferative periostitis. The layers of reactive bone exhibit a parallel orientation to the periosteal surface

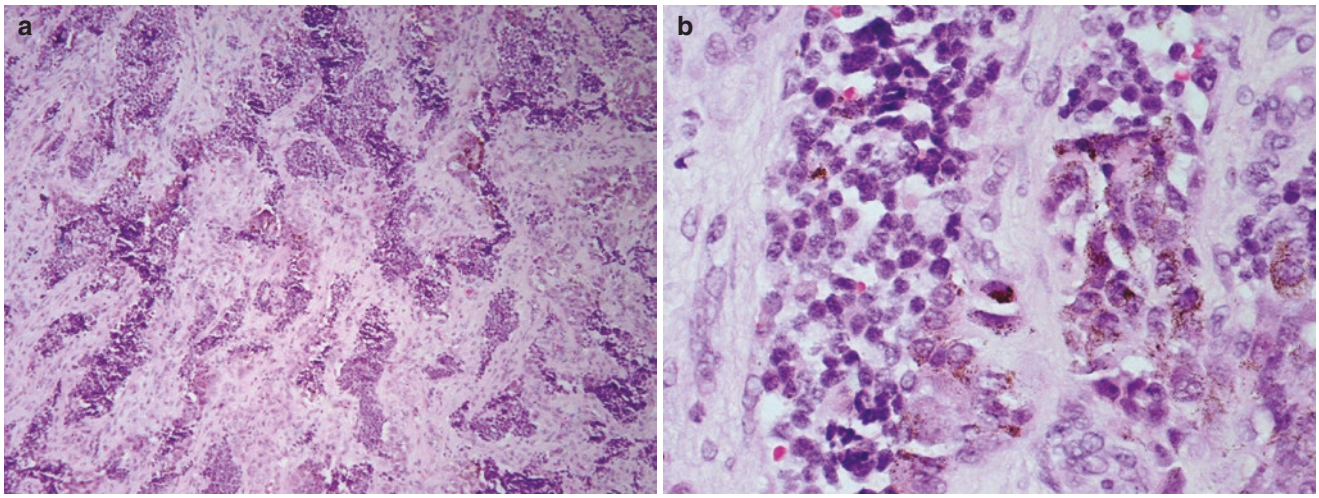


**Fig. 6.2** Melanocytic neuroectodermal tumor of infancy. (**a**, **b**) A biphasic population of "small blue round" cells of neuroectodermal origin are admixed with "melanocytic" cells with variable amounts of melanin pigmentation

two cell populations are further highlighted by different immunohistochemical profiles. The large cells are reactive with cytokeratins and HMB45, while the small cells are reactive to synaptophysin and CD56. Both cell populations are positive for neuron-specific enolase (NSE).

References: [5–7]

3. *What is the presentation of a Stafne bone defect?*

Stafne bone defects are rare incidental findings, with an incidence of less than 1%. These lesions typically appear in 50–70-year-old males as well-defined, solitary, lucent lesions of the lingual mandible, usually less than 2 cm in greatest dimension and located below the inferior alveolar canal. They are theorized to be caused by pressure resorption, usually from adjacent salivary gland tissue. Cases in atypical locations, such as above the inferior alveolar canal or in the anterior mandible, may be biopsied to rule out other lesions.

The histologic findings are most often of normal salivary gland tissue, but non-specific findings of fibro-fatty connective tissue, muscle, or nerve bundles are also reported.

References: [8–10]

4. *What are the histologic features of central giant cell lesions?*

The term central giant cell lesion encompasses a variety of entities with overlapping histopathologic features. These entities include syndromes such as cherubism, Noonan syndrome, neurofibromatosis type 1, and craniofacial cutaneous syndrome (discussed in detail in Question 5) in addition to central giant cell granuloma and Brown tumors of hyperparathyroidism.

The histologic features, common to all these entities, comprise numerous multinucleate osteoclastic giant cells (Fig. 6.3) scattered throughout a hypercellular and richly vascular background of mononuclear spindle to ovoid cells. Thin-walled vessels with foci of hemorrhage are prominent. Spicules of woven bone may be present, particularly at the periphery. Later stages of cherubism contain an increased fibrous stroma with less pronounced vascularity.

References: [11–13]

5. *What syndromes are associated with multiple central giant cell lesions of the jaws? What are the features and associated molecular findings of each syndrome?*

Syndromes that are associated with giant cell lesions of the jaws include cherubism, Noonan syndrome, neurofibromatosis type 1, and craniofacial cutaneous syndrome. The latter three entities are included in a family of disorders termed "RASopathies." Germline mutations in the genes that encode proteins or regulators of the RAS-MAPK (mitogen-activated protein kinases) pathway are causative to these syndromes. The syndromes in the RASopathy family display unique phenotypes with some overlap. Central giant cell lesions of the jaws are reported in small proportions of patients with these conditions.

- *Cherubism* is an autosomal dominant syndrome, though approximately 50% of cases arise de novo. Germline mutations of the SH3-domain binding protein gene (SH3BP2) of 4p16.3 are causative. There is evidence of the downstream effects of SH3BP2 protein on osteoclastic activation. The lesions are limited to maxilla and mandible. They present early in life, at ages 2–7 years, and progress through puberty. Involvement of the gnathic region and maxilla causes bilateral facial swelling and displacement of the orbit, resulting in the "eyes gazing toward heaven"

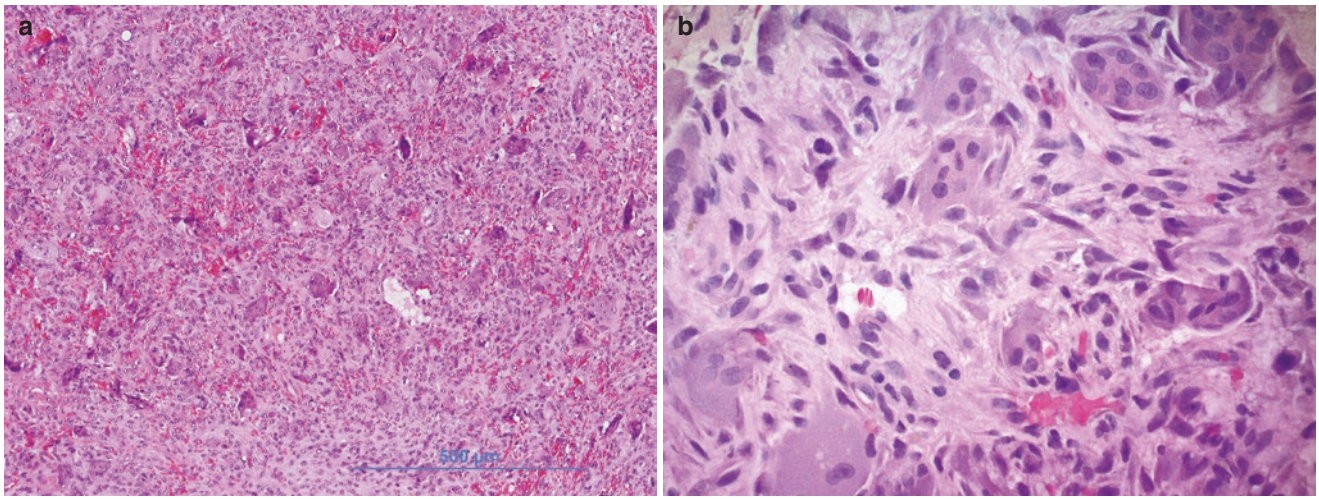


**Fig. 6.3** Central giant cell lesion. (**a**) Multinucleated osteoclastic giant cells are supported by a richly vascularized stroma containing ovoid to spindle mononuclear cells, blood, and hemosiderin deposits. (**b**) The osteoclastic multinucleated giant cells lack atypia

appearance of cherubs that the syndrome is named for. The condition is self-limiting, with postpubescent patients experiencing quiescence or regression of the lesions. The facial features may return to normal later in life, but patients often opt for surgical recontouring.

- *Noonan syndrome (NS)*: Numerous mutations of genes in the RAS-MAPK pathway are associated with Noonan syndrome (NS). NS affects approximately 1 in 1000–2000 newborns and, like most of the RASopathies, is autosomal dominant. These patients have craniofacial abnormalities including a broad forehead, hypertelorism, down-slanting palpebral fissures, and low-set ears. Variable cognitive delay, short stature, webbing of the neck, sternal deformity, pulmonary stenosis, clotting abnormalities, and cryptorchidism are additional features of the syndrome.
- *Noonan syndrome with multiple lentigines (NSML, formerly LEOPARD syndrome)* is rare and an allelic disorder to Noonan syndrome. The two genes implicated in both disorders are PTPN11 and RAF1. NSML patients have similar craniofacial findings to Noonan syndrome patients, with the addition of multiple lentigines and deafness.
- *Neurofibromatosis type 1* is autosomal dominant, affecting approximately 1 in 3000 newborns. It is caused by mutations in the NF1 gene of the RAS pathway. Diagnostic criteria are based on the presence of two of the following clinical features:
  - Café au lait spots.
  - Intertriginous freckling.
  - Lisch nodules of the iris.
  - Neurofibromas.
  - Optic pathway gliomas.
  - Distinctive bone lesions.
  - A first-degree family member with NF1.
  - These patients are also at a greater risk for the development of malignancies including rhabdomyosarcoma and neuroblastomas in pediatric patients and malignant peripheral nerve sheath tumors in adults. Giant cell lesions of the jaws are also limited to case reports in these patients.
- *Cardio-facio-cutaneous syndrome* is caused by mutations in the MAPK pathway, usually of BRAF. The disorder is rare and results in similar facial and cardiac abnormities to Noonan syndrome, with additional ectodermal alterations. These include dark, curly hair, sparse eyebrows and eyelashes, ulerythema ophryogenes, hyperkeratosis and keratosis pilaris, infantile hemangiomas, and numerous acquired melanocytic nevi. Musculoskeletal, ocular, and GI abnormalities are common, as is failure to thrive in infancy. Degrees of neurological deficits, including seizures, motor delay, and learning disability, are present in most to all patients.

References: [11, 13–20]

6. *What findings differentiate central giant cell lesions of the jaws from extra-gnathic giant cell tumors?*

Histologically, the giant cells in giant cell lesions of the jaws are smaller in size than those of giant cell tumors of the bone (see Fig. 6.3). Molecular differences also separate these entities. Over 90% of giant cell tumors of the bone harbor one of two characteristic mutations in H3F3A, a gene that codes for histone 3.3 (H3.3). These mutations are not identified in the giant cell lesions of the jaws, supporting that these lesions have different pathobiology.

References: [11, 21, 22]

7. *What systemic hormone imbalance is associated with multiple giant cell lesions of the jaws?*

Hyperparathyroidism can cause giant cell lesions, termed Brown tumors. These tumors may be identified in all three forms of hyperparathyroidism: primary, secondary, and tertiary. It is not a common manifestation, as fewer than 5% of hyperparathyroidism patients are affected. Mechanistically, parathyroid hormone (PTH) binds osteoblasts, increasing the production of receptor activator of nuclear factor kappa-B ligand (RANKL), which acts to simulate osteoclasts. The excess stimulation of osteoclastic cells is believed to cause these lesions.

The tumors most commonly appear in the pelvis, ribs, femur, and craniofacial bones. Histologically, they are identical to the central giant cell lesions described in question 4.

References: [23, 24]

8. *What are the radiographic and histological differences between a traumatic bone cyst (simple bone cyst, idiopathic bone cavity, hemorrhagic bone cyst), aneurysmal bone cyst, and central giant cell granuloma?*

These lesions have overlap radiographically and histologically. The key differentiating features are presented in Table 6.1.

- *Traumatic bone cyst (TBC):* The name traumatic bone cyst (TBC) is a double misnomer. The etiology is unclear, and neither this entity nor aneurysmal bone cysts (ABCs) have the epithelial linings of true cysts. TBCs are rare, asymptomatic lesions that usually present as incidental findings in patients under the age of 30. Intraoperatively, the surgeon identifies an empty cavity, resulting in a biopsy of scrapings of the surrounding bone.
- *Aneurysmal bone cysts* comprise approximately 1% of all bone tumors and are most common in the long bones. Approximately 2% of cases affect the jaws. Like the extra-gnathic lesions, a proportion of ABCs of the jaws are associated with other bone defects and termed secondary ABCs. The lesions are most commonly benign fibro-osseous lesions, such as ossifying fibroma and fibrous dysplasia. Seventy-five percent of primary ABCs, those not occurring with other pathologies, are associated with a balanced chromosomal translation of *USPS* on 17p13. This abnormality is absent in secondary ABCs.
- *Central giant cell granulomas* occur most frequently in the first and second decades of life but can present at any age. Aggressive lesions may present with pain and expansion or perforation of the cortex. The majority are sporadic and not associated with specific molecular findings. In cases with of multiple lesions, the syndromes or conditions highlighted in questions 5 and 7 are diagnostic considerations.

References: [11, 12, 25–27]

**Table 6.1** Comparison of the radiographic and histologic features of traumatic bone cyst, aneurysmal bone cyst, and central giant cell lesion

| Lesion | Radiographic findings | Histologic findings |
|---|---|---|
| Traumatic bone cyst | Radiolucent<br>Unilocular<br>Well-defined, non-corticated margins<br>Non-expansile<br>Characteristic scalloping between roots of teeth<br>No effect on surrounding structures | Scant amounts of bony fragments and fibrovascular tissue<br>Rare osteoclastic giant cells |
| Aneurysmal bone cyst | Radiolucent<br>Well-defined margins with or without sclerosis<br>Expansile<br>Thin cortical shell results in "ballooned" appearance<br>Thin, wispy septations<br>No effect on surrounding structures | Prominent sinusoidal vessels with focal hemorrhage<br>Connective tissue septations contain multinucleate giant cells, spindled fibroblasts, and reactive woven bone<br>Scattered mitoses<br>Approximately 15% associated with other bony lesions |
| Central giant cell granuloma | Radiolucent<br>Unilocular or multilocular<br>Ill or well-defined margins without sclerosis<br>Expansile, may perforate cortex<br>May displace the teeth and/or cause root resorption | Abundant multinucleate giant cells within a vascular and hypercellular stroma<br>Stromal cells are spindled to ovoid mononuclear cells<br>Spicules of woven bone present as septations or at the periphery<br>Large sinusoidal spaces are absent |

9. *What characterizes a hematopoietic (osteoporotic) bone marrow defect?*

These lesions are detected as incidental findings on diagnostic radiographic studies. They are usually located in the mandible of middle-aged women and may be ill or well-defined radiolucencies. The histologic appearance is that of normal bone marrow with hematopoietic elements.

Reference: [28]

10. *What is the differential diagnosis of cystic lesions of the jaw bones?*

Odontogenic cystic lesions of the jaws fall into categories of inflammatory and developmental. The unicystic ameloblastoma is a benign odontogenic tumor that may be included in the differential diagnosis of odontogenic cysts (discussed further in questions 23 and 24). Non-odontogenic cysts may be developmental or iatrogenic. The clinical and radiographic presentations are key to determining the correct diagnosis (Tables 6.2 and 6.3).

References: [29–32]

**Table 6.2** Odontogenic cysts of the Jaw Bones

| Name | Association or location | Histological features |
|---|---|---|
| *Inflammatory odontogenic cysts* | | |
| Periapical cyst (radicular cyst) | Associated with the root of a non-vital tooth (carious, root canal treated, or history of trauma) | Non-keratinized stratified squamous epithelium, often with inflammatory hyperplasia<br>Moderate to heavy inflammatory infiltrate<br>Abscess and filamentous bacteria may be present<br>Black and granular foreign material often seen in cases associated with a root canal treated tooth<br>See Fig. 6.4 |
| Residual cyst | Persists after extraction of the causative tooth | Similar features to periapical cyst<br>Increased fibrosis and reduced numbers of inflammatory cells in long-standing cases |
| Buccal bifurcation cyst | Buccal furcation of mandibular molars<br>Occurs in children | Identical to periapical cyst. Differentiated by location |
| *Developmental odontogenic cysts* | | |
| Dentigerous cyst | Crowns of impacted teeth | Non-keratinizing stratified squamous epithelium<br>Flat interface between epithelium and the collagenous cyst wall<br>Intense inflammatory cell infiltrate with oral communication<br>Cholesterol clefts are common with inflammation<br>Inflammation may cause epithelial hyperplasia and a resemblance to a periapical cyst. These cases are differentiated by location (Fig. 6.5)<br>See Fig. 6.5 |
| Lateral periodontal cyst | Premolar areas | Thin, non-keratinizing epithelial lining, 1–5 cell layers thick<br>Occasional epithelial whorls with slightly clear cytoplasm but no mucous cells<br>Flat interface to the cyst wall<br>Minimal to no inflammation<br>See Fig. 6.6 |
| Botryoid odontogenic cyst | Premolar areas | Identical features to lateral periodontal cyst but with multiple cystic chambers |
| Glandular odontogenic cyst | Most common in the mandible<br>Predilection for the anterior regions of the jaws | Epithelial lining of variable thickness<br>Occasional whorls, duct-like structures, microcysts, clear cells, cuboidal "hobnail" cells, and/or mucous cells<br>Ciliated cells and papillary proliferations may be present<br>May be multi-chambered<br>See Fig. 6.7 |
| Odontogenic keratocyst | Most common in the posterior mandible<br>May be associated with impacted tooth<br>Multiple are characteristic of nevoid basal cell carcinoma syndrome | Hyperparakeratotic stratified squamous epithelium 6–8 cell layers thick<br>Flat interface to the cell wall<br>Distinct palisading of a hyperchromatic basal layer<br>Corrugation of the parakeratin<br>Daughter cysts and prolific odontogenic rests may be present<br>See Fig. 6.8 |
| Orthokeratinizing odontogenic cyst | Most common in the posterior mandible<br>May be associated with an impacted tooth | Resembles an epithelial inclusion cyst<br>Epithelial lining approx. 4–10 cell layers thick<br>Prominent granular cell layer<br>Orthokeratin fills the lumen with debris<br>See Fig. 6.9 |
| Calcifying odontogenic cyst | Most common in the anterior jaws<br>May be associated with other odontogenic lesions, most commonly odontomas | Ameloblastic epithelium with palisading and hyperchromatism of the basal layer<br>Parabasilar layers show a loose array of epithelial cells reminiscent of the stellate reticulum of a developing tooth<br>Upper layers show expanded eosinophilic cytoplasm and nuclear drop-out of "ghost cells"<br>Ghost cells undergo calcification to form globular masses or stacks resembling lava flows<br>See Fig. 6.10 |
| *Cystic odontogenic tumors* | | |
| Unicystic ameloblastoma | Often associated with an impacted tooth, usually a third molar | Single cystic chamber<br>Epithelial lining with a basal layer of ameloblastic columnar, hyperchromatic cells<br>Basal cells demonstrate nuclear polarization away from the basement membrane<br>Upper cell layers are reminiscent of stellate reticulum<br>Intraluminal and/or intramural proliferations may be present<br>Ghost cells are absent<br>Fig. 6.11 |

**Table 6.3** Non-odontogenic cysts of the jaw bones

| Non-odontogenic cysts of the jaws | | |
|---|---|---|
| Name | Association or location | Histological features |
| Nasopalatine duct cyst | Developmental<br>Arises within the nasopalatine canal | Respiratory type or non-keratinizing stratified squamous epithelium<br>Minimal to no inflammation<br>Medium caliber vessels and nerves present in the cyst wall<br>See Fig. 6.12 |
| Surgical ciliated cyst | Iatrogenic<br>Associated with a previous surgery involving sinus or nasal epithelium (i.e., Le Fort osteotomy or Caldwell-Luc procedure) | Cystic chamber lined by pseudostratified, ciliated columnar epithelium |

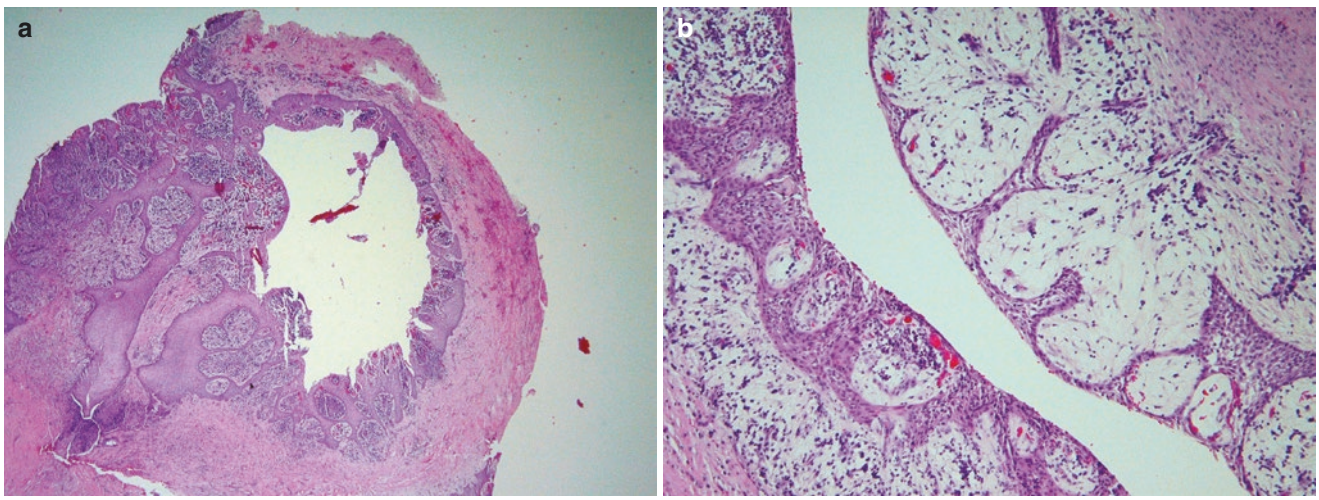


**Fig. 6.4** Periapical (radicular) cyst. (**a**) The cyst is lined by stratified squamous epithelium with varying thickness and frequently exhibits degenerative changes due to inflammation in the wall. (**b**) The lining epithelium often varies between a single layer to multiple layers with inflammatory cell infiltration and elongations into the wall

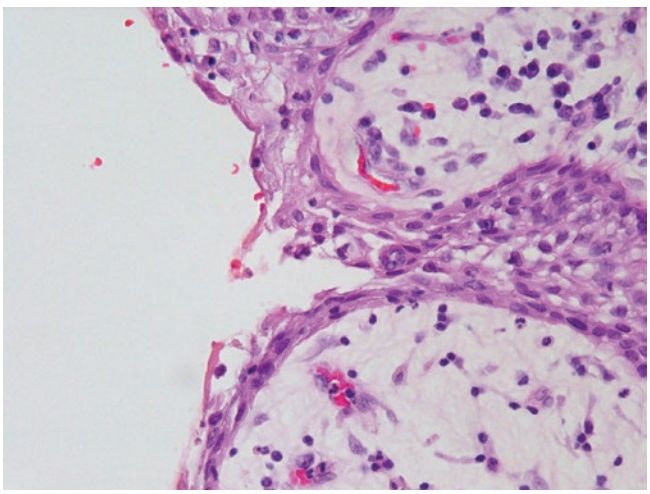

**Fig. 6.5** Dentigerous cyst. The cyst is lined by stratified squamous epithelium with no evidence of hyperchromasia, reverse polarization of the nuclei away from the basement membrane, or vacuolar change on the base of the cells

11. *What criteria are used to differentiate reduced enamel epithelium from cystic epithelium?*

    Biopsies of hyperplastic dental follicles are often submitted to rule out odontogenic cysts that form around the crowns of impacted teeth. Reduced enamel epithelium may be present in these biopsies and comprises remnants of the inner and outer enamel epithelium. This epithelium is simple columnar to cuboidal. Tomes processes of degenerating ameloblasts, resembling cilia, may be apparent at high power. In contrast, a dentigerous cyst will have a stratified squamous epithelium four to eight cell layers thick (Fig. 6.5).

    Reference: [30]

12. *How is crevicular epithelium distinguished from inflamed odontogenic cystic epithelium?*

    This distinction is relevant when determining the presence of an odontogenic cyst, such as a radicular cyst, in the setting of poor dentition and periodontal disease.

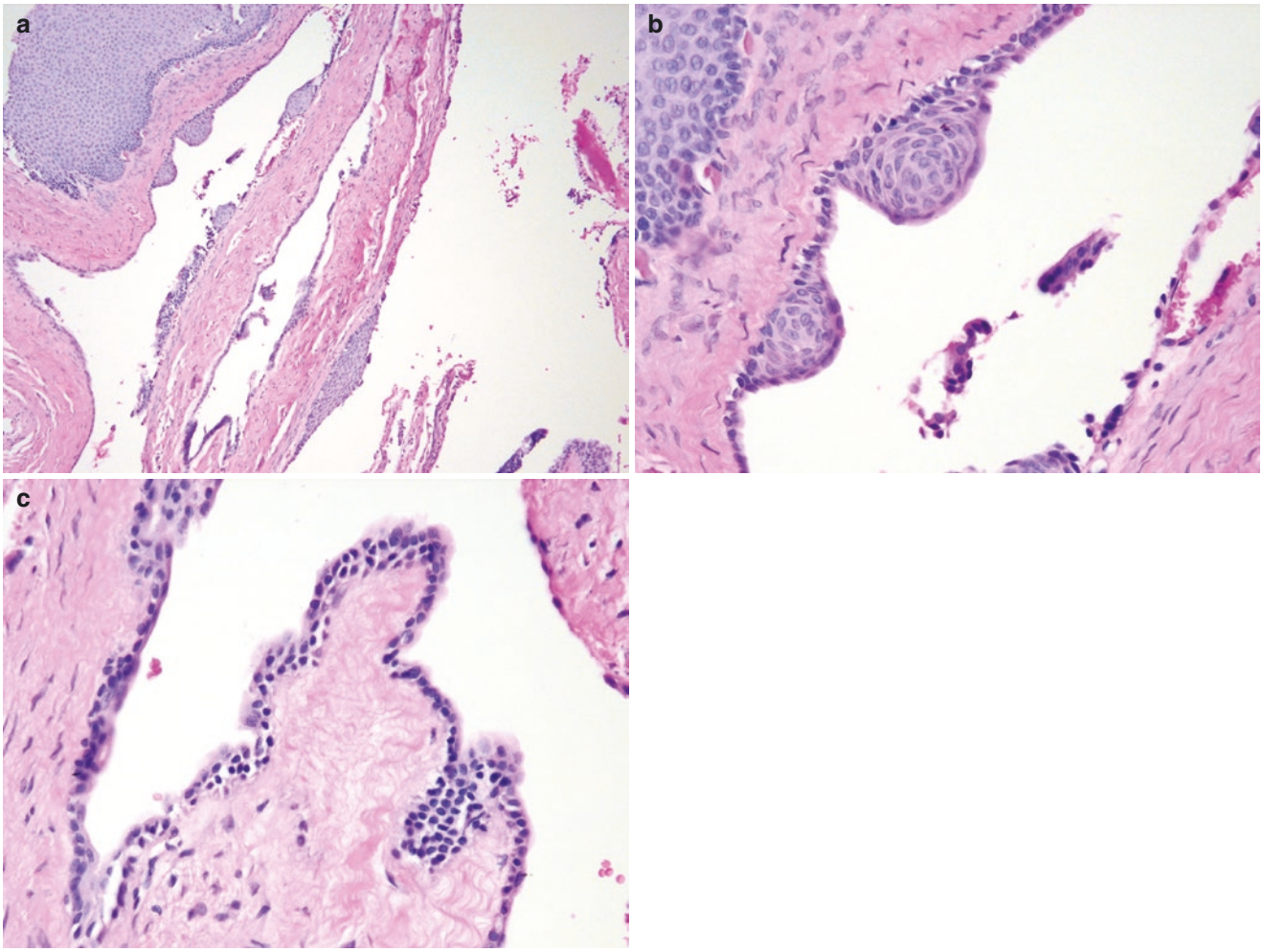


**Fig. 6.6** Lateral periodontal cyst. (**a**–**c**) The cyst is lined by thin stratified squamous epithelium that varies from thin to occasional plaques or "whorls/eddies" of squamous cells that may have focal clear cytoplasm. No mucous cells or duct formation is seen. There is no evidence of columnar basal cells with hyperchromatic nuclei polarized away from the basement membrane (as seen in ameloblastoma and other ameloblastic epithelium-containing odontogenic lesions)

In the presence of inflammation, odontogenic cystic epithelium is histologically indistinguishable from the crevicular epithelium of the periodontium. In some sections, the transition between crevicular epithelium and orthokeratinized epithelium with rete ridges of the gingiva may be apparent. In cases where a transition cannot be identified, clinical and radiographic correlation is essential to determining the correct diagnosis.

Reference: [30]

13. *What are the differentiating features between orthokeratinized odontogenic cyst and odontogenic keratocyst?*

As the names suggest, the primary differentiating feature between these entities is the orthokeratin of the orthokeratinized odontogenic cyst (Fig. 6.9) versus the parakeratin of the odontogenic keratocyst. Additionally, the parakeratin of the odontogenic keratocyst is distinctively corrugated and the basal layer hyperchromatic and palisaded (see Fig. 6.8). The odontogenic keratocyst is more aggressive with higher incidence of recurrence than the orthokeratinized odontogenic cyst, making the distinction significant.

Reference: [30]

14. *What jaw findings raise suspicion for nevoid basal carcinoma syndrome? What are the diagnostic criteria for this syndrome?*

Nevoid basal cell carcinoma syndrome (NBCC) is an autosomal dominant disorder with high penetrance but variable expressivity. It is caused by mutations in the *patched* (*PTCH1*) gene on chromosome 9q22.3. The finding of multiple odontogenic keratocysts, either metachronous or synchronous, should raise suspicion for this syndrome. Over 80% of patients with NBCC experience odontogenic keratocysts, with the mean age of first diagnosis in the mid-teenage years.

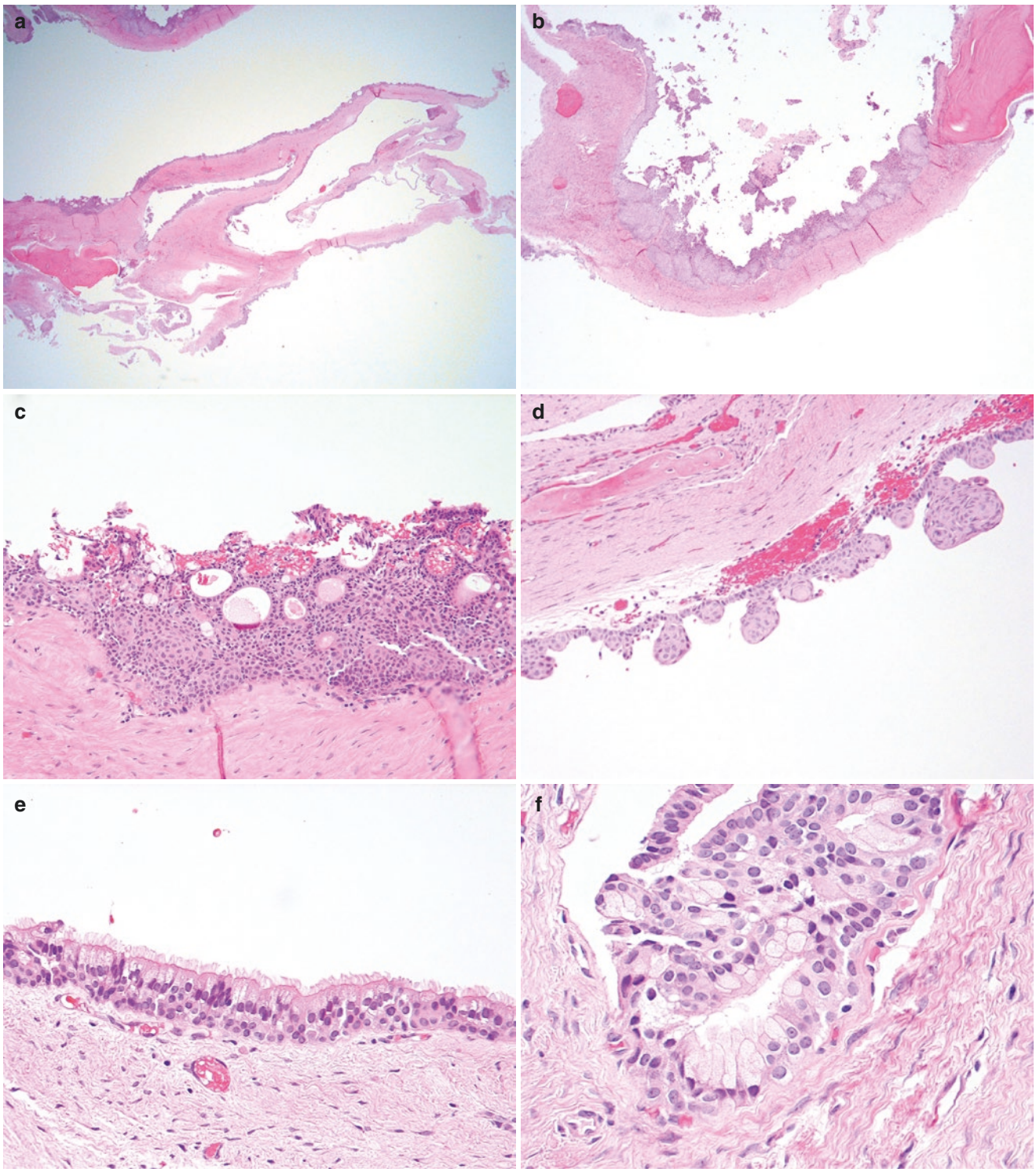


**Fig. 6.7** Glandular odontogenic cyst. (**a**, **b**) The lesion exhibits variable types of lining epithelium. It also may vary in thickness. Usually, only minimal inflammation is seen. (**c**–**f**) The lining epithelium may contain a combination of mucous cells, ciliated cells, duct-like structures, clear cells, and papillary luminal projections

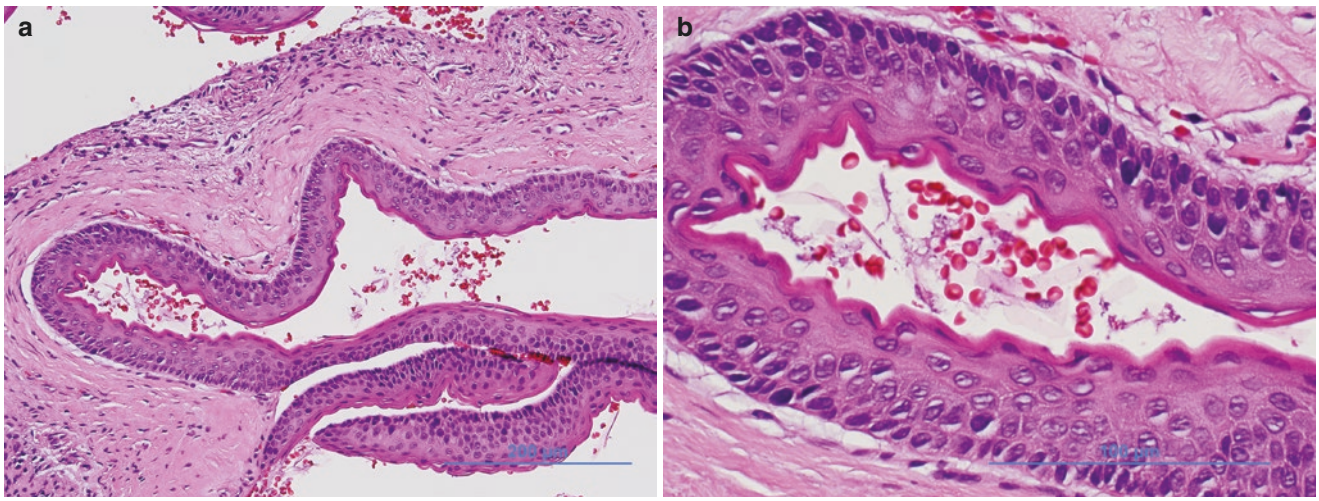


**Fig. 6.8** Odontogenic keratocyst. (**a**, **b**) The cyst is lined by stratified squamous epithelium with a relatively uniform thickness and no rete peg formation. The luminal surface exhibits corrugated parakeratin and the basal cells show palisading of the nuclei but no vacuolization of the cytoplasm between the nuclei and the basement membrane

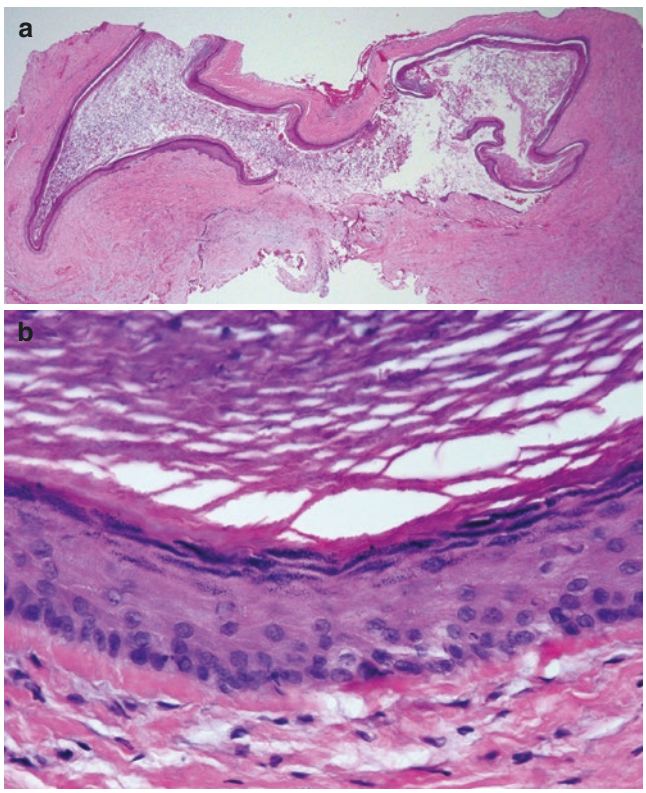


**Fig. 6.9** Orthokeratinizing odontogenic cyst. (**a**, **b**) The cyst exhibits a stratified squamous epithelial lining with overt orthokeratin production and an evident granular cell layer. The basal cells rarely show palisading

Malignancies associated with this syndrome include basal cell carcinomas and medulloblastomas. The age of first diagnosis of basal cell carcinoma ranges from 3 to 53 (median 20 years), with 80% of Whites and 38% of African Americans with the syndrome affected. Medulloblastomas are an uncommon but potentially devastating tumor, affecting less than 5% of nevoid basal cell carcinoma syndrome patients.

Additional head and neck findings include calcification of the falx cerebri and facial abnormalities. Diagnosis is based on two major criteria or one major and two minor criteria, listed in Table 6.4.

References: [33, 34].

15. *What are the histological differences between a lateral periodontal cyst and a radicular cyst?*

The differences between these entities are compared in Table 6.5. Due to the occasional occurrence of lateral radicular canals within a tooth, a radicular cyst may appear radiographically identical to a lateral periodontal cyst. Histologically, a lateral radicular cyst will show a hyperplastic and inflamed cystic lining of odontogenic epithelium, while inflammation is absent or minimal in the lateral periodontal cyst. The epithelium of a lateral periodontal cyst is thinner, with one to five cell layers. Occasional whorls, or plaques, are present. The botryoid odontogenic cyst is a variant of lateral periodontal cyst that shares histological features but with multiple chambers, leading to a multilocular appearance on radiographs.

Reference: [30]

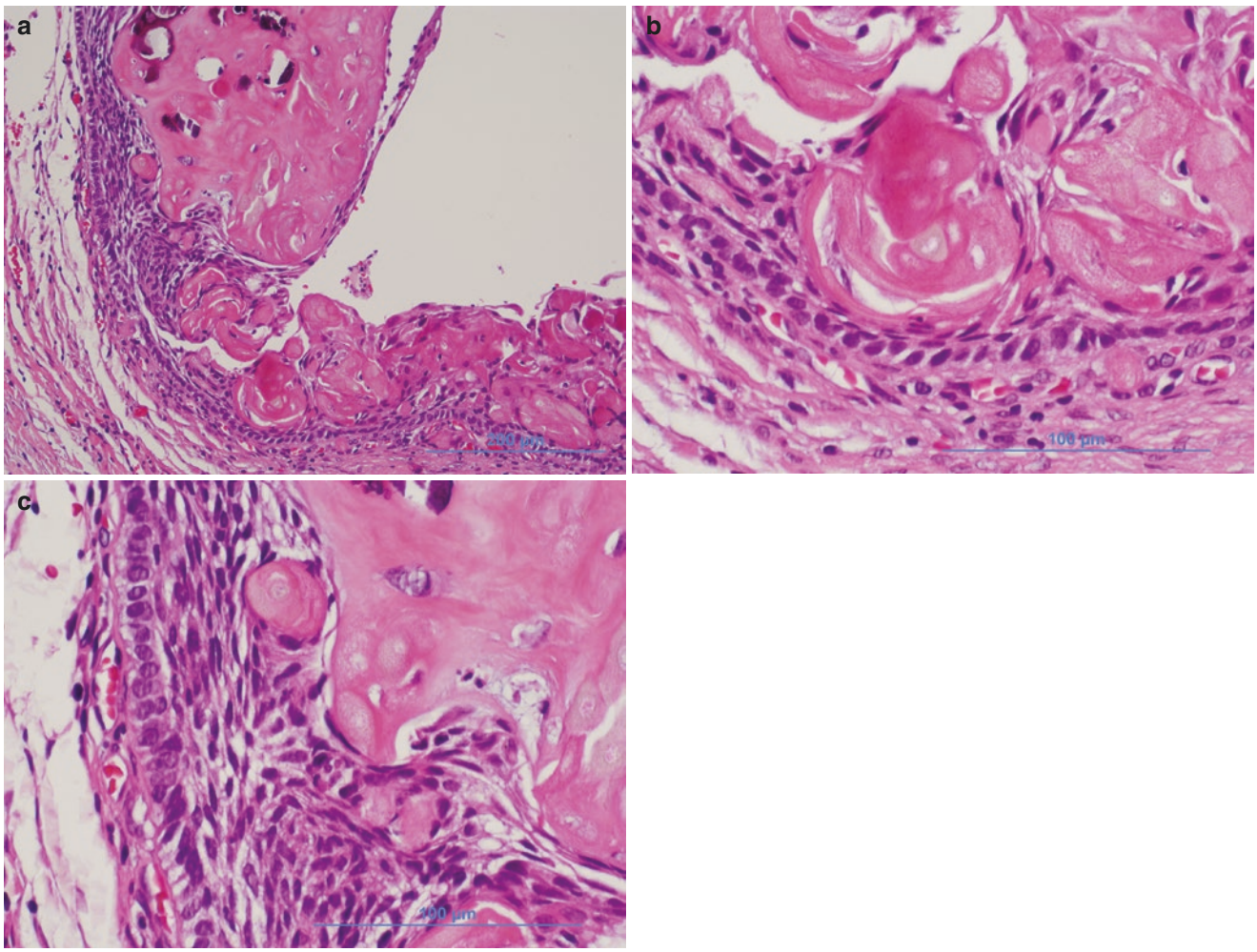


**Fig. 6.10** Calcifying odontogenic cyst. (**a**) A predominantly cystic lesion with variable thickness and luminal production of ghost cell keratinization with occasional calcification of its product. (**b**) The ghost cell keratinization originates from the lining epithelium. (**c**) The basal cells of the lining epithelium often show prominent ameloblastic features, but the presence of ghost cell keratinization (ghost cells) precludes the diagnosis of ameloblastoma

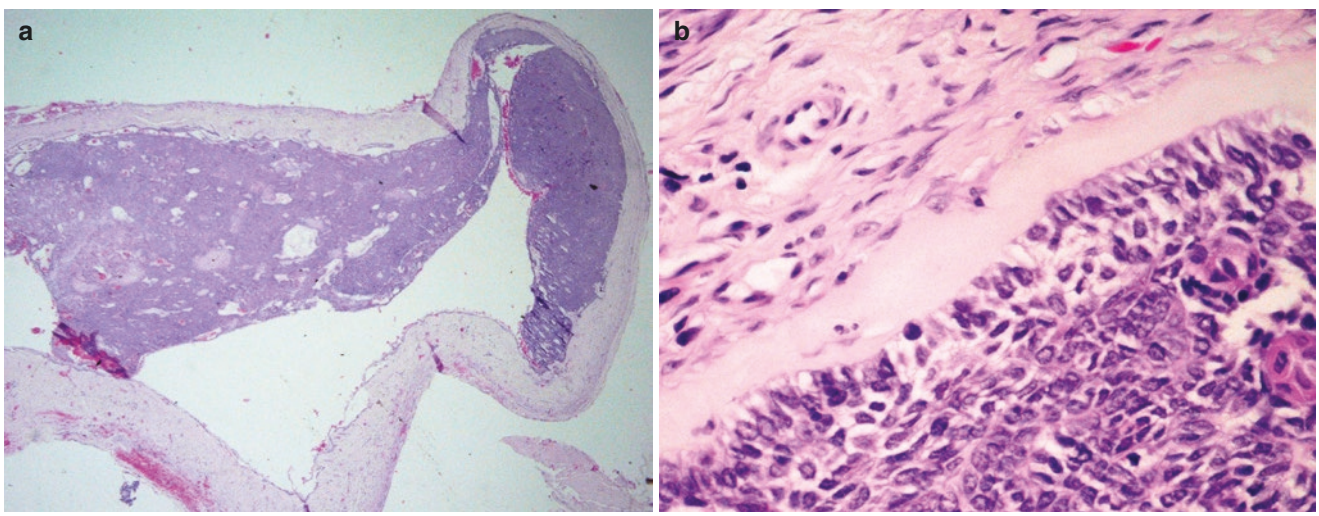


**Fig. 6.11** Unicystic ameloblastoma. (**a**) This neoplastic lesion must be a single cystic cavity with a well-delineated border and no evidence of mural (cyst wall) invasion. The lining of the predominantly cystic lesion occasionally resembles stellate reticulum similar to the one found in the enamel organ during odontogenesis. No ghost cells, mucous cells, duct formation, or orthokeratin is observed. (**b**) The majority of the basal cells lack the typical ameloblastic features, but occasional areas of columnar cells with hyperchromatic nuclei polarized away from the basement membrane and basal vacuolar formation are seen

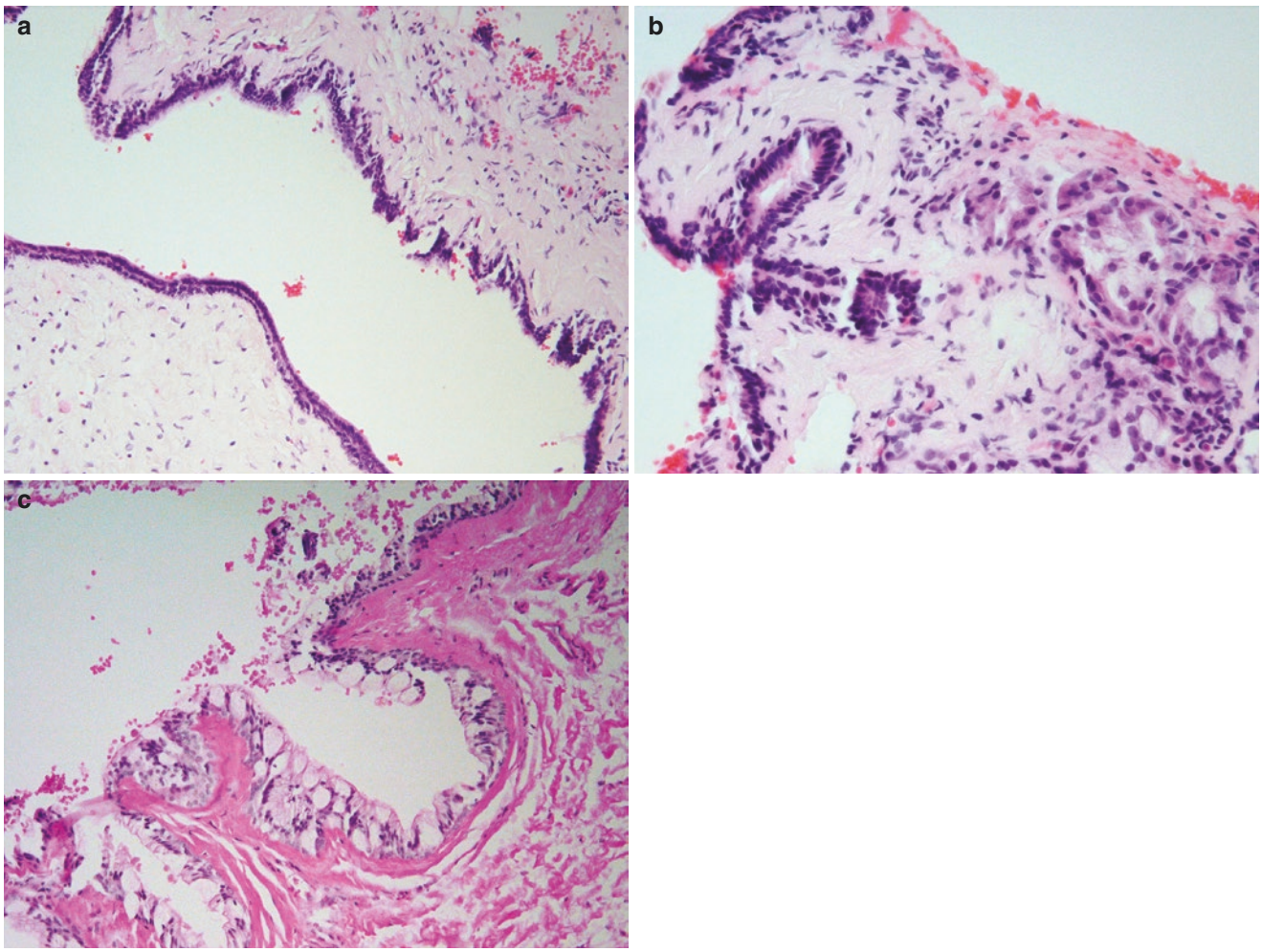


**Fig. 6.12** Nasopalatine duct cyst (incisive canal cyst). (**a**–**c**) The cyst is lined by either stratified squamous epithelium or respiratory epithelium depending on how close it is toward the mouth or nose, respectively. The wall of the cyst can contain neurovascular bundles, salivary gland, or cartilage

**Table 6.4** Diagnostic criteria for nevoid basal cell carcinoma syndrome

| Major criteria | Minor criteria |
|---|---|
| Multiple (>2) basal cell carcinomas or one under the age of 20 years | Macrocephaly |
| Odontogenic keratocysts of the jaw | Facial abnormalities (cleft lip or palate, frontal bossing, hypertelorism, course features) |
| Palmar or plantar pits | Skeletal abnormalities (Sprengel deformity, pectus deformity, syndactyly) |
| Bilamellar calcification of the falx cerebri | Radiological abnormalities (bridging of the sella turcica, vertebral anomalies, flamed shaped lucencies of the hands or feet) |
| Rib anomalies (bifid, splayed) | Ovarian fibroma |
| First-degree relative with NBCC syndrome | Medulloblastoma |

Diagnosis is based on the presence of two major criteria or one major and two minor criteria

**Table 6.5** Comparison of histological features of lateral periodontal cyst and radicular cyst

| | |
|---|---|
| Lateral periodontal cyst | Epithelium of 1–5 cell layers<br>Occasional whorls<br>No to minimal inflammation |
| Radicular cyst | Hyperplastic epithelium<br>Moderate to intense inflammation<br>May have foreign debris or aggregates of bacteria present |

**Table 6.6** Comparison of features of dentigerous cysts and glandular odontogenic cysts

| | |
|---|---|
| Dentigerous cyst | Always associated with an impacted tooth<br>Epithelium of 4–8 cell layers<br>No to minimal mucous cells<br>No to minimal ciliated cells<br>No duct-like structures |
| Glandular odontogenic cyst | May be associated with impacted tooth<br>Surface "hobnail cells" – eosinophilic cuboidal cells that may demonstrate apocrine-like decapitation or snouting<br>Duct-like structures or microcysts lined by cuboidal cells and/or mucous cells<br>Presence of mucous cells<br>Presence of ciliated cells<br>Focal epithelial whorls, similar to those of a lateral periodontal cyst<br>Luminal papillary tufts or projections<br>Clear or vacuolated cells in the basal or spinous layer<br>Multiple compartments<br>Marked variability in thickness of the epithelial lining |

16. *What is the difference between a lateral periodontal cyst and a gingival cyst of the adult?*

The gingival cyst of the adult is the soft tissue analog to the intrabony lateral periodontal cyst. These lesions are histologically identical. Both most commonly occur in the premolar region of the mandible.

Reference: [30]

17. *How is a dentigerous cyst or radicular cyst with mucous cell prosoplasia differentiated from a glandular odontogenic cyst?*

These differences are compared in Table 6.6.

Due to the pluripotency of odontogenic epithelium, both dentigerous cysts and glandular odontogenic cysts may contain mucous cells and cilia (see Fig. 6.7). With glandular odontogenic cysts exhibiting locally aggressive behavior and a propensity for recurrence, achieving the correct diagnosis is clinically significant.

Several studies have explored the diagnostic criteria for glandular odontogenic cyst; however, no standard is universally accepted. Diagnosis is based on a summation of the above features within the stratified squamous epithelial lining.

The presence of duct-like structures or microcysts was found to be the most sensitive and specific criteria to the diagnosis of glandular odontogenic tumor by one case series and is suggested as a "major diagnostic criteria" in another. This finding warrants further evaluation for additional features of glandular odontogenic cyst but is not itself diagnostic.

References: [35–38].

18. *How is a glandular odontogenic cyst differentiated from a central low-grade mucoepidermoid carcinoma? What ancillary studies may be helpful in differentiating these lesions?*

Another histologic mimicker of glandular odontogenic cyst is the central mucoepidermoid carcinoma (MEC). Homologous to those of the salivary glands, low-grade central mucoepidermoid carcinoma shares features with glandular odontogenic cyst; both may have prominent cystic structures and minimal cytologic atypia. Central MEC may arise from pluripotent odontogenic epithelium or minor salivary tissue with extension into the bone. Like glandular odontogenic tumors, central MEC may be associated with impacted teeth. The two entities share such overlap in clinical and histologic features that historically they were believed to be entities along the same continuum. The *MAML2* gene rearrangement characteristic of mucoepidermoid carcinomas is absent in glandular odontogenic tumors, however, contradicting this theory.

Thorough histologic examination is required, and additional sampling to identify solid areas of tumor or definitively invasive islands is warranted in challenging cases. Ancillary studies have found CK18 positivity in 100% of central mucoepidermoid carcinoma but only 12–30% of glandular odontogenic tumors. Molecular studies, such as break-apart fluorescent in situ hybridization (FISH), can be used to evaluate lesions for the *MAML2* rearrangement characteristic of mucoepidermoid carcinoma.

References: [39–42]

19. *What are the histological features of calcified epithelial odontogenic tumor?*

The calcified epithelial odontogenic tumor (also known as Pindborg tumor) is a rare benign but locally aggressive neoplasm with striking histological features that may be mistaken for malignancy.

The tumor cells are polyhedral and eosinophilic and occur in islands, nests, or cords (Fig. 6.13).

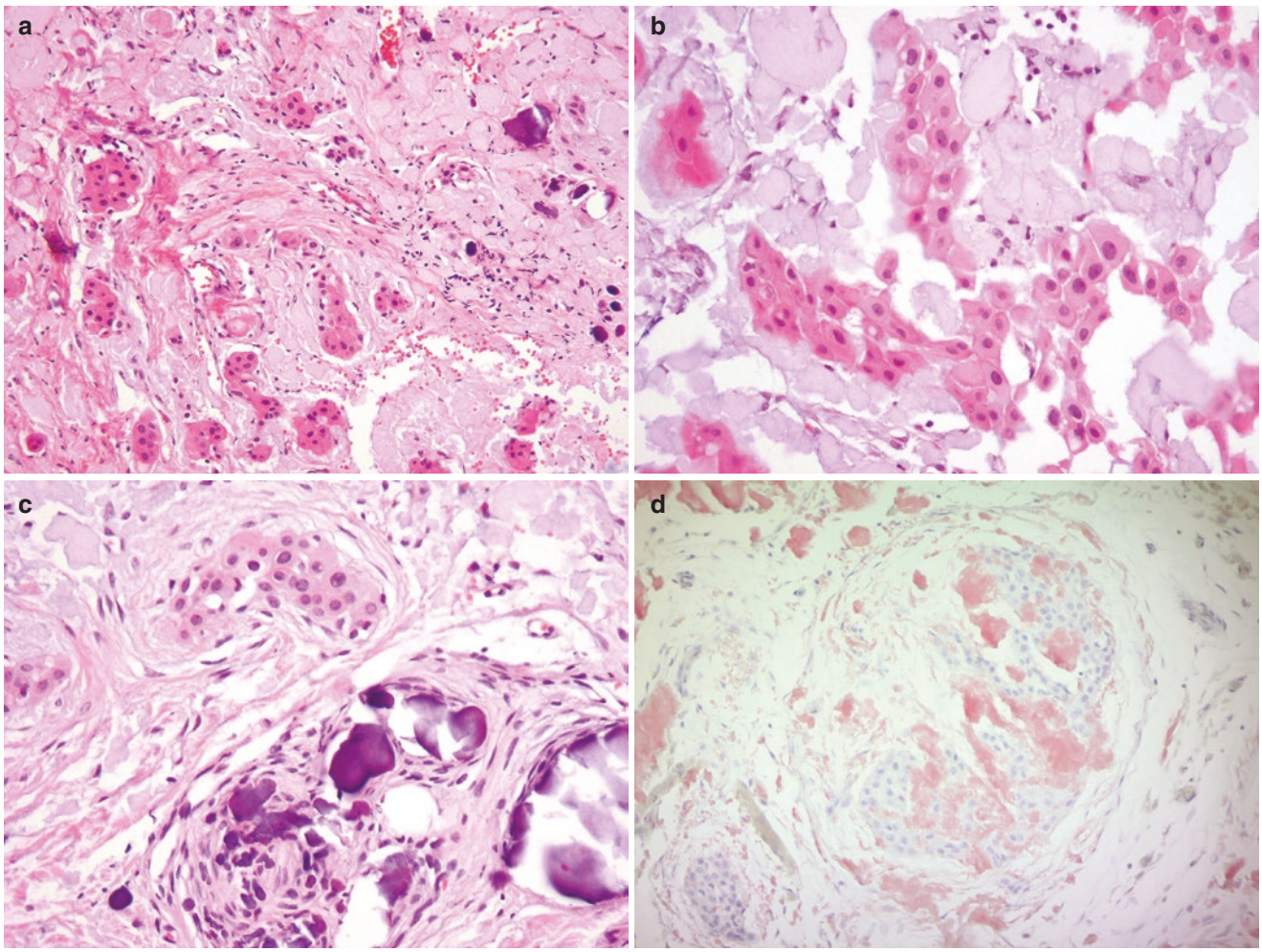


**Fig. 6.13** Calcifying epithelial odontogenic tumor. (**a**) This odontogenic neoplasm exhibits a solid architecture. It is supported by a collagenized stroma with variable amounts of amyloid produced by the neoplastic cells. (**b**) The neoplastic cells are derived from the stratum intermedium of the enamel organ and exhibit a polyhedral architecture with hyperchromatism and enlarged nuclei conveying a "pseudoatypical" morphology. The amount of amyloid may vary from abundant to none. Sometimes, the cells may exhibit clear cytoplasm. (**c**) Some tumors will have variable amounts of concentric basophilic calcifications. (**d**) The amyloid deposits are reactive to special stains like Congo red

Marked variations of nuclear size, ringlike concentric basophilic (Liesegang-like) calcifications, and production of an amyloid-like material are characteristic. Pleomorphism between and within tumors lends to the difficulty of this diagnosis. Histological variants of clear cell, cystic, and Langerhans cell tumors are reported but not shown to impact clinical behavior. Rare cases of malignant transformation have occurred.

References: [30, 43]

20. *What ancillary studies may help determine the diagnosis of calcified epithelial odontogenic tumor?*

A Congo red stain is useful to confirm the presence of odontogenic ameloblastic associated protein, a substance histologically identical to amyloid (see Fig. 6.13d). The clear cell variant is PAS positive and diastase sensitive, revealing glycogen storage.

Due to the rarity of these lesions, immunohistochemical findings are limited to case reports or small case series. Positivity for squamous epithelial markers including pancytokeratin, CK5/6, and p63 is identified in multiple reports, as well as CK19. The Ki-67 index is low in benign lesions, reported as less than 2%. In a case of malignant transformation, the Ki-67 rose to 42% in tumor cells.

References: [44–46]

21. *What are the clinical and histologic differences between calcifying odontogenic cyst, dentinogenic ghost cell tumor, and odontogenic ghost cell carcinoma?*

These differences are outlined in Table 6.7.

References: [30, 47–49]

22. *What are the clinical and histological features of adenomatoid odontogenic tumor?*

**Table 6.7** Clinical and histological features of ghost cell tumors

| | Clinical features | Histologic features |
|---|---|---|
| Calcifying odontogenic cyst (COC) | No sex predilection<br>Most prevalent in second and third decades<br>Usually located in anterior jaws<br>50% associated with impacted teeth | Cystic lumen lined by ameloblastic epithelium<br>Palisaded basal layer with upper layers resembling stellate reticulum<br>Calcifying ghost cells toward luminal surface<br>No cytological atypia<br>Commonly found with other odontogenic tumors, usually odontomas |
| Dentinogenic ghost cell tumor (DGCT) | More common in males<br>Mean age of 33<br>Usually located in posterior jaws | Solid tumor of ameloblastic epithelial islands<br>Palisaded basal layer surrounding cells resembling stellate reticulum<br>Calcified ghost cells<br>Variable amounts of dentin-like material in the connective tissues<br>No cytological atypia |
| Ghost cell odontogenic tumor | More common in males<br>Mean age of 36 | Malignant counterpart to dentinogenic ghost cell tumor<br>May arise de novo or as a transformation of COC or DGCT<br>Groups of ghost cells<br>Brisk mitotic activity, cellular pleomorphism, and/or necrosis in neoplastic epithelial cells |

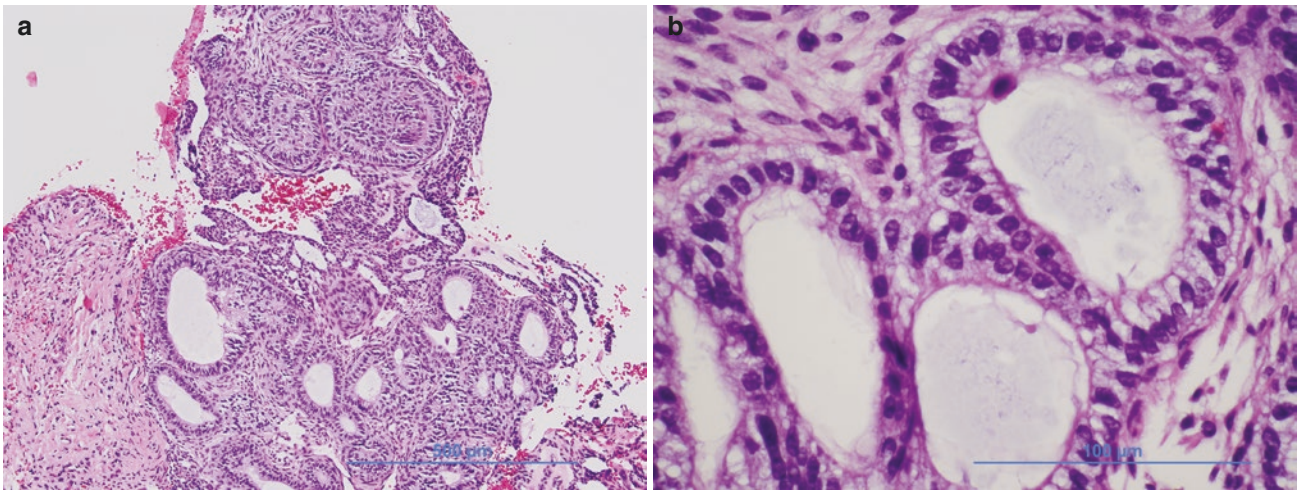


**Fig. 6.14** Adenomatoid odontogenic tumor. (**a**) The neoplasm may contain cystic and solid components usually associated with a dental follicle. There are duct-like structures lined by cuboidal to columnar cells with a well-delineated lumen that may contain amyloid-like material or dystrophic calcifications with occasional concentric pattern. (**b**) The ductal structures may vary in size and number and alternate with solid whorls of spindle-shaped epithelial cells

Adenomatoid odontogenic tumors (AOTs) are slow-growing, benign tumors of pediatric patients, with most cases diagnosed in the second decade of life. Features may be remembered by the "two-thirds" rule:

- Two-thirds occur in females.
- Two-thirds occur in the maxilla.
- Two-thirds are associated with an impacted tooth.
- Two-thirds of the impacted teeth are canines.
- Two-thirds of the radiographs show radiopaque flecks of calcifications.

AOTs are separated into three clinical and radiographic variants. The follicular variant surrounds an impacted tooth. Rather than surrounding solely the crown like a dentigerous cyst, AOTs characteristically surround the crown and portions of the tooth root. The extra-follicular variant is not associated with a tooth and less common. The peripheral variant is extra-osseous and rare. AOTs are epithelial neoplasms with unique histological findings including:

- Solid and cystic components
- Epithelial whorls or pseudorosettes
- Duct-like structures with palisaded nuclei polarized toward the basement membrane (Fig. 6.14)
- Amyloid-like islands of odontogenic ameloblastic associated protein
- Irregular calcifications may include Leisgang-type droplet calcifications

A Congo red stain may be used to highlight the amyloid-like material. While focal areas of AOT may

be reminiscent of calcifying epithelial odontogenic tumor, the presence of pseudo-ducts, cystic spaces, and whorls is distinctive.

References: [30, 51]

23. *What are the Vickers-Gorlin criteria for the diagnosis of ameloblastoma?*

In a 1970 publication, Vickers and Gorlin delineated the diagnostic criteria of ameloblastomas based on their studies of the unicystic variant (Table 6.8); however, these criteria are applied to all variants. Figure 6.15 demonstrates the pertinent features.

References: [30, 51, 52]

24. *What are the clinical, radiographic, and histological differences between subtypes of ameloblastoma?*

There are four growth patterns of ameloblastoma, with histologic subtypes within the first three growth patterns (Table 6.9). The growth patterns are described below:

1. Peripheral – an extra-osseous variant without evidence of a central component. Approximately 2% of ameloblastomas are the peripheral variant.
2. Unicystic – a single cystic chamber lined by neoplastic ameloblastic epithelium. Fifty to eighty percent are associated with impacted teeth and termed "dentigerous" type vs the "non-dentigerous" type without association to a tooth. The unicystic category comprises approximately 6% of ameloblastomas (see Fig. 6.11).
3. Solid – an infiltrative epithelial neoplasm of varying histological patterns. This is the predominant pattern of ameloblastoma.
4. Desmoplastic – an infiltrative neoplastic epithelium within a dominant dense, collagenous stroma. Four to thirteen percent of ameloblastomas are the desmoplastic variant.

Other rare histologic variations of ameloblastoma are the granular cell ameloblastoma and basal cell ameloblastoma. The granular cell ameloblastoma resembles the follicular subtype but with characteristic eosinophilic, large cells centrally located within the epithelial islands. The cytoplasm contains distinctive granules, and the nucleus is displaced to the periphery.

The basal cell variant closely resembles basal cell carcinoma and tends to grow in islands and nests. Rather than a stellate reticulum-like central proliferation, the centers of the islands contain spindled to polyhedral cells with nuclear features similar to those of the basal layer. The basal layer maintains palisading and slight hyperchromatism to the central cells; however the vacuolization and reverse polarity is absent.

Often a single tumor may display a variety of histologic patterns and is then classified according to the predominant pattern. Ameloblastomas are aggressive but benign neoplasms, and mitotic activity is minimal in these tumors. An increase raises suspicion for ameloblastic carcinoma, the rare malignant counterpart of ameloblastoma.

Ameloblastic carcinomas may arise de novo or as transformation from a benign odontogenic lesion. Anaplasia, increased mitoses, and cellular pleomorphism are readily identified within the odontogenic epithelium. Vickers-Gorlin criteria may be focal. Overall 5-year survival is approximately 70%.

Rarely, ameloblastomas can metastasize, most frequently to the lung. Metastatic ameloblastomas show similar histology to the primary site and are frequently associated with multiple recurrences at the primary site.

References: [53–57]

25. *What histologic subtypes of ameloblastoma are associated with more aggressive clinical behavior?*

While the histological subtyping of ameloblastomas is thought to be primarily of academic interest without clinical implications, there is emerging evidence that some histological subtypes correlate with differing clinical behaviors. In a large review of ameloblastomas, with over 3000 cases studied, the follicular variant was associated with the highest recurrence rate at 29.5%. The acanthomatous variant had the lowest recurrence

**Table 6.8** Vickers-Gorlin diagnostic criteria for ameloblastoma (see Fig. 6.15)

| Vickers-Gorlin histologic criteria for ameloblastoma |
|---|
| Hyperchromatism of the epithelial basal cell nuclei |
| Palisading of the basal cell nuclei |
| Polarization of the basal cell nuclei away from the basement membrane |
| Cytoplasmic vacuolization of the basal cells |

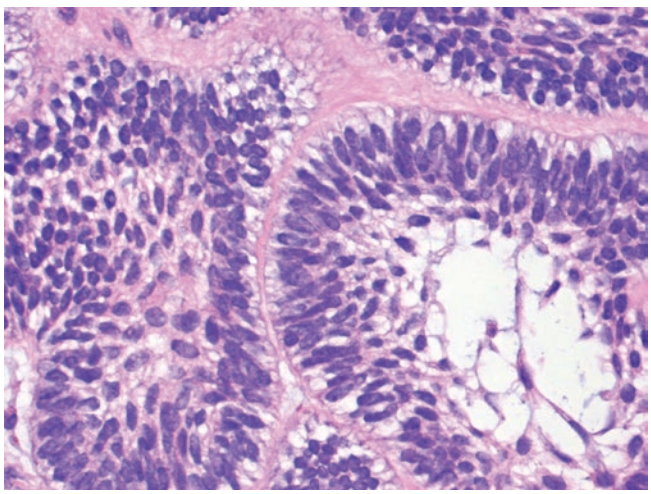

**Fig. 6.15** Ameloblastoma islands demonstrating the Vickers-Gorlin criteria

**Table 6.9** Subtypes of ameloblastomas

| Subtype | | Clinical features | Radiographic features | Histologic features |
|---|---|---|---|---|
| Peripheral | | Present as a gingival swelling<br>Mean age 51 years<br>No significant sex predilection<br>Mandible affected 5× more often than maxilla, 2× more common in anterior regions than posterior | May show cupping of underlying bone | Usually mixed, follicular, or acanthomatous subtypes (see complete descriptions under "solid" subtype) |
| Unicystic | Both | Present as swelling or incidental finding<br>Posterior mandible most common location | Radiolucent<br>Well-defined<br>May expand cortical bone, displace the inferior alveolar canal and/or resorb roots of adjacent teeth | Single cystic lumen lined by ameloblastic epithelium<br>At least focal representation of Vickers-Gorlin criteria<br>Epithelial proliferations into the lumen and/or cyst wall may be present<br>2/3 show invasive tumor epithelium within the cystic wall |
| | Dentigerous | Mean age 16.5 years<br>Male to female ratio 1.5:1 | Unilocular<br>Usually associated with impacted third molar | |
| | Non-dentigerous | Mean age 35 years<br>Male to female ratio 1:1.8 | Unilocular or multilocular<br>Not associated with a tooth | |
| Solid | All | Present as bony swelling<br>Mandible most common location<br>No significant sex predilection | Unilocular or multilocular<br>Well-defined borders<br>May cause expansion and thinning of cortical plates<br>Rarely cause perforation<br>Root resorption may be present | |
| | Follicular | Mean age 39<br>More frequent in molar-ramus region | | Nests and islands of epithelium<br>Vickers-Gorlin criteria in columnar basal cells<br>Inner cell layers of loosely arranged stellate to spindled cells<br>Inner cells with angular nuclei and scant cytoplasm, recapitulating the stellate reticulum<br>Collagenous stroma |
| | Plexiform | Mean age 41<br>More frequent in molar-ramus region | | Anastomosing cords of columnar to cuboidal epithelial basal cells<br>Cords may be focally bilayered with proliferations containing stellate reticulum-like cells<br>Vickers-Gorlin criteria may be focal<br>Loose connective tissue stroma |
| | Acanthomatous | Mean age 51<br>More frequent in incisor-canine region | | Epithelial islands with a basal layer and stellate cells similar to those of the follicular type<br>Central squamatization and keratinization within islands<br>Collagenous stroma |
| Desmoplastic | | Present as painless swelling<br>Mean age 43 years<br>No sex predilection<br>May occur anywhere in jaws, no site predilection | Radiolucent or mixed radiolucent-radiopaque<br>Ill-defined borders<br>Soap-bubble appearance<br>Rarely associated with impacted teeth | Infiltrative odontogenic epithelium arranged in irregular, stellate, or follicular islands and/or cords<br>Dense collagenous stroma<br>Rare foci of Vickers-Gorlin criteria in epithelium |

rate at 4.5%. The unicystic, plexiform, and mixed subtypes had recurrence rates ranging from 14% to 17%.

Reference: [52]

26. *What molecular findings are associated with ameloblastomas?*

Emerging findings of somatic mutations in the MAPK signaling pathway, particularly a *BRAF*-V600E mutation, are reported in over 60% of ameloblastomas. This mutation is not specific to ameloblastomas and is identified in smaller proportions of other odontogenic neoplasms as well as non-odontogenic neoplasms such as melanoma and papillary thyroid carcinoma.

References: [58–60]

27. *What immunohistochemical markers can be helpful to distinguish an ameloblastoma?*

Usually the diagnosis of ameloblastoma is made on characteristic histologic findings; however, immunohistochemical studies may be used to support the H&E findings in the instance of limited sampling. In these instances, calretinin may be used to differentiate amelo-

blastomas from other odontogenic lesions. Calretinin is diffusely reactive in the stellate reticulum-like areas of over 90% of ameloblastomas, while the basilar columnar cells are negative. This marker was not found to be reactive in other odontogenic neoplasms including calcifying epithelial odontogenic tumor, adenomatoid odontogenic tumor, ameloblastic fibroma, nor odontogenic myxoma.

References: [61, 62]

28. *What is the histological differential diagnosis of clear cell lesions of the jaws and what ancillary studies may be used to reach the correct diagnosis?*

The differential diagnosis of clear cell predominant lesions of the jaws includes clear cell odontogenic carcinoma, clear cell calcifying epithelial odontogenic tumor, central clear cell mucoepidermoid carcinoma, and metastasis, especially clear cell renal cell carcinoma. These lesions are further described in Table 6.10.

References: [63–68]

29. *What is the clinical and histologic presentation of squamous odontogenic tumor?*

Squamous odontogenic tumors are exceedingly rare and a diagnostic pitfall due to the overlapping features with several histologic mimickers (see question 30). The features of these tumors are described in Table 6.11 (Fig. 6.17).

References: [69, 70]

30. *What histological features differentiate squamous odontogenic tumor from its mimickers?*

**Table 6.10** Differential features of clear cell lesions of the jaws

| **Lesion** | **Histological features** | **Ancillary studies** |
|---|---|---|
| Clear cell odontogenic carcinoma | Nests and cords of polygonal cells with abundant clear cytoplasm and well-defined cell borders<br>Eccentric nuclei with occasional wrinkled or rasinoid features<br>Minimal to scattered mitoses<br>Central necrosis and anaplasia rare<br>Rare peripheral palisading and ameloblastic differentiation<br>Prominent eosinophilic hyalinized stroma<br>Figure 6.16 | Histochemical:<br>PAS variable<br>Mucicarmine (−)<br>IHC:<br>Pancytokeratin (+)<br>CK19 (+)<br>p40 (+)<br>EMA variable<br>S-100 variable<br>Molecular:<br>*EWSR1* rearrangements (22q12) |
| **Histologic mimicker** | **Differentiating features** | **Ancillary studies** |
| Clear cell calcifying epithelial odontogenic tumor | Presence of amyloid-like material<br>Presence of Leisgang calcifications | Histochemical:<br>PAS (+), diastase sensitive<br>Congo red (+) with apple green birefringence<br>IHC:<br>Pancytokeratin (+)<br>CK5/6 (+)<br>p63 (+)<br>CK19 (+) |
| Clear cell central mucoepidermoid carcinoma | Clear cells arranged in microcysts and nests<br>Focal areas containing mucus, intermediate, and epidermoid cells | Histochemical:<br>PAS (+), diastase sensitive<br>Mucicarmine (+)<br>IHC:<br>Pancytokeratin (+)<br>CK 7 (+)<br>CK 8 (+)<br>CD 10 (−)<br>CK 19 variable<br>Molecular:<br>*MAML2* rearrangements (11q21) in 50–70% |
| Clear cell renal cell carcinoma | Organoid sheets and/or alveolar nests of bland clear cells<br>Cells with central nucleus and abundant clear cytoplasm<br>Prominent and abundant small vessels within thin connective tissue septations surrounding tumor nests<br>Focal hemorrhage<br>Pleomorphism, mitotic figures, conspicuous nucleoli, and necrosis rarely identified | PAS (+), diastase sensitive<br>Mucicarmine (−)<br>IHC:<br>CK 18 (+)<br>PAX8 (+)<br>CD10 (+)<br>RCC (+)<br>Carbonic anhydrase IX (+)<br>CK 7 variable<br>CK 5/6 (−)<br>CK 20 (−) |

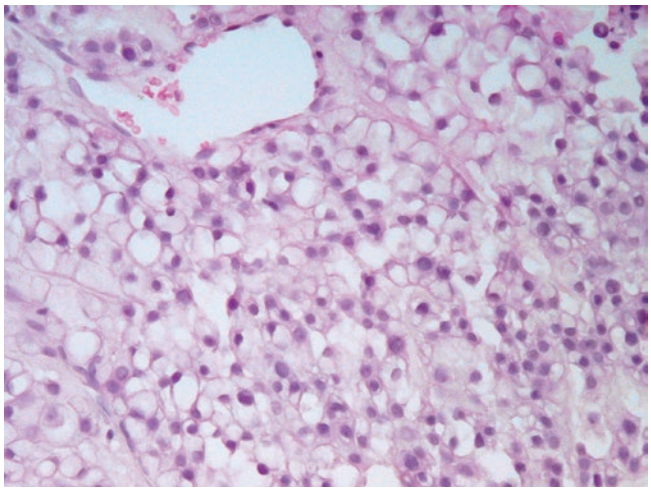

**Fig. 6.16** Clear cell (odontogenic) carcinoma. The monophasic neoplastic cells exhibit optically clear cytoplasm and no evidence of duct formation, mucous cells, ghost cells, amyloid, or significant atypia

**Table 6.11** Features of squamous odontogenic tumor

| Clinical features | Radiographic features | Histologic features |
|---|---|---|
| No sex predilection | Characteristic triangle-shaped radiolucency with base between tooth apices | Islands and cords of squamous epithelium, variable in shape and size |
| Wide age range | Destruction of the alveolar crest | Bland cytological features with few scattered mitosis in the basal layer |
| Present as a localized periodontal defect with swelling of the alveolus and/or tooth mobility | May cause root divergence | Microcysts, ghost cell-like aggregates, keratin pearls, and intracellular keratinization may be present |
| Cases of synchronous lesions in multiple quadrants described | Severe bone loss may cause "floating teeth" appearance | Moderately cellular collagenous stroma |

The histologic mimickers of squamous odontogenic tumor include squamous cell carcinoma and acanthomatous ameloblastoma. The differentiating features of each are compared in Table 6.12.

References: [69, 70]

31. *What histologic features differentiate an ameloblastic fibroma from ameloblastic fibro-odontoma and ameloblastic fibrosarcoma?*

These lesions represent neoplastic proliferations of both the ectomesenchymal and epithelial components of odontogenesis. Ameloblastic fibroma and ameloblastic fibro-odontoma only vary by the presence of dentinoid or tooth-forming matrix in the stroma. Ameloblastic

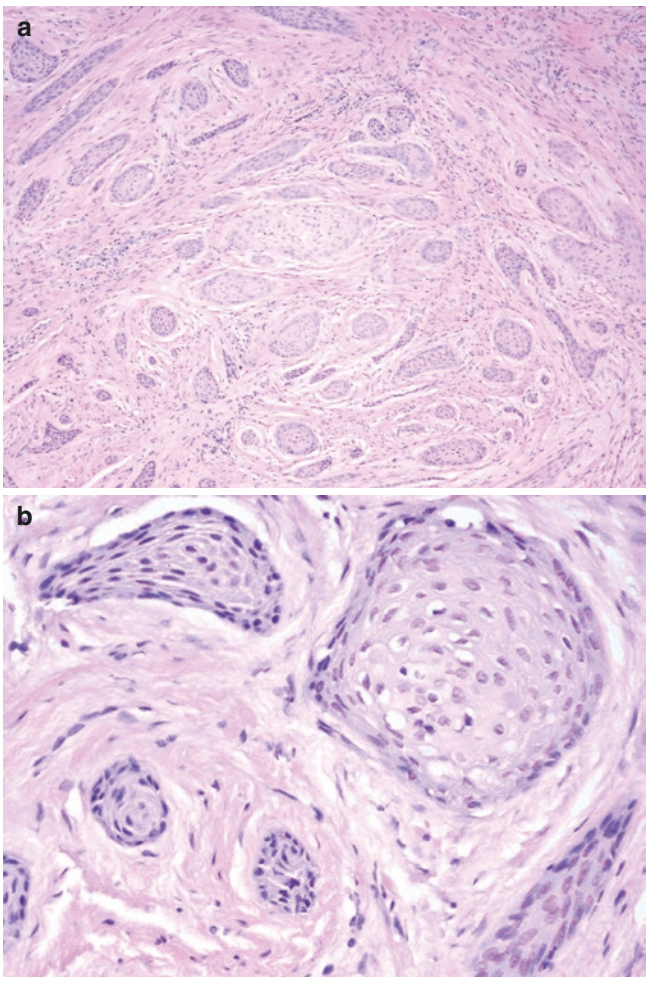


**Fig. 6.17** Squamous odontogenic tumor. (**a**, **b**) Note the evenly distributed islands of bland squamous cells with no evidence of Vickers-Gorlin features, mucous cells, ghost cells, or atypia

**Table 6.12** Comparison of histological features of squamous odontogenic tumor, squamous cell carcinoma, and ameloblastoma

| | |
|---|---|
| Squamous odontogenic tumor | Bland epithelial islands and cords<br>Scattered mitotic figures in the basal layer, none atypical<br>Moderately collagenous stroma<br>Minimal inflammatory response<br>No palisading or polarization of the basal layer |
| Squamous cell carcinoma | Invasive epithelial islands, nests, cords, or single cells, usually arising from surface epithelium<br>Marked cytological atypia and pleomorphism<br>Frequent mitotic figures, often atypical<br>Intense inflammatory response often elicited<br>Necrosis, perineural invasion, and lymphatic invasion may be identified |
| Ameloblastoma | Islands of ameloblastic epithelium with hyperchromatism, palisading, and polarization of the basal layer<br>Stellate reticulum-like cells identifiable within islands |

fibrosarcoma is the malignant counterpart to these lesions. See Table 6.13 for a histological comparison.

References: [71, 72]

32. *What is the differential diagnosis of a myxomatous lesion of the jaws?*

Myxomatous lesions of the jaw include benign and malignant processes, and the differential diagnosis varies based on patient demographics, clinical presentation, and radiographic findings. These features are summarized in Table 6.14.

Occasionally, a dental papilla may be submitted with an odontoma, impacted tooth, or in isolation. Clinicopathologic correlation is important to prevent over-interpretation.

References: [73–80]

33. *What are the clinical, gross, and histologic differences between a complex odontoma and a compound odontoma?*

Odontomas are considered by many to be hamartomatous lesions of aberrant odontogenesis. They are subtyped into complex and compound variants, which are detailed in Table 6.15.

Reference: [81]

34. *What odontogenic neoplasms have peripheral variants and how do the behaviors of central and peripheral lesions differ?*

Ameloblastomas, calcifying cystic odontogenic tumor, dentinogenic ghost cell tumor, adenomatoid odontogenic tumor, and odontogenic fibromas have peripheral variants. The peripheral variants are benign, without propensity for aggressive behavior or recurrence.

Reference: [30]

35. *What lesions with a predominant fibrous component occur within the jaws?*

Fibrous lesions that occur within the jaws include odontogenic fibromas, desmoplastic fibromas, sclerosing odontogenic carcinoma, and desmoplastic ameloblastoma. Sclerosing odontogenic carcinoma is a recently characterized, low-grade malignancy with characteristic perineural invasion. The *EWSR1* rearrangement, characteristic of clear cell odontogenic carcinoma, is absent in sclerosing odontogenic carcinoma.

**Table 6.13** Comparison of histological features of ameloblastic fibroma, ameloblastic fibro-odontoma, and ameloblastic sarcoma

| | |
|---|---|
| Ameloblastic fibroma | Islands and cords of varying sizes of odontogenic epithelium<br>Some islands demonstrate ameloblastoma-like features and meet Vickers-Gorlin criteria (see question 23)<br>Richly cellular stroma of loose, primitive-appearing connective tissue resembling dental papilla<br>A cell-free zone is often identified at the epithelium and connective tissue interface, See Fig. 6.18 |
| Ameloblastic fibro-odontoma | Identical features to ameloblastic fibroma but with the production of amorphous conglomerates of dentin and/or enamel |
| Ameloblastic fibrosarcoma | Identical to the ameloblastic fibroma but with features of malignancy in the mesenchymal component, including high numbers of mitotic figures and pleomorphism. Approximately 50% arise from ameloblastic fibromas |

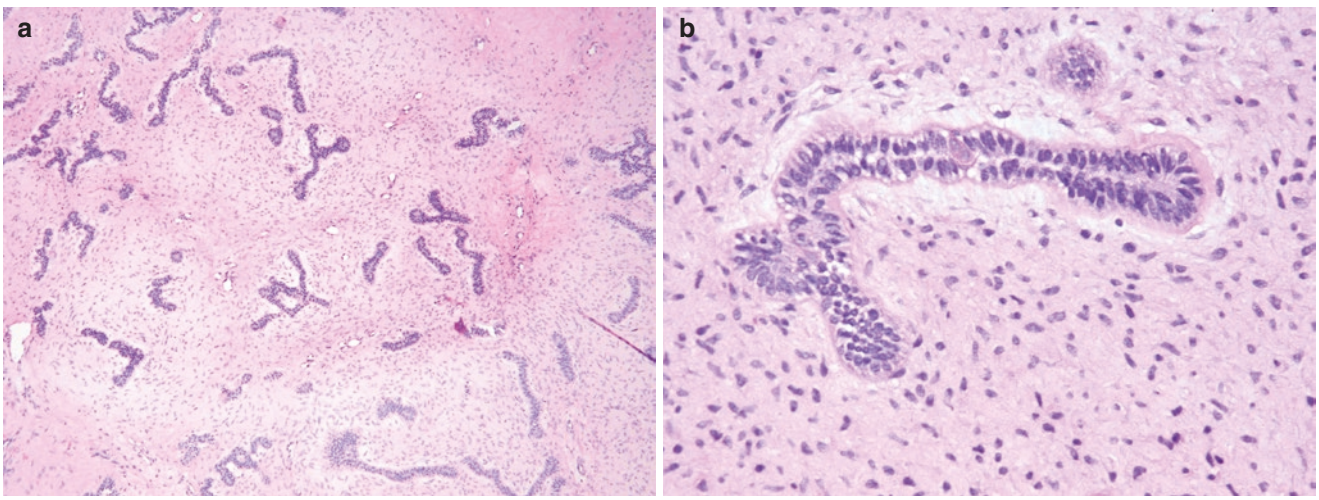


**Fig. 6.18** Ameloblastic fibroma. (**a**) A mixture of bland mesenchymal stroma with myxoid characteristics supports thin cords and small islands of ameloblastic epithelium. (**b**) The ameloblastic epithelial cords and islands do not develop cystic changes or any of the other variants of ameloblastoma such as acanthomatous, basaloid, desmoplastic, or granular changes

**Table 6.14** Features of myxomatous lesions of the jaws

| Lesion | Clinical findings | Radiographic findings | Histologic findings | Ancillary studies |
|---|---|---|---|---|
| Primordial odontogenic tumor | Primarily children, no sex predilection<br>Asymptomatic bony swelling<br>Mandible most frequently affected | Radiolucent<br>Well-defined<br>Associated with impacted tooth | Loose primitive connective resembling dental papilla<br>Haphazard stellate to spindled cells with dark nuclei and minimal cytoplasm<br>Periphery of simple, ameloblastic columnar epithelium with palisading and reverse nuclear polarization and invaginations into the underlying mesenchymal tissue | IHC<br>Ectomesenchymal cells<br>Vimentin (+)<br>SMA variable<br>Epithelial cells<br>CK 5(+)<br>CK 14(+)<br>CK 19(+) |
| Odontogenic myxoma (Fig. 6.8) | Wide age range, no sex predilection<br>Mandible and maxilla equally affected<br>Presents as painless swelling or incidental radiographic finding | Radiolucent<br>Multilocular with "soap bubble" or "honey combed" appearance | Haphazard arrangement of stellate to spindled ectomesenchymal cells<br>Few collagen fibrils<br>Rare rests of odontogenic epithelium<br>See Fig. 6.19 | Vimentin (+)<br>Beta-catenin (+)<br>S100 (−)<br>Negative muscle markers |
| Embryonal rhabdomyosarcoma | Primarily children<br>Slight male predominance<br>Rapidly enlarging masses with or without pain, paresthesia, trismus, facial palsy, or nasal drainage | Radiolucent<br>Irregular borders<br>Destruction of tissue planes | Proliferation of primitive cells resembling stages in developing fetal skeletal muscle<br>Variable hypercellular and paucicellular zones<br>Scattered stellate, round, and spindled cells<br>Mononuclear giant cells with large nuclei may be present<br>Occasional cells with striations may be identified | Immunohistochemistry<br>Myogenin (+)<br>MyoD1 (+)<br>Desmin (+)<br>Molecular<br>Complex genetic changes including a an allelic loss at of the 11p15.5 locus |

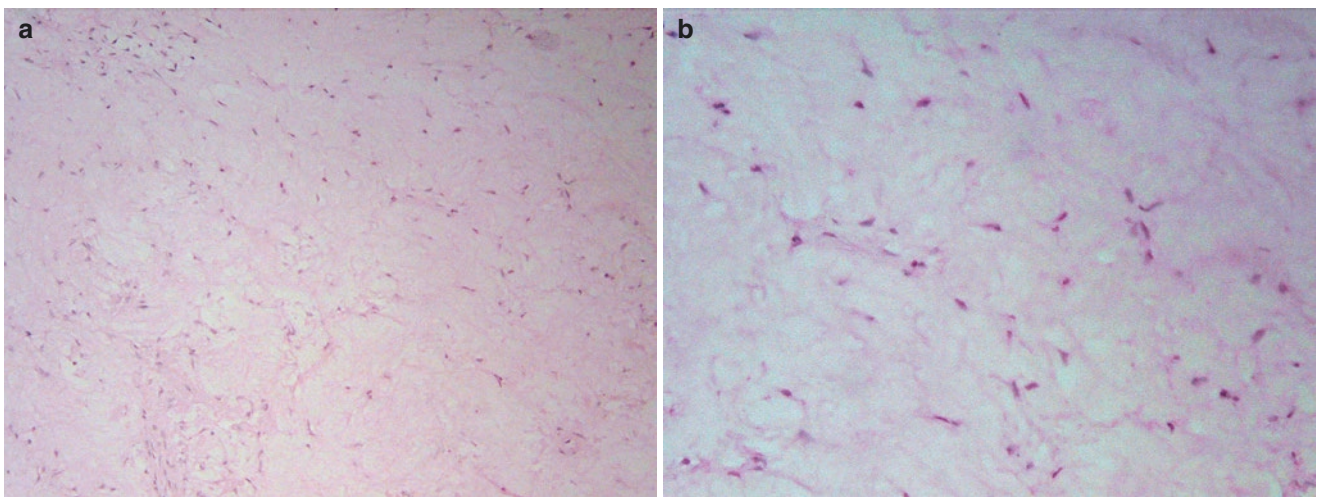


**Fig. 6.19** Odontogenic myxoma. (**a**, **b**) A bland myxoid stroma with none or minimal inactive odontogenic rests and no atypia

A comparison of the odontogenic fibroma, desmoplastic fibroma, and sclerosing odontogenic carcinoma is presented in Table 6.16.

Desmoplastic ameloblastoma is further discussed in question 24.

Rarely, other soft tissue lesions with fibrous components may occur within the jaws, including myofibroma and neurofibroma. Bone-producing fibrous lesions are discussed in questions 36 through 39.

References: [30, 32, 33, 82–85]

36. *What is a benign fibro-osseous lesion and what entities fall into this category?*

The term benign fibro-osseous lesion is a histologic descriptor of a process whereby normal bone is replaced with proliferations of fibrous tissue and the bone in varying stages of osteogenesis.

The etiologies of these entities differ. Ossifying fibromas are neoplastic. Fibrous dysplasia is caused by a post-zygotic *GNAS1* mutation and may be associated with syndromes, most notably McCune-Albright syn-

**Table 6.15** Features of compound and complex odontomas

| | Clinical features | Gross features | Histologic features |
|---|---|---|---|
| Compound odontoma | No sex predilection<br>Most commonly diagnosed in second decade<br>Most common in anterior maxilla<br>Often incidental finding<br>May prevent eruption of a permanent tooth | Multiple small, malformed "tootlets" with identifiable crown and root structures<br>See Fig. 6.20 | Enamel, dentin, and cementum layers arranged in a tooth-like configuration with an identifiable central pulp chamber<br>Small divergences from normal may be identified<br>Associated soft tissue may comprise a hyperplastic dental follicle or dentigerous cyst, ghost cells, or calcifying odontogenic cyst |
| Complex odontoma | No sex predilection<br>Most commonly diagnosed in second and third decades<br>Most common in posterior mandible<br>Often incidental finding<br>May prevent eruption of a permanent tooth | Dense, roughly spherical hard tissue mass | Haphazard conglomerate of cementum and dentin<br>Enamel prisms may be identified but are often lost during decalcification<br>Occasional spaces within the hard tissues contain loose connective tissue of the pulp<br>Peripheral tissues may contain simple columnar ameloblastic epithelium and/or mesenchymal tissue representative of the dental follicle and/or papilla<br>May contain ghost cells and/or association with a calcifying odontogenic cyst |

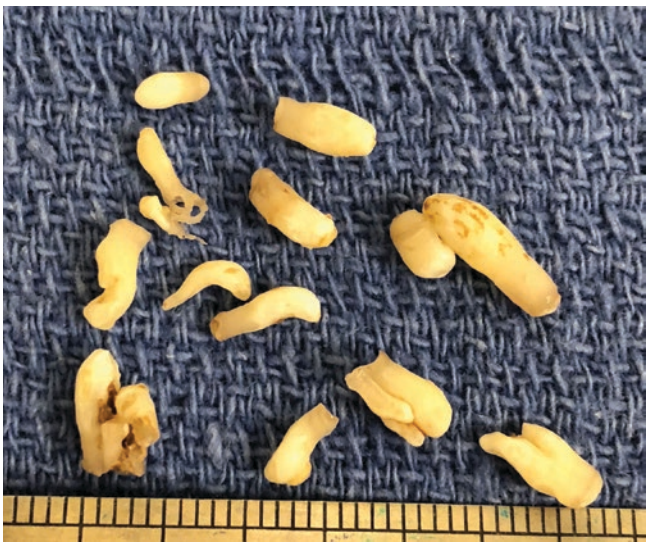

**Fig. 6.20** Compound odontoma. A compound odontoma consists of multiple tooth-like structures that each exhibit morphologic features recognizable as parts of a normal tooth, such as roots, crowns with cusps and grooves, and dental follicles if included. Contrasting from complex odontoma (not shown) which would consists of amorphous masses of dental components with no recognizable anatomy. Both types of odontoma may contain all types of dental tissue microscopically; the difference between each other is the morphology of a tooth in each piece of compound odontoma and the lack of it in complex odontoma

drome. The etiologies of the cemento-osseous dysplasias are not well-defined.

Cemento-osseous dysplasia is exclusive to the jaws and ossifying fibromas to the jaws and craniofacial bones. Fibrous dysplasia may be monostotic or polyostotic and commonly affects the craniofacial bones as well as the femur, ribs, and others.

References: [86, 87]

37. *What are the key clinical, radiographic, and histologic differences between conventional ossifying fibroma, fibrous dysplasia, and cemento-osseous dysplasia?*

Due to overlapping histologic features between the benign fibro-osseous lesions, the importance of clinical and radiographic correlation in determining the correct diagnosis cannot be overstated. Furthermore, the temporal radiographic and histologic evolution of these lesions adds complexity to these diagnoses. See Table 6.17 for a comparison of these lesions.

References: [86–88]

38. *What are the clinical, radiographic, and histologic differences between the variants of ossifying fibroma?*

The aggressive variants of ossifying fibroma tend to be diagnosed earlier in life than the conventional ossifying fibroma, usually under the age of 30. While benign, they present with rapid progression with the capacity for displacement and/or destruction of adjacent structures. The two subtypes, trabecular and psammomatoid, differ by age demographics, location, and histopathological features (Table 6.18).

References: [86, 88, 89]

39. *What is the clinical, radiographic, and histologic presentation of a cementoblastoma and how is this entity differentiated from benign fibro-osseous lesions?*

Cementoblastomas are rare mesenchymal odontogenic tumors. They are most commonly diagnosed in the second and third decades of life, without sex predilection. The mandibular premolars and molars are most commonly affected. Pain, mimicking that of an odontogenic infection, is a frequent symptom; however, the tooth is characteristically vital without evidence of gross caries.

Radiographically, these lesions appear as a well-defined roughly spherical radiopaque mass attached to

**Table 6.16** Comparison of select fibrous lesions of the jaws

| Entity | Description | Radiographic features | Histologic features |
|---|---|---|---|
| Odontogenic fibroma | Rare odontogenic mesenchymal neoplasm<br>Occurs in adults<br>Approximately equal distribution between the jaws | Usually unilocular<br>Well-defined<br>Corticated borders | Fibrous connective tissue with fusiform or stellate fibroblasts<br>Variably density of collagen, often with blue-hued fibromyxoid areas<br>Variable amounts of odontogenic epithelial islands<br>See Fig. 6.21 |
| Desmoplastic fibroma | Locally aggressive with propensity for recurrence<br>Considered intraosseous counterpart to soft tissue fibromatosis<br>Wide age range<br>Most common in the posterior mandible | Unilocular or multilocular<br>Ill or well-defined<br>Variable marginal sclerosis<br>May perforate the cortex | Paucicellular, non-encapsulated proliferation of fibrous connective tissue<br>Variable density of collagen fibers<br>Bland fibroblastic cells without atypia |
| Sclerosing odontogenic carcinoma | Exceedingly rare, described only in case reports<br>Considered a low-grade malignancy without metastatic potential | Not well characterized | Prominent dense, sclerotic stroma harbors neoplastic odontogenic epithelial cells<br>Cells are polygonal with pale cytoplasm<br>Thin cords infiltrate between collagen bundles<br>Perineural invasion and extent beyond surgical margins is common |

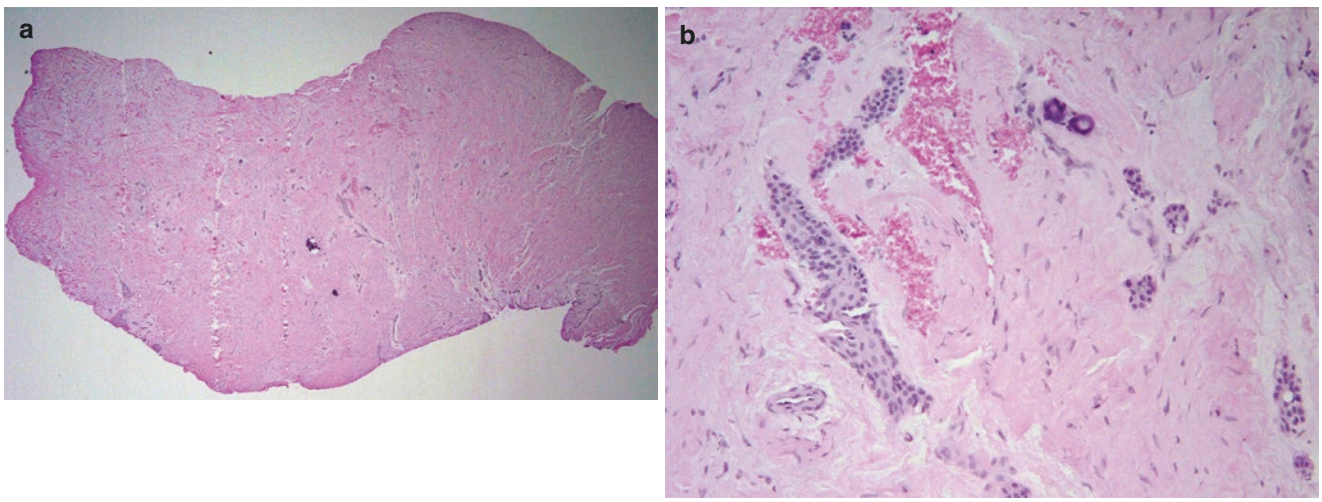


**Fig. 6.21** Odontogenic fibroma. (**a**) This solid neoplasm is supported by a collagenous matrix with no evidence of amyloid formation and contains inactive odontogenic rests with no Vickers-Gorlin features of ameloblastoma nor ghost cell formation. (**b**) Occasional calcifications are seen

**Table 6.17** Features of benign fibro-osseous lesions

| | Clinical features | Radiographic features | Histologic features |
|---|---|---|---|
| Ossifying fibroma, conventional | Male-to-female ratio 1:2.5<br>Most commonly diagnosed in third and fourth decades<br>Most common in the mandible<br>Often incidental finding or painless swelling | Well-circumscribed, unilocular<br>Mixed density with increasing internal radiopacities over time<br>Central contents surrounded by a radiolucent halo<br>May displace adjacent structures including teeth, the inferior alveolar nerve, and bony cortices | Hypercellular stromal proliferation of spindled fibroblasts<br>Interspersed trabeculae of woven bone and cementoid calcifications<br>Calcifications show brushed borders and prominent osteoblastic rimming<br>Rare to absent mitotic figures, no cellular pleomorphism<br>See Fig. 6.22 |

(continued)

**Table 6.17** (continued)

| | Clinical features | Radiographic features | Histologic features |
|---|---|---|---|
| Fibrous dysplasia | No sex predilection<br>Most often diagnosed in the second and third decades, syndromic cases may present earlier<br>Most commonly affects the maxilla<br>Presents as a progressive facial asymmetry | Ill-defined with margins blending into the normal adjacent bone<br>Early lesions may be predominantly radiolucent with progression to a "ground class" diffuse opacity<br>Cortices become thinned and expanded<br>Adjacent structures may be displaced | Stroma of spindled fibroblasts and numerous blood vessels<br>Variable amounts and sizes of immature bony trabeculae<br>"Chinese script" shaped trabeculae<br>Osteoblastic rimming is generally absent<br>artifactual clefting between trabeculae and stroma<br>Lamellar maturation may be identified with long standing<br>Rare to absent mitotic figures, no cellular pleomorphism |
| Cemento-osseous dysplasia | Female predilection<br>Most commonly diagnosed in middle age<br>All variants most commonly affect those of African and Asian descent, most strikingly the florid variant<br>Presents as an incidental finding | Radiographic presentation varies with lesional stages<br>Initial appearance is a periapical radiolucency. Increasing amounts of internal radiopacities are seen with lesional progression. At the end stage, a sclerotic radiopaque mass is surrounded by a radiolucent rim outside of which is thin, sclerotic bone<br>Florid: lesions identified in multiple quadrants<br>Periapical: lesions identified at periapex of multiple teeth, usually mandibular anterior<br>Focal: solitary lesion usually at the apex of a mandibular molar | All subtypes show identical histological features:<br>Early stage: variably cellular fibrous stroma with scant calcification. Focal hemorrhage<br>Mid-stage: Increased trabeculae resembling "ginger roots" and/or spherules of calcifications. Rest and reversal lines may be present. Osteoblastic rimming is not prominent<br>Late stage: Sclerotic coalesced masses of lamellar bone with little fibrous stroma<br>See Fig. 6.23 |

the apex or lateral root of a tooth. A radiolucent halo surrounds the mass.

Histologically, sheets of cementum-like tissue with prominent rest and reversal lines are punctuated with spaces containing loose fibrous connective tissue. Cementoblasts border the hard tissues, and occasional cementocytes in lacunae are identified. Continuity with the cementum of the root surface is apparent.

These lesions may show histologic and radiographic overlap with the sclerotic form of cemento-osseous dysplasia and/or osteoblastoma; however the clear relationship with the tooth root is distinguishing for a cementoblastoma diagnosis.

References: [90, 91]

40. *How are osteoid osteomas and osteoblastomas differentiated?*

These lesions overlap in demographic predilection and histologic presentation. Both affect young males, under the age of 30. The overlapping histologic features include:

- A nidus of woven bony trabeculae deposited in lace-like or sheet configurations
- Plump osteoblasts line the bony trabeculae
- Woven bone often displays a purple or blue hue
- Occasional scattered osteoclasts
- Peripheral loose connective tissue separates the nidus from the surrounding bone
- Abundant congested vessels and focal hemorrhage

The key differentiating factor is lesional growth potential. Whereas osteoid osteomas are less than 2 cm, osteoblastomas usually range from 2 to 5 cm, with rare cases documented over 10 cm.

Clinical presentation and location also vary. Osteoid osteomas characteristically present with nocturnal pain, disproportionate to the size of the lesion, which is relieved by NSAIDs. They are more common in the femur and tibia. Osteoblastomas are associated with a more irritating, constant pain and are more common in the spine. Both are rare in the craniofacial bones.

References: [92, 93]

41. *How are osteosarcomas of the jaws distinct from osteosarcomas of the extra-gnathic skeleton?*

Approximately 6% of osteosarcomas arise in the jaws. These lesions display demographic and behavioral differences from extra-gnathic osteosarcomas. Both gnathic and extra-gnathic osteosarcomas display a bimodal age distributions with second peaks in the sixth decades; however, the first peak is in the second decade for the extra-gnathic variants, while gnathic osteosarcomas tend to occur in the third and fourth decades, approximately a decade later.

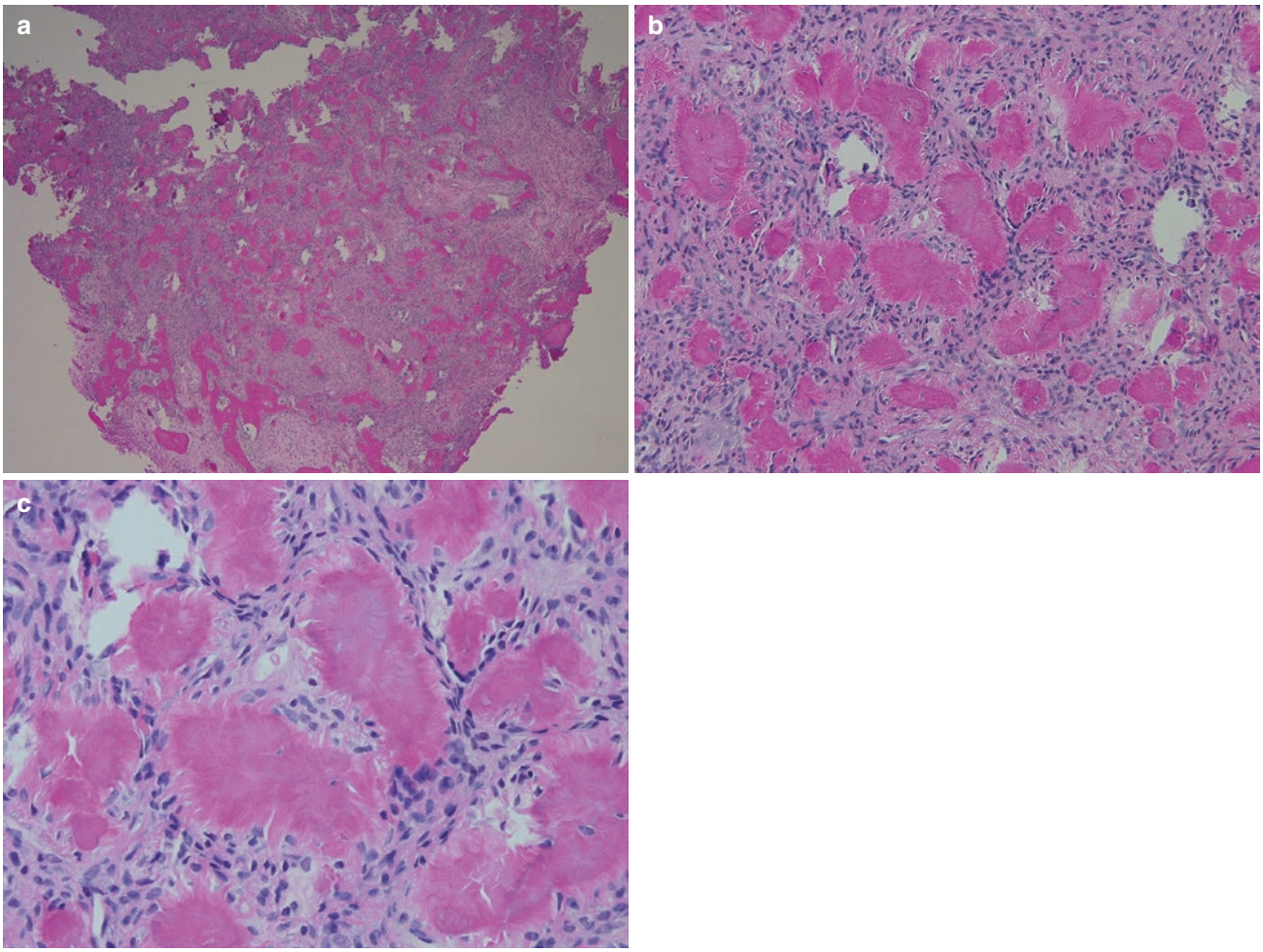


**Fig. 6.22** Central ossifying fibroma. (**a**–**c**) This solid mesenchymal neoplasm is supported by a dense collagenized stroma with hypercellularity but no atypia. The nuclei exhibit ovoid to spindle shape. Admixed within the stroma are areas of ossification and dystrophic-type calcification or psammomatoid calcification. The calcified component shows a brushed border effect and osteoblastic rimming

Whereas extra-gnathic osteosarcomas are aggressive with metastasis at diagnosis in 85–90% of cases, approximately 20% of jaw lesions metastasize on average 2 years after diagnosis. Extra-gnathic osteosarcomas are sensitive to chemotherapy, with overall survival rates in the 70–80+% range. Response to chemotherapy is the main predictive factor of survival outcome. In contrast, the response of gnathic osteosarcomas to chemotherapeutic agents is unclear, and margin status is the main predictor of outcome. The overall survival rate is approximately 65%.

References: [94–97]

42. *How are osteosarcomas differentiated from other bony lesions of the craniofacial skeleton?*

The majority of head and neck osteosarcomas are high grade, making their diagnosis less equivocal; however, this question may arise when deliberating a benign fibro-osseous lesion versus a low-grade osteosarcoma. The clinicopathologic picture is of importance. Histologic or radiographic evidence of an infiltrative, bone-producing lesion is considered the most reliable method of distinction.

Molecular studies have identified the presence of supernumerary ring chromosomes in low-grade osteosarcomas, leading to amplifications of *MDM2* and *CDK4*. Studies of low-grade osteosarcomas show these amplifications to be present using immunohistochemical means of detection, while benign fibro-osseous lesions are nonreactive. However, additional investigations have shown amplification of *MDM2* in fibro-osseous lesions by qRT-PCR, and immunohistochemical studies are not currently considered to be reliable in distinguishing these lesions.

References: [94, 96]

43. *What are differentiating factors between chondroblastic osteosarcoma and chondrosarcoma?*

The differentiation between these two malignancies is challenging and important, as approximately 40% of gnathic osteosarcomas are of the chondroblastic subtype. The key differentiating factor to separate a chon-

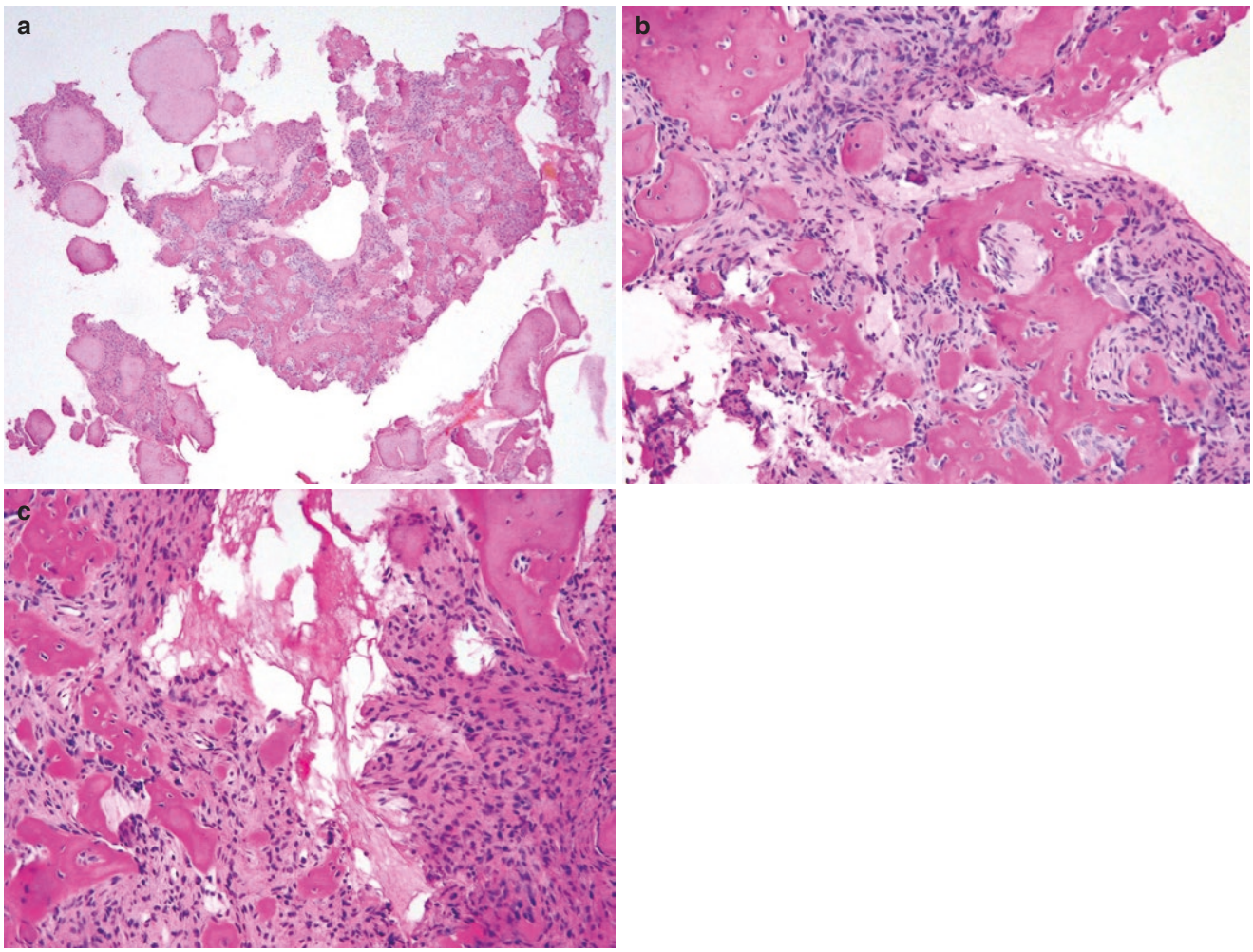


**Fig. 6.23** Focal cemento-osseous dysplasia. (**a**) The lesion is usually removed in multiple small pieces that include dense sclerotic bone, woven bone, and fibrous stroma with evidence of extravasated blood. (**b**, **c**) The collagenized stroma supports a spindle cell population of fibroblastic cells. No significant osteoblastic rimming of the calcified component nor "brush border" effect is seen

**Table 6.18** Features of the aggressive ossifying fibromas

| | Clinical features | Radiographic features | Histologic features |
|---|---|---|---|
| Ossifying fibroma, aggressive trabecular | Male predilection<br>Most commonly diagnosed at ages 8–12 years<br>Most common in the maxilla<br>Present as progressive and sometimes rapid facial asymmetry with obstructive effects depending on location | Well-defined borders<br>Mixed internal density without radiolucent halo<br>May display "ground glass" internal contents<br>May cause expansion and destruction of surrounding structures<br>May cause displacement and/or root resorption of teeth | Hypercellular stroma of spindled fibroblasts<br>Anastomosing trabeculae of woven bone<br>Prominent rimming of plump osteoblasts around trabeculae with osteocytes in lacunae<br>Unencapsulated, with infiltration and destruction of surrounding bone<br>Occasional mitotic figures, none atypical. No cellular pleomorphism<br>Infrequently associated with aneurysmal bone cysts |
| Ossifying fibroma, aggressive psammomatoid | Slight male predilection<br>Wide age range of diagnosis, mean 17 years<br>Most common in the orbital bones and paranasal sinuses<br>Presents as progressive and sometimes rapid facial asymmetry with obstructive effects depending on location | Well-defined borders<br>Mixed internal density without radiolucent halo<br>May display "ground glass" internal contents<br>May cause expansion and destruction of surrounding structures | Hypercellular stroma of spindled fibroblasts<br>Spherical droplets of cementum-like osteoid, not uniform in size, showing concentric calcification<br>Largely free of osteocytes in lacunae<br>Droplets may coalesce and be mixed with immature trabeculae<br>Unencapsulated, with infiltration and destruction of surrounding bone<br>May be associated with aneurysmal bone cysts |

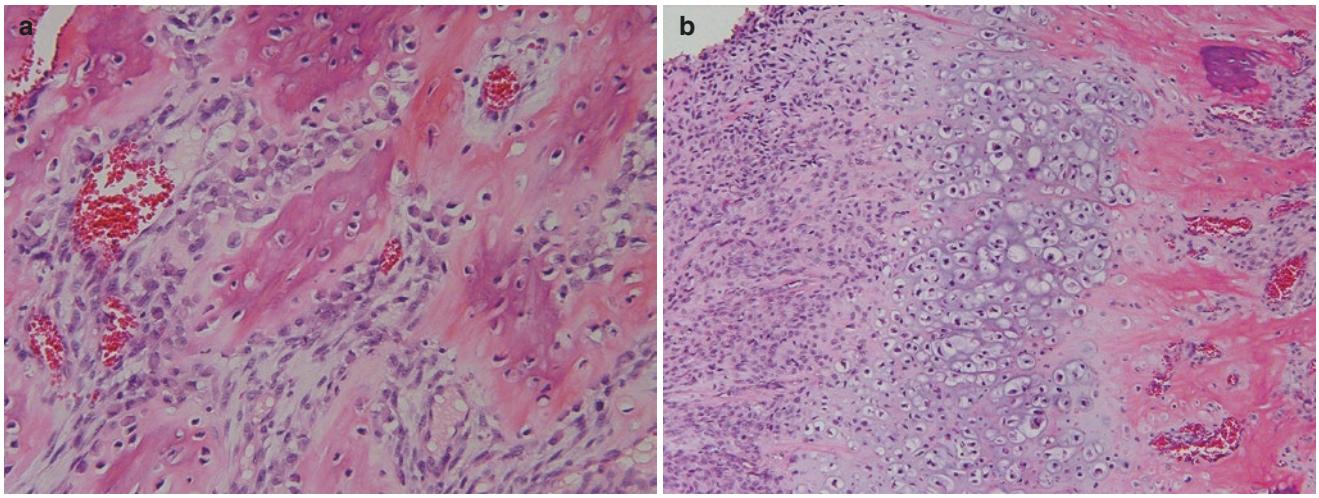


**Fig. 6.24** Chondroblastic osteosarcoma. (**a**) The immediate production of osteoid by the malignant mesenchymal cells is the hallmark of osteosarcoma of the jaws. (**b**) Some chondroblastic osteosarcomas of the jaws will have a significant chondroid component; however, a thorough evaluation yields evidence of direct osteoid formation by the malignant mesenchymal stroma

droblastic osteosarcoma from a chondrosarcoma is the definitive production of osteoid from epithelioid or spindled cells (Fig. 6.24a). Other supportive factors are grade and location. The majority of chondrosarcomas in the gnathic regions are low-grade. High-grade cartilage-producing malignancies, especially of the mandibular body, are most likely chondroblastic osteosarcomas (Fig. 6.24b).

Reference: [96]

44. *How is a chordoma differentiated from a chondrosarcoma?*

Chordomas are rare notochord tumors that predominately arise at the skull base and cervical spine or sacrum. They are characterized by distinct neoplastic cells, termed physaliferous cells, which contain abundant eosinophilic cytoplasm with bubbly vacuoles. Chordomas occur across a wide age range without significant sex predilection, similar to chondrosarcomas of the skull base. The chondroid chordoma subtype produces a cartilaginous matrix. Histologic features and immunohistochemical studies differentiate these neoplasms (Table 6.19).

Reference: [96]

45. *What salivary gland neoplasms may occur within the jaw bones?*

The occurrence of central salivary gland tumors within jaws is rare. Two theories on their histogenesis are proposed: (1) these tumors arise from pluripotent odontogenic rests, and (2) salivary tissue is trapped within the gnathic bones during embryogenesis. Central mucoepidermoid carcinoma is the most commonly occurring, accounting for approximately 65–70% of central salivary gland tumors. Adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma, and benign pleomorphic adenoma follow in order of decreasing frequency; however, others are reported.

**Table 6.19** Histologic and immunohistochemical comparison of chondroid chordoma and chondrosarcoma

| | Histologic features | Immunohistochemical profile |
|---|---|---|
| Chondroid chordoma | Bubbly physaliferous cells with distinct cell borders<br>Lobular arrangement with fibrous septations | Brachyury (highly specific) positive<br>Cytokeratins positive<br>EMA positive<br>S100 positive |
| Chondrosarcoma | Less abundant cytoplasm, no vacuoles<br>No lobular architecture | S100 positive<br>Variable EMA<br>Others negative |

These tumors are histologically and molecularly identical to those of the salivary glands, as proven by immunohistochemical and molecular studies. Features of salivary gland neoplasms are discussed in Chap. 5.

References: [98, 99]

## Case Presentations

### Case 1

#### Learning Objectives

1. To become familiar with the histologic features of the lesion
2. To generate a differential diagnosis and understand the distinguishing histologic features

3. To become aware of the need to correlate the clinical and radiographic features of the lesion as well as the potential for syndromic association

**Case History**

A 28-year-old male visited his dentist and a panoramic radiograph revealed a well-delineated radiolucent lesion of the right posterior mandible. No expansion of the cortical bone was detected, and the patient was asymptomatic. An incisional biopsy of the lesion was submitted.

**Gross Findings**

The specimen consisted of multiple small strips of thin soft tissue admixed with keratinaceous debris. The specimen was entirely submitted.

**Histologic Findings** (Fig. 6.25)

- The specimen consisted of an epithelial cystic lining supported by mildly inflamed connective tissue.
- The epithelium produced parakeratin on the luminal surface and the luminal cells exhibit a slightly corrugated architecture. No orthokeratin is identified.
- The basal cells of the epithelium are cuboidal and show mild hyperchromatism and are aligned along the basement membrane but lack polarization away from it.
- No significant rete peg formation is seen.

**Differential Diagnosis**

- Dentigerous cyst
- Periapical cyst
- Lateral periodontal cyst
- Glandular odontogenic cyst
- Calcifying cystic odontogenic tumor

**IHC and Other Ancillary Studies** (See Fig. 6.11d–f)

- Not necessary nor helpful

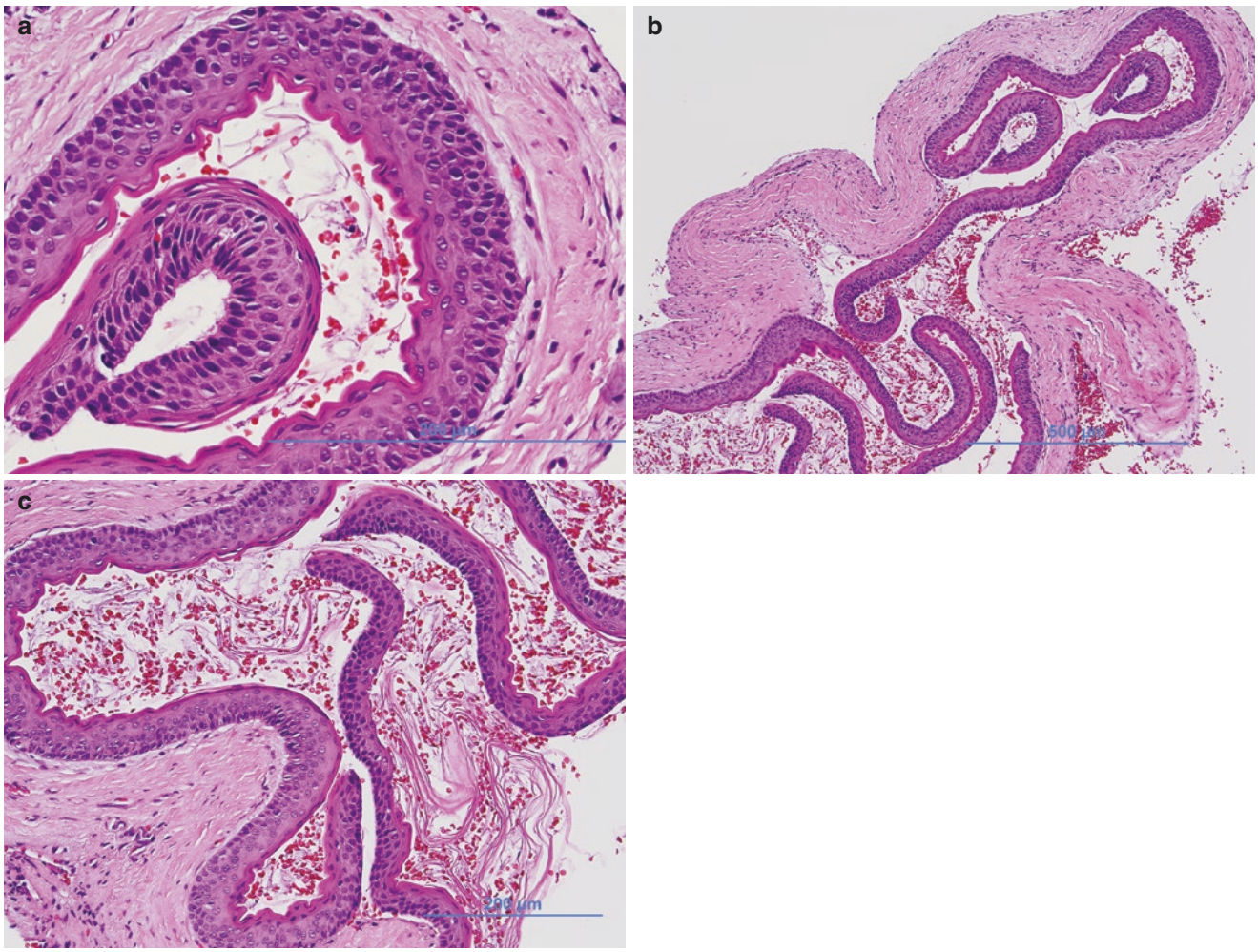


**Fig. 6.25** (**a**–**c**) Odontogenic keratocyst

**Final Diagnosis** *Odontogenic keratocyst*

**Take-Home Messages**

1. The histopathology of odontogenic keratocyst is pathognomonic, and if the features are there, the diagnosis is straightforward. With significant inflammation in the cyst, the typical features are lost, and the diagnosis may be impossible.
2. Odontogenic keratocyst is a benign cystic "neoplasm" associated with *PTCH1* gene mutations.
3. Multiple lesions are associated with nevoid basal cell carcinoma syndrome in some patients.
4. It has a relatively higher recurrence rate than other odontogenic cysts.
5. If orthokeratin is seen in the luminal side, the diagnosis of orthokeratinizing odontogenic cyst is more appropriate, and the recurrence rate is lower.
6. If marsupialization has been attempted, the histologic features are lost, and the epithelium looks like that of a nonspecific cyst lined by stratified squamous epithelium.

References: [100–105]

## Case 2

**Learning Objectives**

1. To become familiar with the clinical, radiographic, and histologic features of the tumor
2. To generate the differential diagnosis

**Case History**

A 45-year-old female presented with a left mandible expansive mass. A panoramic radiograph revealed a 5-cm mixed radiolucent and radiopaque lesion with mild cortical perforation. All the teeth in the area are vital and asymptomatic. An incisional biopsy of the lesion was performed.

**Gross Findings**

The specimen consists of multiple strips of cystic epithelium with calcified luminal accretions. The specimen was entirely submitted.

**Histologic Findings** (Fig. 6.26)

- The cyst is comprised of a connective tissue wall and luminal odontogenic epithelium.
- The epithelium exhibits cuboidal to columnar basal cells with hyperchromatic nuclei, some of which are polarized away from the basement membrane.
- The epithelium transitions into ghost cell-type keratinization resembling pilomatrixoma.
- The ghost cells occasionally undergo mineralization.

**Differential Diagnosis**

- Ameloblastoma
- Ameloblastic fibroma
- Odontogenic keratocyst
- Dentinogenic ghost cell tumor
- Odontoma with dental follicle

**IHC and Other Ancillary Studies**

- Not necessary

**Final Diagnosis** *Calcifying odontogenic cyst (calcifying cystic odontogenic tumor)*

**Take-Home Messages**

1. Calcifying odontogenic cyst is the cystic counterpart of dentinogenic ghost cell tumor (solid variant).
2. It exhibits histologic features very similar to pilomatrixoma.
3. The basal cells resemble ameloblastoma, but there is no microcystic change/cytoplasmic vacuoles between the nuclei and the basement membrane, and the cells are variable cuboidal to columnar, as opposed to tall columnar in ameloblastoma. Ameloblastoma does not produce ghost cells nor calcification.

References: [30, 47, 101, 106, 107]

## Case 3

**Learning Objectives**

1. To become familiar with the histologic features of the tumor
2. To generate the differential diagnosis
3. To be informed of the significant bias in age and location of this tumor

**Case History**

A 17-year-old female patient presented with failure of eruption of her upper right canine tooth. A radiograph revealed an impacted tooth in the maxilla surrounded by a well-delineated predominantly radiolucent lesion that encompassed the entire crown and portion of the root of the tooth. Small calcifications were present within the radiolucent lesion. The tooth was extracted with the associated lesion. The entire soft tissue was submitted for examination.

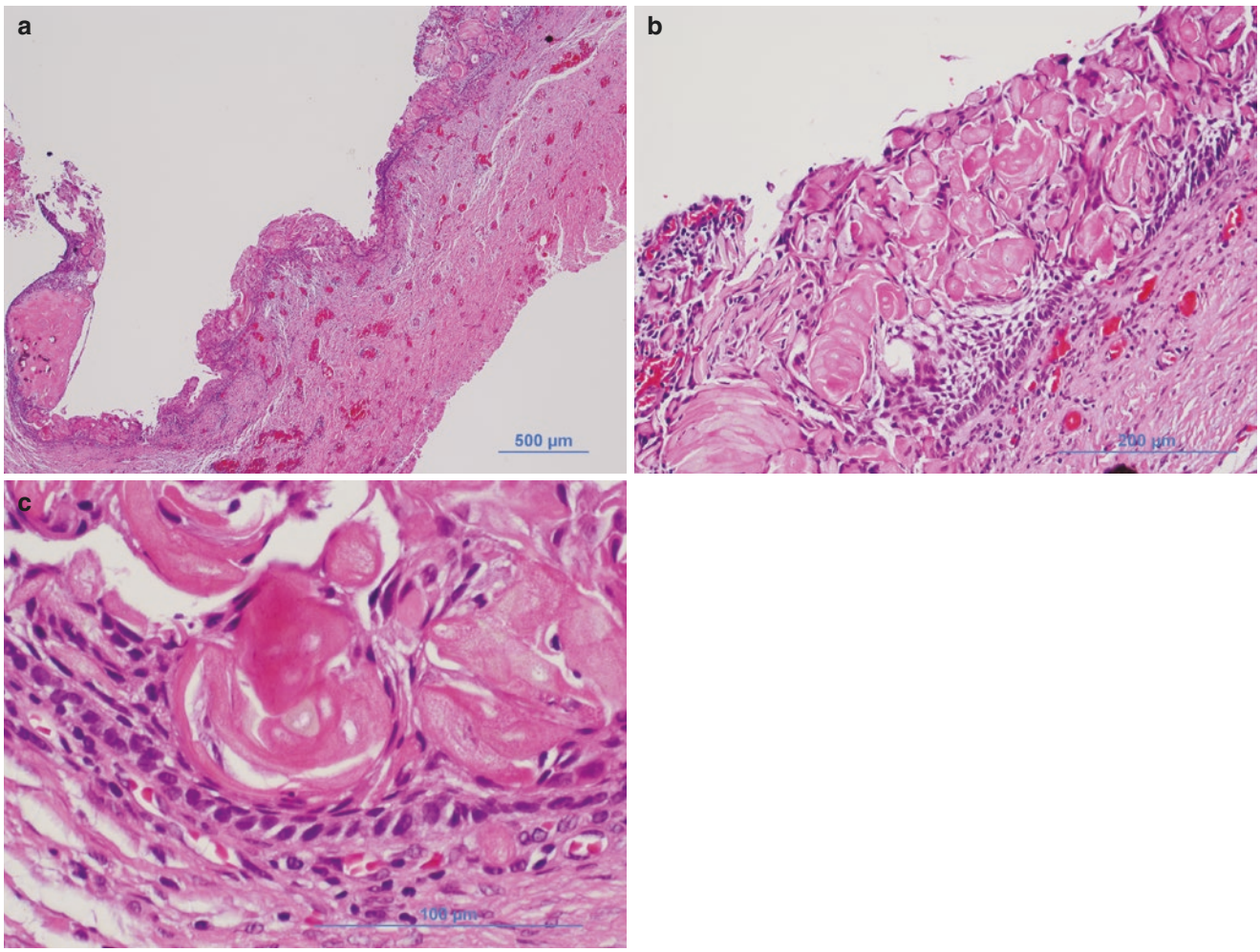


**Fig. 6.26** (**a**–**c**) Calcifying odontogenic cyst

**Gross Findings**
The specimen consisted of an intact canine tooth with a cyst associated with the crown and half of the root of the tooth. The cyst covered the entire crown and attached to the tooth midway between the cemento-enamel junction and the apex of the tooth.

**Histologic Findings** (Fig. 6.27)
- The lesion may present with an impacted tooth or not.
- If it is associated with a tooth, it may originate from the dental follicle, which may impart a cyst-like morphology, and the tumor will be an intraluminal growth.
- The neoplastic epithelial cells are arranged in either solid masses with a whorl-like morphology or in pseudocystic spaces.
- The tumor cells will form duct-like structures with a central lumen and peripheral ameloblastic-like layer of cuboidal to columnar cells, solid aggregates of cells with a central "pore"-like structure that may contain an amyloid-like material that occasionally undergoes calcification.
- No keratinization or ghost cell formation is seen.
- Atypia and mitotic figures are not identified.

**Differential Diagnosis**
- Ameloblastoma
- Calcifying cystic odontogenic tumor
- Glandular odontogenic cyst
- Calcifying epithelial odontogenic tumor

**IHC and Other Ancillary Studies**
- The cells are derived from the enamel organ or epithelial root sheath and therefore are cytokeratin positive.
- Other immunohistochemical studies are of marginal benefit if any at all.

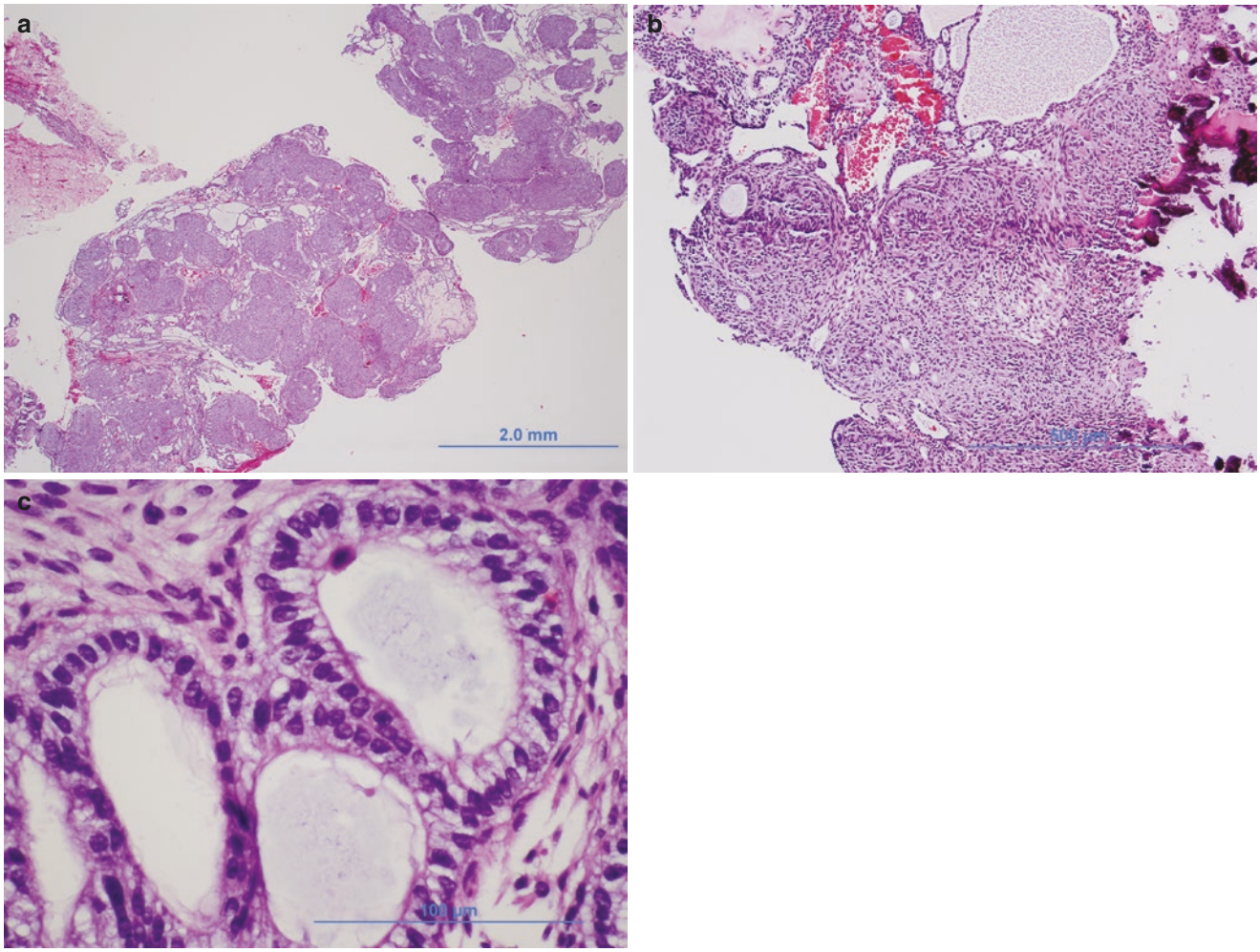


**Fig. 6.27** (**a**–**c**) Adenomatoid odontogenic tumor

**Final Diagnosis** *Adenomatoid odontogenic tumor*

### Take-Home Messages

1. Adenomatoid odontogenic tumor has a strong predilection to occur in patients between 10 and 20 years of age, most commonly in females, and associated with impacted maxillary canines. Other presentations are possible but not as common.
2. This lesion may begin as a radiolucent lesion and progress to a mixed radiolucent-radiopaque lesion due to the calcification of the amyloid-like material inside some of the epithelial nests.
3. Must be differentiated from solid ameloblastoma due to its significantly different biologic behavior and treatments.

References: [30, 108, 109]

## Case 4

### Learning Objectives

1. To become familiar with the gross histologic features of the tumor
2. To become familiar with the immunohistochemical features of the tumor
3. To evaluate potential aggressive behaviors based on histological features

### Case History

A 35-year-old male presented with an expansile, non-painful enlargement of the posterior mandible in the area of the left molars. A radiograph revealed an underlying multilocular radiolucent lesion with well-delineated margins and small areas of cortical perforation, as well as early dental root resorption. An incisional biopsy was submitted.

**Gross Findings**

A fragmented specimen measuring 1cm in aggregate was received and entirely submitted.

**Histologic Findings** (Fig. 6.28)

- The tumor consisted of islands and cords of neoplastic epithelium of odontogenic origin resembling ameloblasts/inner enamel epithelium.
- The epithelial islands had a basal cell layer with a columnar architecture, with hyperchromatic nuclei that polarized away from the basement membrane.
- Between the nuclei of the basal cells and the basement membrane, the cells exhibited intracytoplasmic vacuolization with an optically clear center. As the cells matured away from the basement membrane, they elongated and only focally connected to each other, resembling the stellate reticulum of the enamel organ.
- Few mitotic figures were present without atypical forms.

**Differential Diagnosis**

- Ameloblastic fibroma
- Adenomatoid odontogenic tumor
- Calcifying cystic odontogenic tumor
- Odontogenic keratocyst

**IHC and Other Ancillary Studies**

- Cytokeratin positive due to the enamel epithelium tissue of origin
- Focal positive reaction to calretinin in the central (spinous cell layer/stellate reticulum) area of the islands

**Final Diagnosis** *Conventional (solid/multicystic) ameloblastoma*

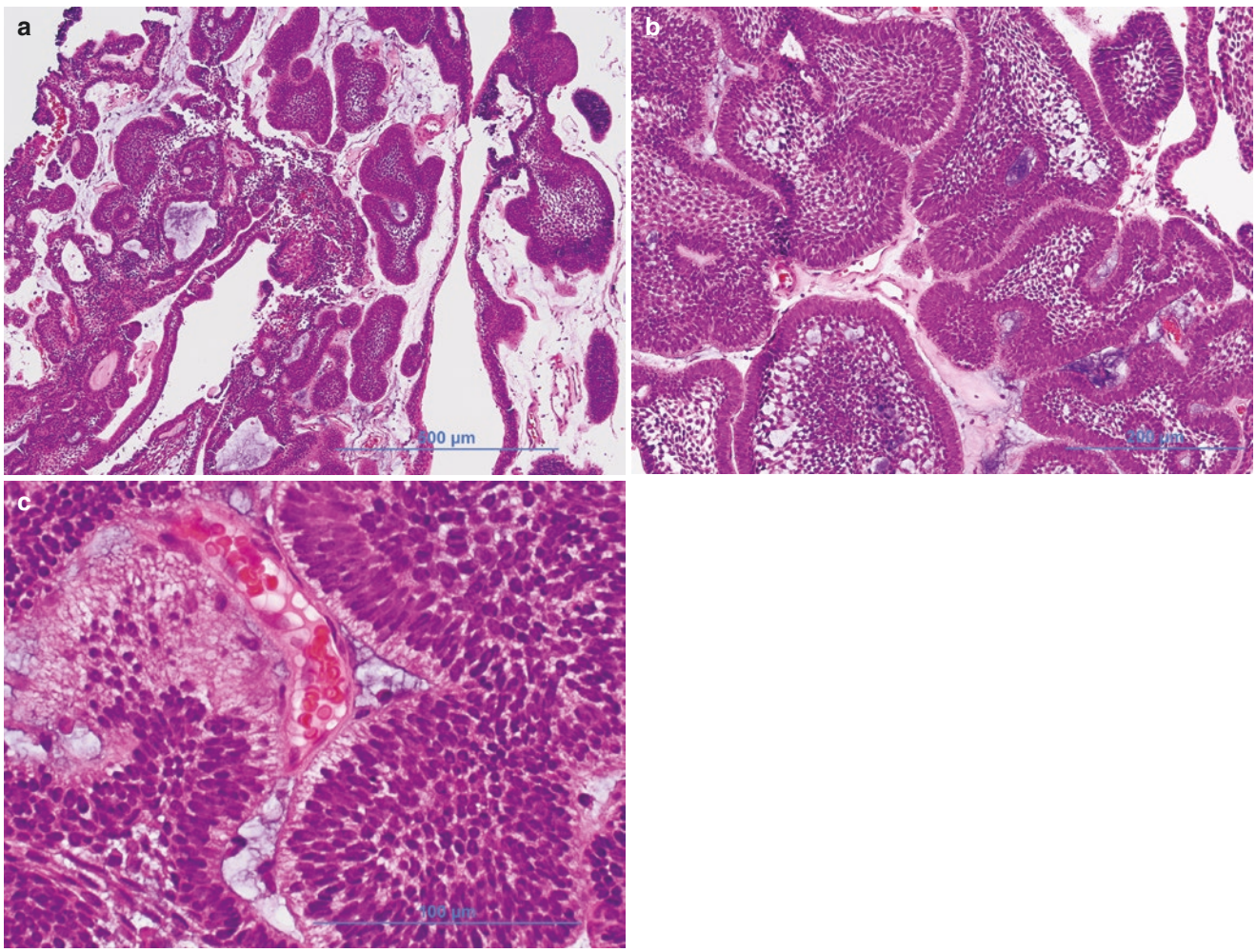


**Fig. 6.28** (**a**–**c**) Conventional (solid/multicystic) ameloblastoma

**Take-Home Messages**

1. Ameloblastoma is an odontogenic tumor derived from the enamel organ cells and retains some embryonic features that allow it to be locally infiltrative.
2. It may develop multiple growth patterns (unicystic, multicystic/solid/conventional, peripheral) and cytologic variants (basaloid, acanthomatous, follicular, plexiform, desmoplastic, granular).
3. Most tumors have a mixture of growth patterns and cytologic variants.
4. The diagnosis of unicystic ameloblastoma usually needs to be subtyped as intraluminal, luminal, or mural depending on the extent of the tumor islands. The mural variant of unicystic ameloblastoma has a biologic behavior similar to conventional ameloblastoma and requires more extensive treatment that the other unicystic variants.

References: [30, 100, 110–112]

## Case 5

**Learning Objectives**

1. To recognize that jaw biopsies that contain multinucleated osteoclastic-type giant cells are common
2. To become familiar with the differential diagnosis for central giant cell lesions of the jaws
3. To be able to recommend clinical and laboratory correlations in order to rule out syndromes and metabolic disorders that may be associated with central giant cell lesions
4. To appreciate that making a diagnosis of central giant cell granuloma is a diagnosis of exclusion

**Case History**

A 24-year-old Caucasian female presented with a mildly expansile multilocular radiolucency on the symphysis of the mandible. The teeth in the area of the lesion were reported to be vital and asymptomatic. The lesion was the only lesion identified in the patient's jaws by means of a panoramic radiograph. The two central incisors showed minimal root resorption. An incisional biopsy was submitted along with a copy of the panoramic radiograph.

**Gross Findings**

A multifragmented curettage-type specimen was harvested from the intrabony lesion and entirely submitted.

**Histologic Findings** (Fig. 6.29)

- The tumor consisted of solid areas of mesenchymal stroma with high vascularity and abundant hemosiderin deposits admixed with osteoclastic multinucleated giant cells.
- Occasional mitotic figures were identified.
- Occasional focal areas of reactive osteoid formation were present.

**Differential Diagnosis**

- Central (reparative) giant cell granuloma
- Aneurysmal bone cyst
- Giant cell tumor of bone
- A Brown tumor of secondary hyperparathyroidism
- Cherubism or Noonan syndromes
- Foreign body reaction
- Pigmented villonodular synovitis
- Osteoclast-rich osteosarcoma

**IHC and Other Ancillary Studies**

- Immunohistochemistry is usually not necessary.
- Clinical, radiographic, and laboratory correlation is always mandatory before final diagnosis.
- In order to evaluate for hyperparathyroidism, it is useful to assess calcium, phosphate, vitamin D, and parathyroid hormone levels, as well as rule out multifocal disease.
- Cherubism and Noonan syndrome will present with multifocal disease in young patients.
- Aneurysmal bone cysts usually will be painful, rapidly expansile, and affect a younger population; they also include sinusoidal spaces in the tissue samples.

**Final Diagnosis** *Central giant cell granuloma*

**Take-Home Messages**

1. The usual initial diagnosis for an osteoclast-containing lesion of the jaws is "central giant cell lesion" with a comment regarding the need for clinical, radiographic, and laboratory correlations for a final diagnosis.
2. If a radiograph is submitted along with the specimen, it is very useful to determine if the lesion is single or multifocal. Multifocal lesions suggest systemic or metabolic diseases. A single lesion favors central giant cell granuloma or aneurismal bone cyst.

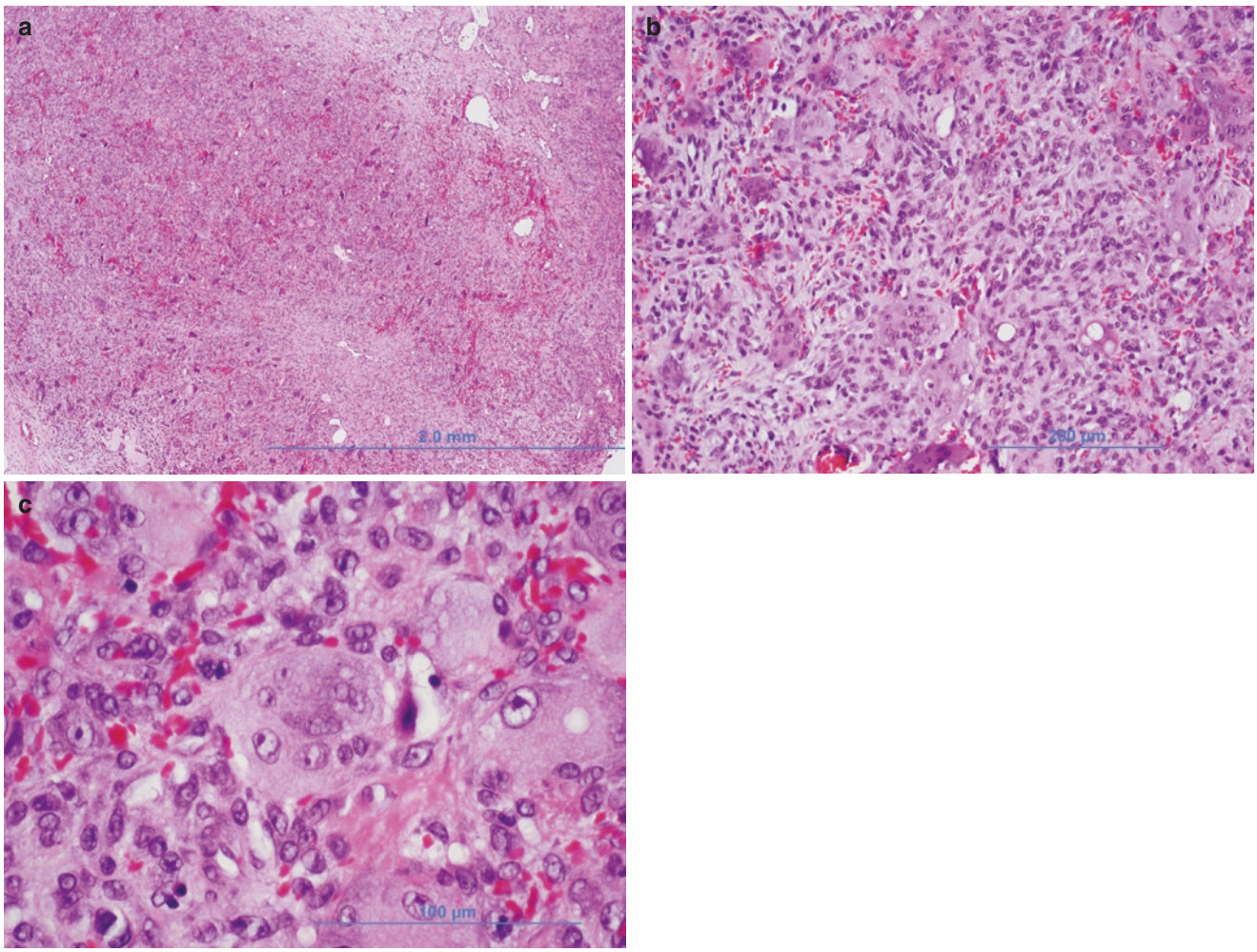


**Fig. 6.29** (**a**–**c**) Central giant cell granuloma

3. Sometimes, a central giant cell granuloma-like reaction can be identified with other lesions such as central odontogenic fibroma.

References: [18, 23, 88, 113–118]

## Case 6

### Learning Objectives

1. To recognize that the diagnosis of benign fibro-osseous lesions requires clinical and radiographic correlation in order to reach an accurate diagnosis
2. To recognize the histopathologic features of the condition
3. To differentiate cemento-osseous dysplasia from other benign fibro-osseous conditions and benign neoplasms

### Case History

A 66-year-old African-American female with history of breast cancer treated with surgery and radiation 20 years ago presented to with generalized mixed radiolucent/radiopaque lesions on all quadrants of the mandible and the maxilla. She was asymptomatic, and there was no evidence of cortical bone expansion. The mucosa overlying the lesions was intact. As part of the pre-prosthesis protocol, an alveoloplasty was performed, and the tissue was submitted for examination.

### Gross Findings

A multifragmented curettage-type specimen was harvested from the intrabony lesion and consisted of small fragments of bloody bone and soft tissue admixed in about equal proportions. Small dense bone-like fragments were also present. The entire specimen was decalcified and entirely submitted.

**Histologic Findings** (Fig. 6.30)

- The specimen consisted of multiple small fragments of a benign fibro-osseous proliferation with evidence of extravascular blood pools.
- The soft tissue component was well-vascularized collagen harboring a slightly hypercellular population of cells with spindle-shaped nuclei and no atypia.
- The calcified component consisted of osteoid with a woven bone pattern of mineralization and regularly scattered osteoblasts in lacunae.
- The edges of the woven bone lacked significant osteoblastic rimming and did not exhibit osteoid edges ("brushed border/raked border").
- No atypia was observed.
- Pools of blood within the tissue were present, with no sinusoidal or vascular channels. Hemosiderin was occasionally seen.
- Some fragments of very dense woven bone were occasionally seen.

**Differential Diagnosis**

- Cemento-osseous dysplasia
- Central ossifying fibroma (osteofibrous dysplasia of long bones)
- Osteoblastoma
- Osteoid osteoma
- Low-grade osteosarcoma
- Fibrous dysplasia

**IHC and Other Ancillary Studies** (Fig. 6.15d–f)

- Immunohistochemistry is usually not necessary
- Clinical and radiographic correlation is always mandatory before final diagnosis.
- In rare occasions, traumatic bone "cyst" type spaces may develop, which are inconsequential for the prognosis of the condition

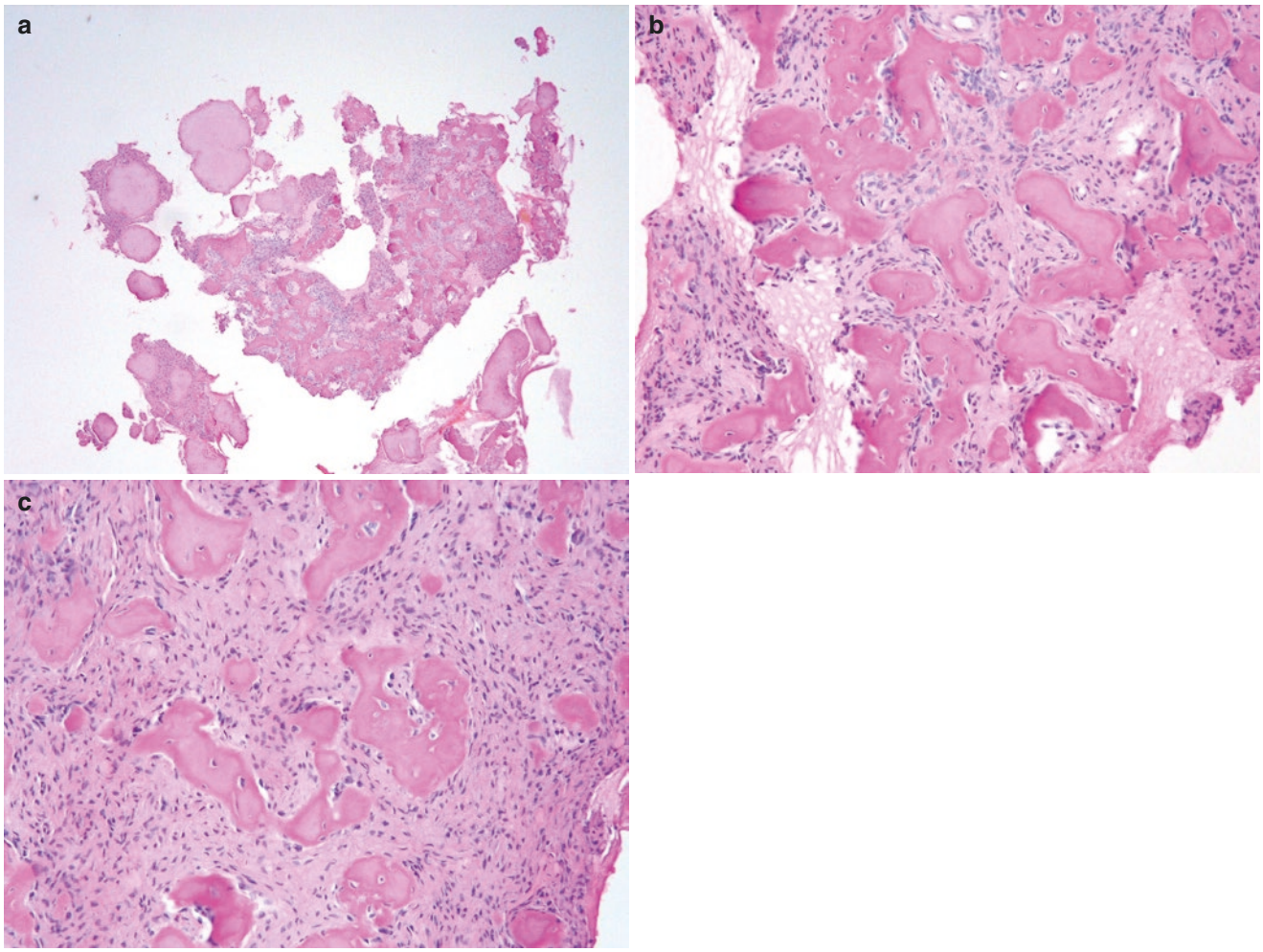


**Fig. 6.30** (**a**–**c**) Benign fibro-osseous lesion consistent with florid osseous dysplasia

**Final Diagnosis** *Benign fibro-osseous lesion (in this case, due to the clinical and radiographic features described, this represents florid osseous dysplasia)*

### Take-Home Messages

1. Benign fibro-osseous lesions of the jaws must be properly correlated with the clinical and radiographic features for accurate diagnosis. The overlap between lesions with significantly different biologic behavior and treatment is large, and misdiagnosis or inappropriate treatment may be rendered if not correlated properly.
2. The absence of osteoblastic rimming is most important for diagnosis. If osteoblastic rimming is seen, the lesion may be in its growing phase, or may be a completely different lesion altogether.
3. Traumatic bone cyst-like spaces may be seen occasionally, and they may also induce occasional pain and swelling in some patients.

References: [114, 119–124]

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# Ear and Temporal Bone

7

Danielle Elliott Range

## List of Frequently Asked Questions

1. What are the anatomic and histologic components of the ear?
2. What are the major congenital anomalies of the ear and temporal bone?
3. What are the common keratinous lesions of the external auditory canal (EAC)?
4. What are the common skin tumors of the external ear and EAC?
5. What are the common tumors of ceruminous glands and how are they diagnosed?
6. What are the inflammatory cartilaginous lesions of the ear?
7. What are the benign bony lesions of the ear?
8. What is an aural polyp?
9. What is the difference between middle ear adenomas and carcinoid tumors?
10. What are the genetics associated with middle ear paragangliomas and how are malignant ones diagnosed?
11. How are middle ear adenomas and paragangliomas distinguished?
12. What are the clinical and histologic characteristics of temporal bone and ear schwannomas?
13. What are the clinical and histologic characteristics of temporal bone and ear meningiomas?
14. What is aggressive papillary tumor of middle ear and how does it differ from endolymphatic sac tumors?
15. What are the most common metastatic tumors to the temporal bone region?

1. *What are the anatomic and histologic components of the ear?*

   The "ear" comprises the external ear, including the auricle and external auditory canal (EAC), the middle ear, the inner ear, and their components. The bony portion of the EAC, the middle, and inner ear are all enclosed in the petrous portion of the temporal bone.

   - Parts of the temporal bone that relate to the ear include the internal auditory canal (also called the internal auditory meatus) and the canals that house the internal carotid artery, internal jugular vein, and facial nerve.
   - Most structures of the ear are lined by either a single layer of squamous epithelium or a low cuboidal epithelium (middle ear mucosa). Table 7.1 summarizes the above anatomical components and their histologic composition.

   Reference: [1]

2. *What are the common congenital anomalies of the ear and temporal bone?*

   Congenital anomalies in this region generally take the form of choristomas and branchial anomalies (Table 7.2).

   - Choristomas are histologically normal tissue found in an anatomic location that is not native to that tissue type.
     - The most common type of heterotopia in the middle ear is salivary gland tissue.
     - Neuroglial tissue in the middle ear is exceedingly rare, and many believe it likely represents encephaloceles and are not true choristomas (Fig. 7.1).
       - The presence of neuroglia tissue in the middle ear should be identified as an encephalocele unless unequivocally proven otherwise. This is an important consideration as it encourages the clinician to search for, thoroughly, and definitively exclude, a connection to the central nervous system and avoid serious complications.

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- Branchial anomalies involving the ear and temporal bone are related to the first branchial arch and cleft (Fig. 7.2).
  References: [2–9]

**Table 7.1** Anatomy and histology of the ear and temporal bone

| Region | Structure | Anatomy/histology |
|---|---|---|
| External ear | Auricle | Skin<br>Elastic cartilage |
| | External auditory canal | Outer 1/3: elastic cartilage and skin with sebaceous glands and deep ceruminous glands<br>Inner 2/3: bone and flattened skin |
| Middle ear | Tympanic membrane | Fibrous tissue covered by flattened skin laterally and medially by middle ear mucosa |
| | Ossicles | Bones (stapes, incus, malleus) covered by middle ear mucosa |
| | Mastoid cavity and air cells | Bone and spaces connected to the middle ear and lined by middle ear mucosa |
| | Eustachian tube | Lined by respiratory mucosa. Connects the middle ear to the nasopharynx |
| Inner ear | Labyrinth: outer osseous layer and inner membranous layer | Contains the cochlear, semicircular canals, saccule, utricle, endolymphatic duct and sac |
| | Internal auditory canal | Bony canal that houses the vestibulocochlear nerve (CN8) and connects the inner ear with the posterior cranial fossa |

*CN* cranial nerve

3. *What are the common keratinous lesions of the external auditory canal (EAC)?*

The EAC is lined by skin, comprising keratinizing, stratified squamous epithelium and adnexal structures. As a result, some common skin lesions can occur in this location, including seborrheic keratosis, squamous cell carcinomas, and squamous papillomas. Lesions unique to the EAC such as cholesteatomas and keratosis obturans (KO) are discussed here (Table 7.3).

- Cholesteatomas and keratosis obturans (KO) are both characterized by the accumulation of keratin within the ear.
  - Cholesteatomas are rare in the EAC but have identical histologic features with those of the middle ear and the congenital forms.
  - Acquired cholesteatomas will be detailed here to highlight the differential diagnosis with KO.
  - Middle ear cholesteatomas (Fig. 7.3) may be associated with meningiomas, middle ear adenomas, and aural polyps.
- Seborrheic keratosis of the EAC is rare and identical to those at other body sites.
  - They are plaque-like, hyperkeratotic tumors composed of a proliferation of normal-appearing squamous cells which merge with more basaloid squamous cells. Keratin cyst formation is characteristic, and cytologic atypia is absent. The lesion shows a sharp demarcation from the adjacent epidermis.
- Squamous papillomas are rare but have been reported in the auricle, EAC, and middle ear. They are identi-

**Table 7.2** Congenital anomalies of ear and temporal bone region

| | Choristoma | | First branchial anomalies | |
|---|---|---|---|---|
| | Salivary tissue | Neuroglial tissue | Cyst, fistula, sinus | Accessory tragus |
| Age (years) | 0–20 | 40–50 | 0–17 (mean 2.4) | 0–20 |
| Clinical presentation | Unilateral ear pain<br>Hearing loss<br>Mass behind TM | Presents with chronic otitis media<br>History of recurrent infections or trauma | Symptoms related to infection and drainage of tract or fistula<br>Sinuses are most common | Present with preauricular, polypoid skin lesion<br>May be multiple or single, bilateral or unilateral |
| Histology | Serous and mucinous glands with ducts and fibroadipose tissue<br>±Chronic inflammation<br>Covered by normal middle ear mucosa | Varying amounts of glial tissue and neurons, typically without ependymal, leptomeningeal, or choroid plexus tissue<br>Chronic inflammation and reactive gliosis | Typically a squamous-lined tract or fistula with varying amounts of chronic and acute inflammation | Polypoid fragment of skin with adnexal structures, hair and underlying fibroadipose tissue<br>±Core of elastic cartilage |
| Other findings | May be associated with ossicular and facial nerve abnormalities | Must be considered an encephalocele until unequivocally proven otherwise | Involved areas dictate the clinical presentation: periauricular, ear, EAC, parotid region, angle of jaw<br>Rarely associated with other anomalies | Rarely associated with other anomalies: Treacher-Collins syndrome, Townes-Brocks syndrome, VACTERL syndrome, and 4p syndrome (Wolf-Hirschhorn syndrome) |

*TM* tympanic membrane

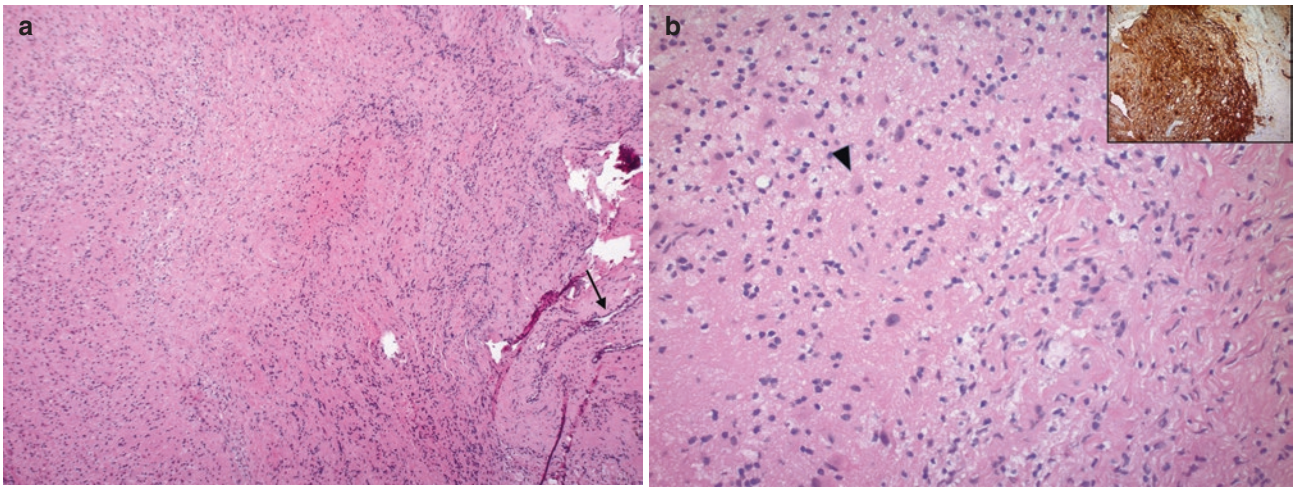


**Fig. 7.1** Neuroglial tissue. (**a**) Brain tissue with underlying middle ear mucosa (arrow) and reactive fibrous changes. (**b**) Higher magnification of the glial tissue shows a fibrillary background and scattered neurons (arrowhead) which are positive for GFAP (inset)

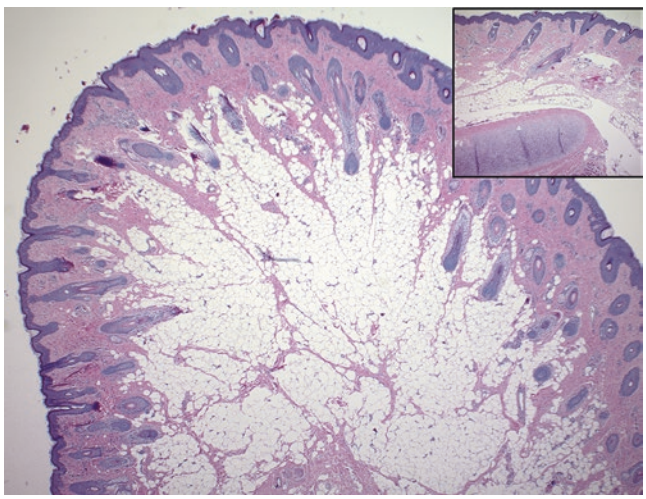

**Fig. 7.2** Accessory tragus. Polypoid skin fragment with underlying fibroadipose tissue and core of elastic cartilage (inset)

cal to squamous papillomas elsewhere, described in detail in Chap. 2.

- Squamous cell carcinoma (SCC) most commonly involves the external ear including the auricle and cartilaginous EAC; rare cases involve the middle ear.
- Specifically, SCC of the temporal bone is an aggressive tumor with overall 5-year survival rates of less than 50%.
  - Patients are usually elderly and present at an advanced stage due to delayed diagnosis or misdiagnosis of otitis.
  - Morbidity and mortality are related to direct tumor extension, as lymph node metastases are a late occurrence.
  - Carcinomas of the bony canal spread out toward the cartilaginous canal or inward to involve the middle ear.
  - Middle ear tumors invade the mastoid, middle cranial fossa, Eustachian tube, and skull base.
  - Histologically, SCCs in this region is typically keratinizing and identical to those seen in other epidermal sites.

References: [1, 10–17]

4. *What are the common skin tumors of the external ear and EAC?*
   - According to the Armed Forces Institute of Pathology (AFIP), basal cell carcinomas (BCC) account for 21% of all neoplasms of the ear and temporal bone. They are the most common cutaneous tumors of the external ear and generally have an indolent clinical course.
     - Sun exposure is the most significant risk factor. Consequently, the auricle is the most common site.
     - Grossly, BCC is a pearly, white subepithelial nodule with a central ulceration.
     - BCC comprises nests of monotonous, basaloid cells with scant cytoplasm. Tumor nests show peripheral palisading of tumor cells and may demonstrate retraction from the surrounding stroma.
     - The infiltrative or morphea-like variant comprises cords and single file cells invading a desmoplastic stroma.
     - Squamous metaplasia with keratin formation can be seen and should not be confused with SCC.
     - Stromal changes include desmoplasia and mucin production.
   - Melanomas of the external ear occur most commonly on the auricle, though EAC and middle ear melanomas have been reported. Melanomas of the external ear typically occur in white males with an average age of 66 years old.

**Table 7.3** Comparison of cholesteatomas and keratosis obturans

| | Middle ear cholesteatoma | EAC cholesteatoma | Keratosis obturans |
|---|---|---|---|
| Patients | Adults, usually 30–40yo | Elderly | Young |
| Clinical | History of trauma, surgery, or chronic otitis media<br>Associated perforated TM | Otorrhea<br>Chronic, dull pain<br>Rarely hearing loss<br>Normal TM<br>History of trauma, surgery, chronic otitis externa | Hearing loss<br>Acute, severe pain<br>Thickened TM |
| Location | Middle ear<br>Unilateral | EAC<br>Unilateral | EAC<br>May be bilateral, especially in children |
| Histology | Cystic lesion lined by keratinizing squamous epithelium with granular cell layer<br>Filled with layered, concentric, keratinous debris<br>May only show keratinous debris | Cystic lesion lined by keratinizing squamous epithelium with granular cell layer<br>Filled with keratinous debris randomly arranged<br>May only show keratinous debris | Inflammatory lesion caused by excessive retention of exfoliated keratinocytes forming a keratin plug<br>Keratinous debris arranged in concentric layers |
| Complications | Ossicles and bony canal may be eroded in chronic cases | Localized bony erosion of canal is typical<br>Focal epithelial ulceration<br>Osteonecrosis<br>Abscess formation<br>Hearing loss | Circumferential bony erosion<br>Widening of EAC<br>No osteonecrosis<br>No ulceration<br>Secondary infection |
| Treatment | Surgical excision, recurrences may occur | Surgical excision, recurrences may occur | Ear cleaning and removal of keratin plug |

*EAC* external auditory canal, *TM* tympanic membrane

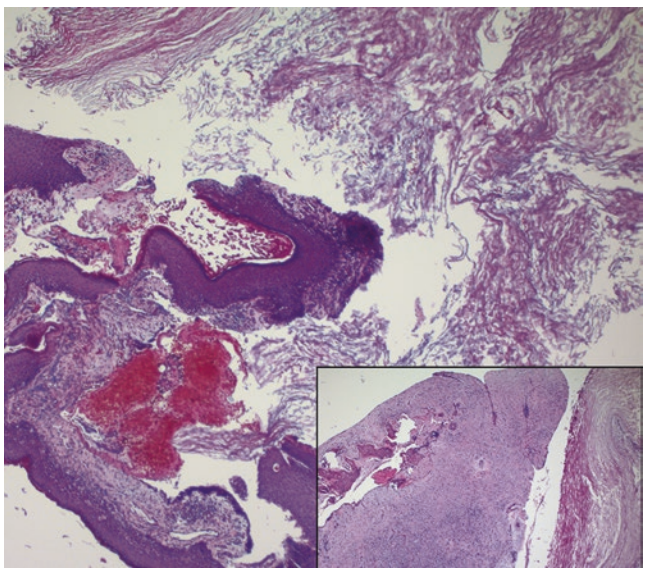

**Fig. 7.3** Cholesteatoma. Strips of benign squamous epithelium associated with abundant keratinous debris. (Inset) Concentric layers of keratin and a fragment of fibrotic soft tissue with bone erosion

  - The most common growth types in decreasing frequency are superficial spreading, lentigo maligna, and nodular.
  - The most common histologic types are epithelioid and spindle types.
    - Nests, cords, and sheets of tumor cells start at the dermal-epidermal junction with eventual downward growth into the dermis.
    - The cells vary in appearance from small, nevoid cells with scant cytoplasm to larger cells with moderate amounts of eosinophilic to amphophilic cytoplasm, vesicular nuclei with prominent nucleoli or coarse chromatin.
    - Intracytoplasmic pigment is typical in the epithelioid variant.
    - Cells are keratin negative and positive for S100, HMB-45, Mart-1, Sox-10, and MiTF.
  - Stage and depth of invasion, as measured by Breslow thickness or Clark level, determine prognosis.
  - Deep et al. and Patel et al. performed large, population-based studies which show an excellent prognosis for stage 1 and 2 disease with a 5- and 10-year disease-specific survival (DSS) of 90%. Five-year DSS drops to 50% for stage 3 and 20% for stage 4.

  References: [1, 18–22]

5. *What are the common tumors of ceruminous glands, and how are they diagnosed?*

   Ceruminous glands are specialized apocrine glands found in the deep dermis of the outer half of the EAC. They are the origin of most glandular lesions in the EAC. In general, tumors arising from the adjacent parotid gland with extension into the EAC or middle ear should be excluded, as well as metastases. Ceruminous gland adenomas and carcinomas are broad terms that encompass a few different entities (Table 7.4).

- Ceruminous adenomas and adenocarcinoma, NOS, typically show prominent apocrine change. A dual-cell population of basal cells and luminal cells is present in both but may be focal in the carcinomas. The existence of true myoepithelial cells (with smooth muscle differentiation) in the adenocarcinomas is not clear. The distinction between the two tumors can be difficult (Table 7.5).
- Ceruminous gland adenoid cystic carcinoma (CG-AdCC) and mucoepidermoid carcinoma (CG-MEC) are identical to their salivary gland counterparts. Both are even rarer than the conventional ceruminous adenocarcinoma (CG-ACA, NOS). A few differences should be noted:
  - The morphologic patterns of CG-AdCC (Fig. 7.4) do not correlate with tumor grade or behavior like their salivary gland counterparts. This may be a result of its rarity and the absence of sufficient data. However, CG-AdCC behaves similarly with locally aggressive growth and a prolonged disease course plagued by multiple recurrences and distant metastases.
- The ductal cell population and apocrine differentiation may be focal.
- Cutaneous BCC is in the differential diagnosis of the solid variant of CG-AdCC and should be excluded as the prognosis is worse for the latter. CG-AdCC has frequent PNI, some cribriform architecture, and lacks palisading.
  - Ceruminous gland mucoepidermoid carcinomas have the classic three cell types: epidermoid, intermediate, and mucous cells.
- Ceruminous gland pleomorphic adenoma is the most common among the adenomas and has the classic biphasic histomorphology of pleomorphic adenomas in other sites. Sheets of myoepithelial cells and chon-

**Table 7.4** Terminology of ceruminous gland tumors

| Ceruminous adenomas | Ceruminous carcinomas |
|---|---|
| Ceruminous adenoma, NOS (conventional type) | Ceruminous adenocarcinoma, NOS (conventional type) |
| Ceruminous pleomorphic adenoma | Ceruminous adenoid cystic carcinoma |
| Ceruminous syringocystadenoma papilliferum | Ceruminous mucoepidermoid carcinoma |

*NOS* not otherwise specified

**Table 7.5** Clinicopathologic features of ceruminous adenoma and adenocarcinoma, NOS

| | Ceruminous adenoma | Ceruminous adenocarcinoma, NOS | |
|---|---|---|---|
| | | Low-grade | High-grade |
| Age (years) | 50–60 | 50–60 | |
| Presentation | Painless<br>Subcutaneous nodule<br>Unilateral hearing loss | Pain, otorrhea<br>Ulceration<br>Unilateral hearing loss | |
| Location | Outer, cartilaginous EAC | Cartilaginous EAC with extension into middle ear<br>Destruction of petrous and temporal bone | |
| Gross findings | Circumscribed, unencapsulated, cystic<br>Rarely ulcerated | Infiltrative with firm, solid cut surface | |
| Histology | Proliferation of glands and tubules<br>Glands may be back to back<br>Hyalinized or fibrous stroma<br>Basal cells and myoepithelial cells present | Proliferation of glands and tubules<br>Basal cells may be focal<br>Invasion with desmoplasia | Irregularly shaped, infiltrative glands, sheets, cords<br>±Cribriform patterns<br>Basal cells may be focal<br>Invasive with desmoplasia<br>Necrosis, PNI |
| Cytology | Inner cuboidal/columnar cells with abundant eosinophilic cytoplasm, apical snouting<br>Golden-yellow, lipofuscin-like, cytoplasmic granules<br>Round, bland nuclei, fine chromatin, small nucleoli<br>No atypia, mitoses or necrosis | Glands are lined by 1–2 layers of cuboidal/columnar cells with abundant eosinophilic cytoplasm, apical snouting<br>No golden-yellow, lipofuscin-like, cytoplasmic granules<br>Oval, vesicular or hyperchromatic nuclei, variably prominent nucleoli<br>None to scattered mitoses | Glands are lined by 1–2 layers of cuboidal/columnar cells with abundant eosinophilic cytoplasm<br>May be poorly differentiated with loss of apocrine features<br>Marked pleomorphism<br>Brisk mitotic activity<br>Metastases must be excluded |
| Positive stains | Cytoplasmic granules: PAS, Sudan black, Ziehl-Neelsen | p53: <10% – 30% of cells | |
| Luminal cells | CK7, CD117 (weak) | CK7, CD117 (strong), EMA, AR | |
| Abluminal cells | S100, CK5/6, p63 | S100, CK5/6, p63 | |

*EAC* external auditory canal, *LG* low-grade, *HG* high-grade, *PNI* perineural invasion

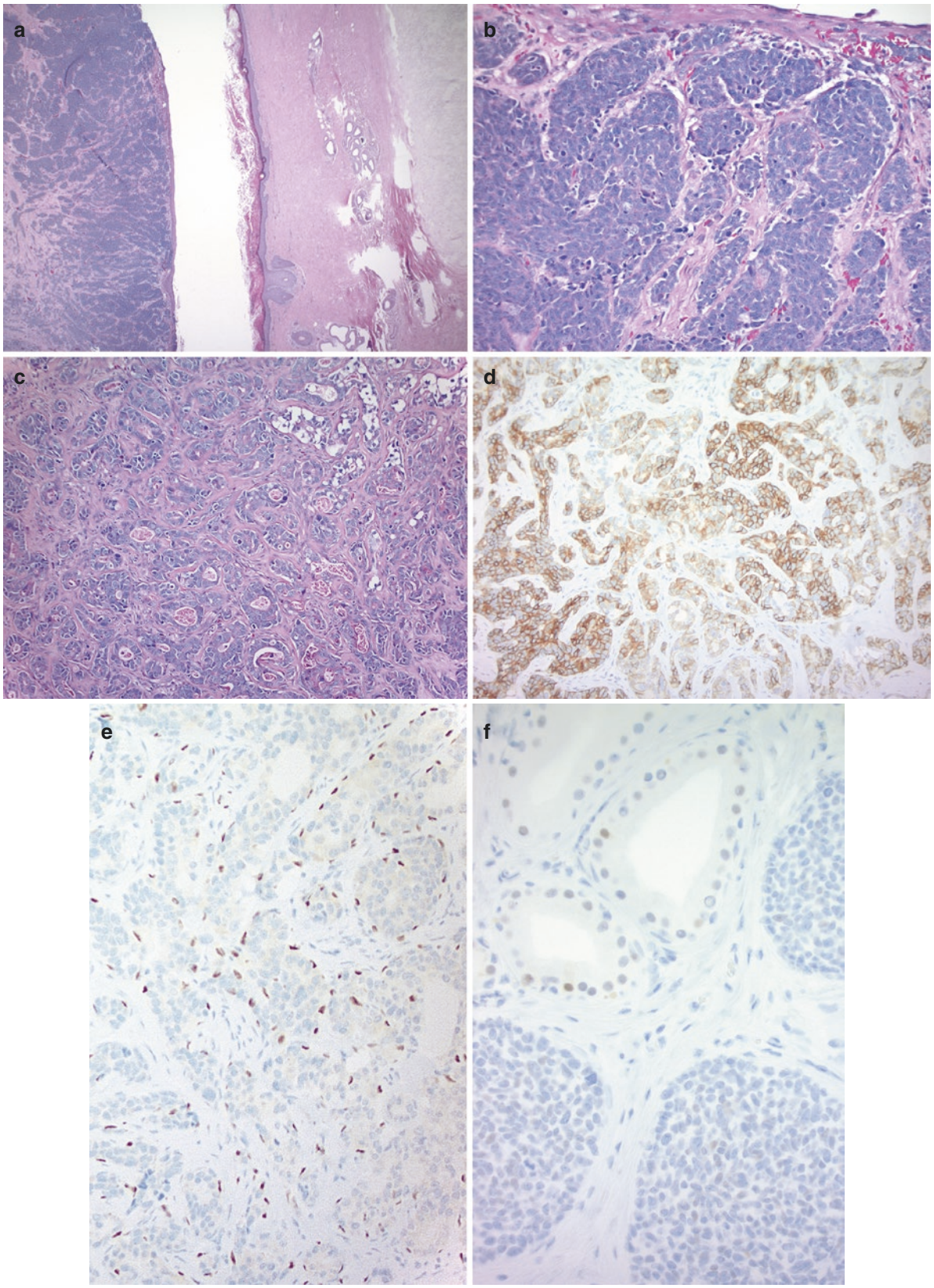


**Fig. 7.4** Ceruminous gland adenoid cystic carcinoma. (**a**) Section of external auditory canal lumen shows a basaloid tumor underlying atrophic epithelium on the left. Normal epidermis lines the canal on the right with underlying normal ceruminous glands and elastic cartilage. (**b**) The tumor cells are angulated, basaloid cells with scant cytoplasm arranged in solid nests and (**c**) tubules. (**d**) The tumor cells stain strongly for CD117. (**e**) A stain for p63 highlights scattered abluminal cells. (**f**) Androgen receptor IHC shows weak nuclear staining of rare tumor cells. Normal cerumen glands are positive for AR

dromyxoid stroma aid in the distinction from CG-ACA, NOS.
  - Ductal cells will show some apocrine differentiation with apical snouting and lipofuscin-type granules.
- Ceruminous gland syringocystadenoma papilliferum is rare. It is identical to its dermal counterpart.
  - CGSCP is characterized by a cyst formed from invagination of the skin surface epithelium.
  - Numerous papillary structures protrude into a cyst and are lined by an inner layer of basal cells and an outer layer of apocrine cells.
  - The fibrovascular cores have a dense plasmacytic infiltrate.

References: [23–26]

6. *What are the inflammatory cartilaginous lesions of the ear?*
   - Idiopathic cystic chondromalacia (Fig. 7.5) and chondrodermatitis nodularis chronicus helicis (Fig. 7.6) are both idiopathic, mass-producing inflammatory lesions of the auricle (Table 7.6).
   - Relapsing polychondritis (RP) is an inflammatory disease affecting hyaline and elastic cartilage. The disease is characterized by recurrent episodic flares involving cartilage of the auricle, nose, and upper respiratory tract.
     - RP presents with bilateral chondritis of the pinna with diffuse edema and tenderness.
     - Patients may suffer from systemic manifestations including keratitis, conjunctivitis, migratory arthralgias, cardiac valve insufficiency, and kidney disease.
     - Biopsies show a marked, mixed inflammatory infiltrate of cartilage with erosion and necrosis.

   References: [27–33]

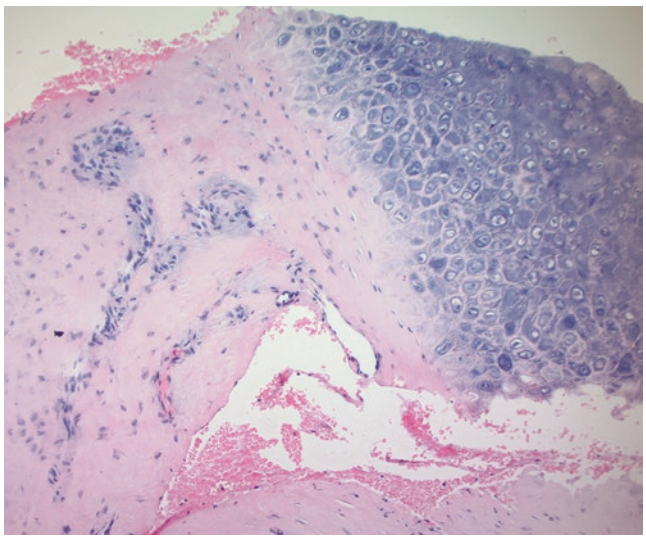

**Fig. 7.5** Idiopathic chondromalacia. Pseudocyst filled with blood and serum and lined by granulation tissue with fibrosis. Elastic cartilage is noted adjacent to the lesion (right)

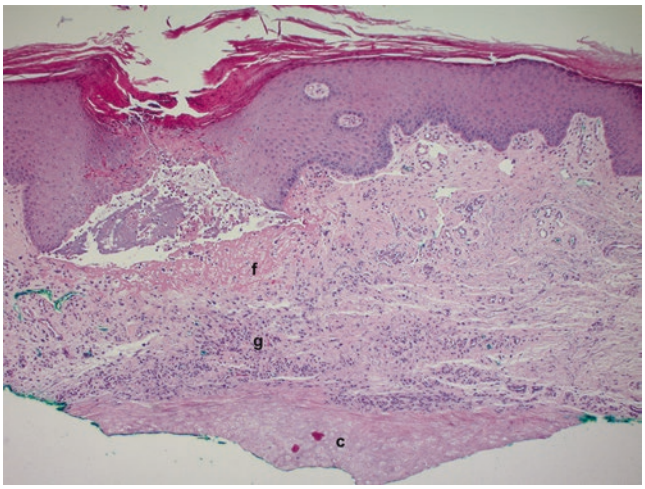


**Fig. 7.6** Chondrodermatitis nodularis chronicus helicis. Acanthotic epidermis with parakeratosis and a central ulcer. The ulcer base contains (f) fibrinoid necrosis with underlying (g) granulation tissue, inflammation, and (c) degenerated cartilage

**Table 7.6** Clinicopathologic features of inflammatory lesions of ear cartilage

| | Chondromalacia | Chondrodermatitis nodularis chronicus helicis |
|---|---|---|
| Patient | Young to middle-aged, male | Middle-aged to older, male |
| Location | Scaphoid fossa | Superior helix |
| Symptoms | Painful, subcutaneous nodule | Painful, red nodule with central ulcer |
| Duration | Weeks to years | Sudden onset |
| Pathogenesis | Trauma, ischemic necrosis | Exposure to cold, actinic damage, trauma |
| Pathology | Fluid-filled pseudocyst caused by degeneration of cartilage<br>Fibrous tissue or granulation tissue may line the cyst<br>Chronic inflammation<br>±Reactive atypia | Epidermal changes adjacent to the ulcer: PK, HK, acanthosis, or PEH<br>Granulation tissue in ulcer base with fibrinoid necrosis<br>Acute and chronic inflammation<br>Inflamed perichondrium and cartilage<br>±Stromal necrobiosis with palisading histiocytes |
| Clinical differential diagnosis | Chondrodermatitis nodularis chronicus helicis<br>Relapsing polychondritis | Basal cell carcinoma<br>Squamous cell carcinoma |
| Treatment | Surgical excision | Surgical excision, pressure relief, topical nitroglycerin |

*PK* parakeratosis, *HK* hyperkeratosis, *PEH* pseudoepitheliomatous hyperplasia

**Table 7.7** Benign osseous lesions of the ear

| | Exostosis | Osteoma | Otosclerosis |
|---|---|---|---|
| Patients | Cold water swimmers, surfers<br>Male, <50 years old | Male, <50 years old (EAC)<br>Female > male (mastoid) | Female > male<br>20–30 years old |
| Location | Medial EAC | EAC, mastoid, rarely middle ear | Middle ear, stapes |
| Clinical | Bilateral, multiple | Unilateral, solitary | Bilateral (85%)<br>Family history (50%) |
| Symptoms | Asymptomatic until obstructive symptoms:<br>– Recurrent otitis externa<br>– Conductive hearing loss<br>– Tinnitus | Asymptomatic until obstructive symptoms:<br>– Conductive hearing loss<br>– Aural fullness | Conductive or mixed hearing loss<br>±Vestibular changes |
| Pathology | Broad-based, bony growth<br>Resembles cortical bone<br>Onion-skin layering of dense bone<br>Periosteal and skin covering<br>No trabeculae or marrow spaces | Pedunculated bony growth<br>Resembles cancellous bone with trabeculae of normal, lamellar bone<br>Marrow space filled with fibroconnective tissue<br>May have cortical bone at periphery<br>Periosteal and skin covering | Early phase: bone resorption with formation of perivascular spaces<br>Increased osteoclasts<br>Late phase: woven bone with dense sclerosis causes stapedial footplate fixation<br>Stapes specimen may be normal* |
| Treatment | Medical treatment of otitis<br>Surgery for refractory cases | Surgical excision | Surgical stapedectomy with prosthesis |

*EAC* external auditory canal
*Otosclerosis frequently involves the bone *adjacent to* the stapes, limiting footplate motion; the excised stapes footplate may be histologically normal

7. *What are the benign bony lesions of the ear?*

The more common bony lesions in the ear and temporal bone include mass-like lesions of bone, like osteoma and exostosis, as well as reactive bone formation as seen in otosclerosis (Table 7.7).

References: [34–39]

8. *What is an aural polyp?*

An aural or otic polyp is an inflammatory polyp of the middle ear, a complication of chronic otitis media.

- Patients are usually children with complaints of otorrhea and conductive hearing loss.
- A mass presents in the middle ear with possible extension into the EAC and resultant perforation of the tympanic membrane.
- Histologic sections show polypoid granulation tissue that may be ulcerated or covered by cuboidal or respiratory epithelium (Fig. 7.7)
  - The stroma ranges from edematous to fibrous with chronic inflammation, including plasma cells. Neutrophils and eosinophils may also be present.
  - Squamous and glandular metaplasia may be seen in the stromal tissue.
  - Foreign body-type giant cells, cholesterol granulomas, and debris may be seen.
  - Langerhans cell histiocytosis and infection should be excluded.
- Chronic otitis media and cholesteatoma are frequent underlying causes.
- Bilateral aural polyps are associated with Samter's triad: aspirin intolerance, asthma, and sinonasal polyps.

References: [1, 40, 41]

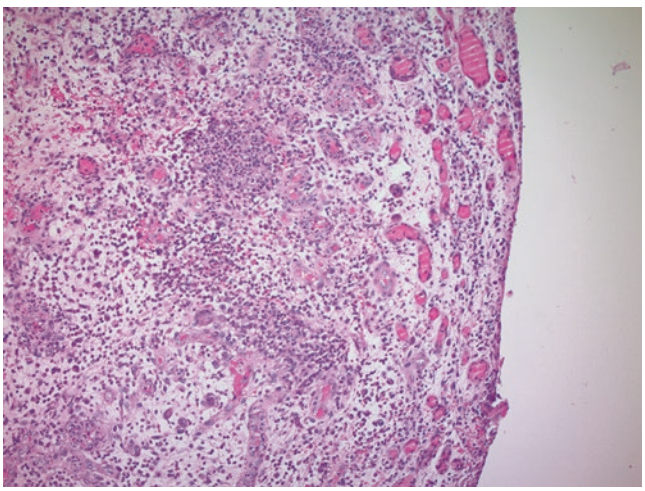

**Fig. 7.7** Aural polyp. Polypoid, inflamed granulation tissue partially lined by middle ear mucosa

9. *What is the difference between middle ear adenomas and carcinoid tumors?*

Middle ear adenomas and middle ear carcinoids are currently thought to represent the same entity (Fig. 7.8). It is an epithelial tumor that demonstrates morphologic and immunophenotypic evidence of both glandular and neuroendocrine differentiation; its features are summarized in Table 7.8. There remains controversy around the appropriate terminology. The 4th edition of the WHO Classification of Head and Neck Tumors refers to these tumors as adenomas despite a handful of reported cases

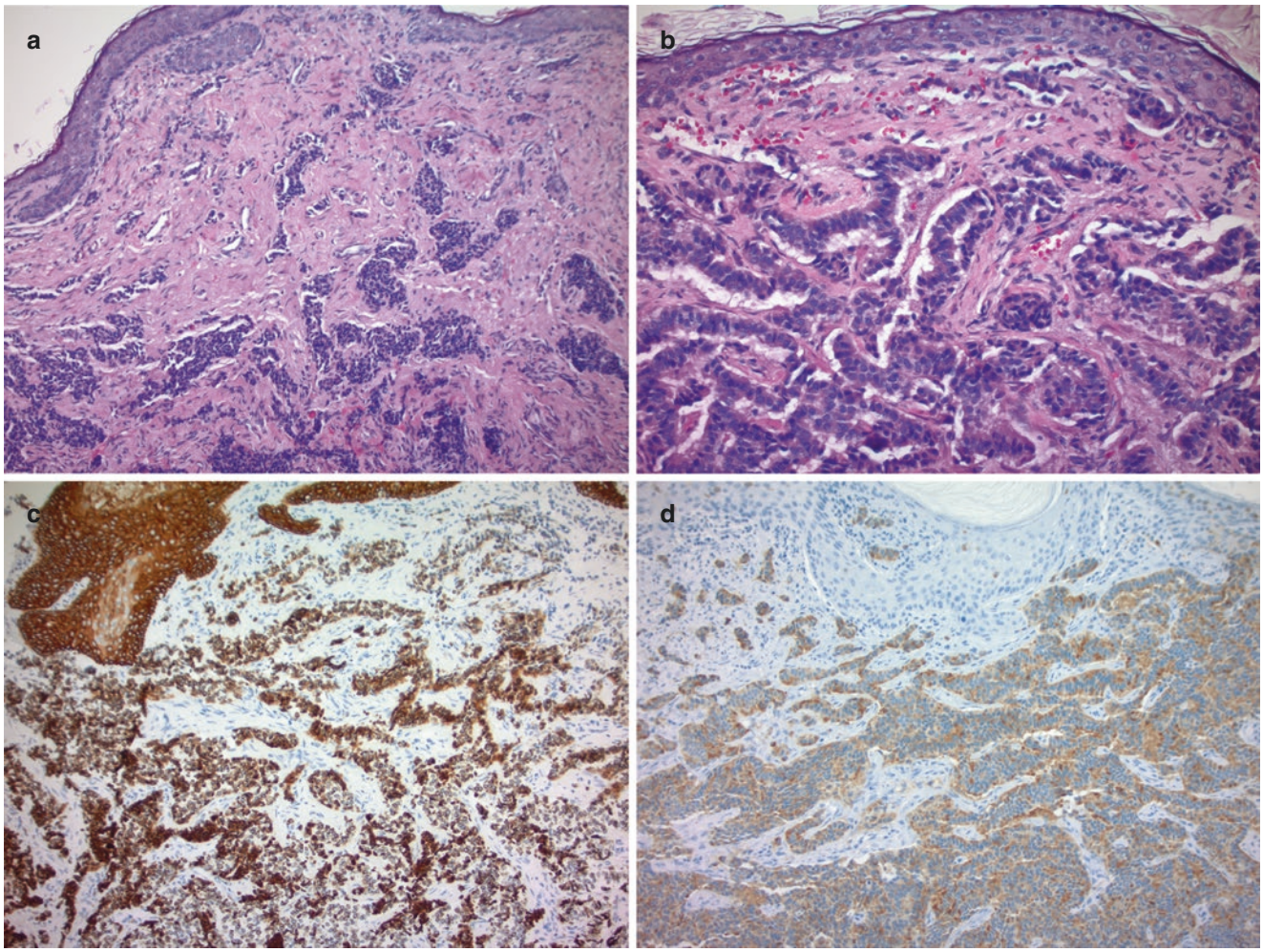


**Fig. 7.8** Middle ear adenomatous neuroendocrine tumor. (**a**) Crushed nests and (**b**) trabeculae of tumor cells are present in a fibrous stroma. (**c**) The tumor stains strongly for pan-cytokeratin and (**d**) synaptophysin

which have metastasized to the bone, liver, and regional lymph nodes.

- There is an 8% metastatic rate including some disease-related deaths and a 20% recurrence rate.
- Middle ear adenomatous neuroendocrine tumor (MEANT) is one of the proposed names that embodies both its behavior and phenotype.

References: [42–46]

10. *What are the genetics associated with middle ear paragangliomas, and how are malignant ones diagnosed?*

Paragangliomas are neuroendocrine tumors that arise from paraganglia which are present throughout the body. They are the most common inherited neoplasm in humans, and their diagnosis should prompt a referral for genetic counseling.

- There are four types of head and neck paragangliomas, in order of frequency:
  1. Carotid body (60%)
  2. Middle ear (30%)
  3. Vagal (10%)
  4. Laryngeal (<1%)
- PGL syndromes 1 through 5 now represent the most common hereditary disorder.
- Genetic mutations in any one of the five subunits of the succinate dehydrogenase enzyme complex (SDHA, SDHB, SDHC, SDHD, and SDHA2) result in SDH-deficient tumor cells and loss of SDHB expression by immunohistochemistry (IHC).
- 10–20% of apparently sporadic cases of head and neck PGL may be inherited. The SDHB IHC stain can be used to screen patients for familial PGL syndromes, but genetic testing is required to confirm and identify the specific mutation.
- Approximately 2% of MEPGL are associated with familial inheritance. This is critical, as certain genetic alterations offer prognostic information on rates of metastases, clinical aggression, and association with other tumor types.

Middle ear paragangliomas (MEPGL) were historically known as glomus tympanicum or jugulotympanic

**Table 7.8** Clinicopathologic features of middle ear adenomatous neuroendocrine tumor

| | |
|---|---|
| Gender | M = F |
| Age (years) | Mean = 50 (range 16–80) |
| Clinical presentation in order of frequency | Hearing loss<br>Aural mass/fullness<br>Ear pain, tinnitus |
| Architecture | Unencapsulated, submucosal |
| Morphologic patterns | Glandular, trabecular, solid/plasmacytoid, organoid<br>80% will show more than one pattern |
| Cytologic features | Cuboidal cells lining duct-like structures<br>Salt and pepper chromatin<br>±Focal pleomorphism<br>Rare or no mitoses |
| Growth | Ossicular involvement common<br>Nerve compression<br>Temporal bone erosion (features are related to mass effect, not malignancy or tumor aggression)<br>Pagetoid spread to overlying mucosa |
| Immunohistochemistry | Keratin+<br>Neuroendocrine marker expression is variable |

paragangliomas. MEPGL are the most common tumors of the middle ear, affecting middle-aged patients with a 3:1 female predominance.

- Clinical presentation includes otalgia, otorrhea, and pulsatile tinnitus.
- MEPGL are slow growing but may eventually involve the bone.
- Histologic features include:
  - Solid nests of epithelioid cells with abundant eosinophilic to amphophilic cytoplasm and round nuclei with fine salt and pepper chromatin.
  - Tumor nests are surrounded by inconspicuous, spindled sustentacular cells.
- 2% of MEPGL will metastasize.
- There are no histologic features that predict behavior, despite the presence of seemingly worrisome features such as infiltrative tumor border, perineural invasion, bone involvement, and atypia.

References: [47–52]

11. *How are middle ear adenomas and paragangliomas distinguished?*

Morphology and immunohistochemical studies can aid in the distinction between MEANT and MEPGL (Table 7.9).

References: [42, 44, 47, 48]

12. *What are the clinical and histologic characteristics of temporal bone and ear schwannomas?*

Schwannomas are benign peripheral nerve sheath tumors. The most common tumor of the temporal bone is the vestibular schwannoma (VS) (acoustic neuroma). It arises from the vestibular branch of cranial nerve VIII (vestibulocochlear nerve) at the level of the internal auditory canal or the cerebellopontine angle (CPA).

**Table 7.9** Comparison of middle ear adenomatous neuroendocrine tumor and paraganglioma

| | MEANT | MEPGL |
|---|---|---|
| Gland formation | Present | Absent |
| Cytokeratin expression: Pan-keratin, CK7 | Present | Absent |
| Neuroendocrine marker expression: chromogranin, synaptophysin, CD56 | Present | Present |
| S100-positive sustentacular cells | Absent | Present |

- Patients are usually middle-aged with a female predominance.
- Symptoms include progressive, unilateral sensorineural hearing loss and tinnitus.
- Histology is identical to those in other locations and shows an encapsulated, bland spindle cell proliferation with:
  - Fusiform, wavy nuclei in a fibrillary background.
  - Verocay bodies that have nuclear palisading around central eosinophilic areas.
  - Hypercellular Antoni A areas alternate with hypocellular, edematous Antoni B areas.
  - Scattered thick-walled vessels with perivascular hyalinization.
- Abrupt, degenerative nuclear atypia (enlarged, hyperchromatic) can be seen, but necrosis, increased mitoses, and nuclear pleomorphism are absent.
- VS are slow growing and may be watched clinically. Surgical excision is primarily driven by tumor growth or worsening symptoms and can be difficult given the proximity to involved structures.
- 90% of patients with neurofibromatosis type 2 (NF2) have bilateral VS.
  - NF2 patients present with VS at an earlier age (<30 years old).
  - VS in NF2 are bilateral; tend to be multicentric, more cellular, and more infiltrative with a higher likelihood of recurrence and malignant transformation.

References: [53–56]

13. *What are the clinical and histologic characteristics of temporal bone and ear (TBE) meningiomas?*

Meningiomas are benign, slow-growing tumors derived from arachnoid cap cells found in the dura of the central nervous system (CNS). Recent classification systems divide meningiomas into primary extradural and primary intracranial meningiomas. Primary extradural meningiomas (PEM) have no connection to the dura and are thought to arise from ectopic arach-

noid cap cells. TBE meningiomas can be either PEM or secondary:

- Approximately 90% of all PEM arise in the head. Primary meningiomas of the TBE region are exceedingly rare.
  - Meningiomas of the TBE account for 20–30% of all PEM of the head.
- Secondary meningiomas are the most common type seen in the TBE. They arise from the direct extension of an intracranial tumor and represent less than 2% of all intracranial meningiomas (Table 7.10). Routes of extension include:
  - Posterior petrous ridge
  - Tegmen tympani
  - Jugular bulb
  - Internal auditory meatus
- Histologic features and classification of TBE meningiomas are identical to the intracranial tumors:
  - Tumor cells are arranged in syncytial lobules and nests with a characteristic whorled pattern.
  - Cells have a moderate amount of eosinophilic cytoplasm with indistinct cell borders.
  - Nuclei are round to oval with fine chromatin and occasional intranuclear inclusions.
- Tumor growth can be infiltrative, and bone invasion is not uncommon.
- Symptomatic tumors require surgery, but complete excision is difficult given location and attempt at hearing preservation. Recurrence rates are about 20%.

References: [57–60]

14. *What is an aggressive papillary tumor of middle ear, and how does it differ from endolymphatic sac tumors?*

**Table 7.10** Characteristics of temporal bone and ear meningiomas

| | |
|---|---|
| Patient | Female predominance, mean age = 25–30 years |
| Symptoms | Mimics otitis media:<br>Conductive hearing loss<br>Otalgia<br>Otorrhea |
| Location | Middle ear > temporal bone<br>EAC |
| Histologic type | Meningothelial 80%<br>Transitional ≈ Psammomatous |
| Grade | Benign 90%<br>Atypical 5%<br>Malignant 5% |
| IHC positive stains | Vimentin, EMA, PR, var S100 (wk), var CK, var Cam5.2 |
| IHC negative stains | GFAP, chromogranin, synaptophysin |

*IHC* immunohistochemical, *PR* progesterone receptors, *var* varies from case to case, *wk* weak expression, *GFAP* glial fibrillary acidic protein

There is controversy about the origins of both endolymphatic sac tumor (ELST) and aggressive papillary tumor of the middle ear (APTME). This is complicated by the interchangeable use of these terms in the literature. The WHO Classification asserts that these are distinct entities. However, there are several features of both lesions which are similar, if not identical. ELST may represent a precursor lesion of APTME. APTME tends to show extensive invasion of adjacent structures precluding an accurate assessment of tumor location. Tysome et al. noted that ELST is always associated with either bone erosion or a dilated endolymphatic sac or vestibular aqueduct. Others have not confirmed this finding. For our purposes, we will consider these tumors as the same entity for the following reasons: identical clinical presentation, immunohistochemical profile, histologic appearance, and association with von Hippel-Lindau disease (VHL).

- APTME/ELST is a rare, histologically benign, locally aggressive, slow-growing tumor possibly derived from the endolymphatic sac of the inner ear.
- There is a wide age range from adolescence to the elderly with a mean age of 30 years old and a female predominance.
- Patients present with a Meniere-like constellation of symptoms: sensorineural hearing loss, tinnitus, and vertigo. Facial nerve involvement is not uncommon.
- Duration of symptoms to diagnosis is typically several years (range 1–22 years).
- Bone invasion is common; metastases and death are rare but usually related to cranial involvement.
- APTME/ELST are associated with von Hippel-Lindau disease (VHL). Fifteen percent of VHL patients are diagnosed with APTME/ELST, and they show some features that differ from patients with sporadic cases. VHL patients are:
  - Diagnosed at an earlier age
  - More likely to be bilateral
  - Clear female predominance with a 2:1 ratio
- Histologic features include:
  - Infiltrative, hypervascular tumors with a bland cytomorphology.
  - Two growth patterns: papillary or follicular/glandular.
  - Lining cells are cuboidal to low columnar with pale pink to clear cytoplasm, arranged in a single, flattened layer. Occasional ciliated cells can be seen.
  - Nuclei are uniformly bland with rare mitoses and no atypia or necrosis.
  - Cystic glandular spaces filled with eosinophilic (PAS positive) material resembling colloid.

- Immunohistochemical stains:
  - Positive for CK19, CK7, CK5/6, EMA, NSE, CD56, vimentin
  - Negative for transthyretin, thyroglobulin, TTF-1
  - Variable staining for S100, synaptophysin, GFAP, low Ki-67 proliferative index (<1%)
- The differential diagnosis includes tumors common to the ear. Immunohistochemical stains can aid in the diagnosis for all of the following:
  - Paraganglioma
  - Middle ear adenoma
  - Metastatic renal cell carcinoma – a special consideration in VHL patients
  - Papillary thyroid carcinoma
  - Choroid plexus papillomas (CPP) – given the tendency of APTME/ELST to involve the cerebellopontine angle
- CPP are typically negative for GFAP, CK5/6, and EMA and positive for synaptophysin, S100, and transthyretin with variable expression for pan-cytokeratin.

References: [46, 61–72]

15. *What are the most common metastatic tumors to the temporal bone region?*
    - Metastases to the temporal bone and ear are primarily described as case reports and autopsy series (Table 7.11). In general, temporal bone and ear metastases are rare and generally asymptomatic. Symptomatic cases are likely a manifestation of end-stage disease.
    - Gloria-Cruz et al. performed an autopsy study of 212 patients with primary, nondisseminated malignant tumors and found 47 patients with metastases to their temporal bones. These include tumors that were either:
      1. Isolated metastases from solid or hematogenous tumors (75%)
      2. Direct extension from metastases to intracranial, leptomeningeal, or regional sites (25%)

    References: [73–77]

**Table 7.11** Characteristics of metastatic tumors to the ear and temporal bone in decreasing frequency

| | |
|---|---|
| Symptoms | Hearing loss (40%)<br>Asymptomatic (36%) |
| Site of origin of the metastasis | Breast<br>Lung<br>Prostate |
| Location of temporal bone metastases | Petrous apex<br>Mastoid |
| Location of ear metastases | Internal auditory canal<br>Middle ear<br>Eustachian tube<br>External ear |

## Case Presentations

### Case 1

#### Learning Objectives

1. To form the differential diagnosis of a middle ear mass
2. To generate a comprehensive immunohistochemical panel to diagnosis a middle ear tumor

#### Case History

A 51-year-old female presents with complaints of ear pain and tinnitus over several months. Physical exam reveals a bulging tympanic membrane and blood in the ear canal. CT scans show a hypervascular soft tissue mass with focal bone involvement.

#### Gross Findings

Multiple tan-red, bloody tissue fragments aggregating 1.0 cm.

#### Histologic Findings (Fig. 7.9a, b)

Nests of monotonous, epithelioid cells in a hemorrhagic, vascular stroma. Inconspicuous, small spindled cells surround the tumor nests. The tumor cells are bland and have moderate to abundant eosinophilic cytoplasm and round nuclei with finely, stippled chromatin.

#### Differential Diagnosis

- Middle ear adenomatous neuroendocrine tumor
- Middle ear/temporal bone meningioma
- Metastatic carcinoma, including renal cell carcinoma

#### IHC and Other Ancillary Studies (Fig. 7.9c, d)

- Positive: Synaptophysin, S100 (sustentacular cells), focal chromogranin
- Negative: Pan-cytokeratin, CK7

#### Final Diagnosis *Middle ear paraganglioma (MEPGL)*

#### Take-Home Messages

1. Paragangliomas are the most common tumors of the middle ear and should be at the top the differential diagnosis.
2. A negative keratin stain excludes most other tumors at this site including middle ear adenomatous neuroendocrine tumor and metastatic carcinomas. An S100 IHC

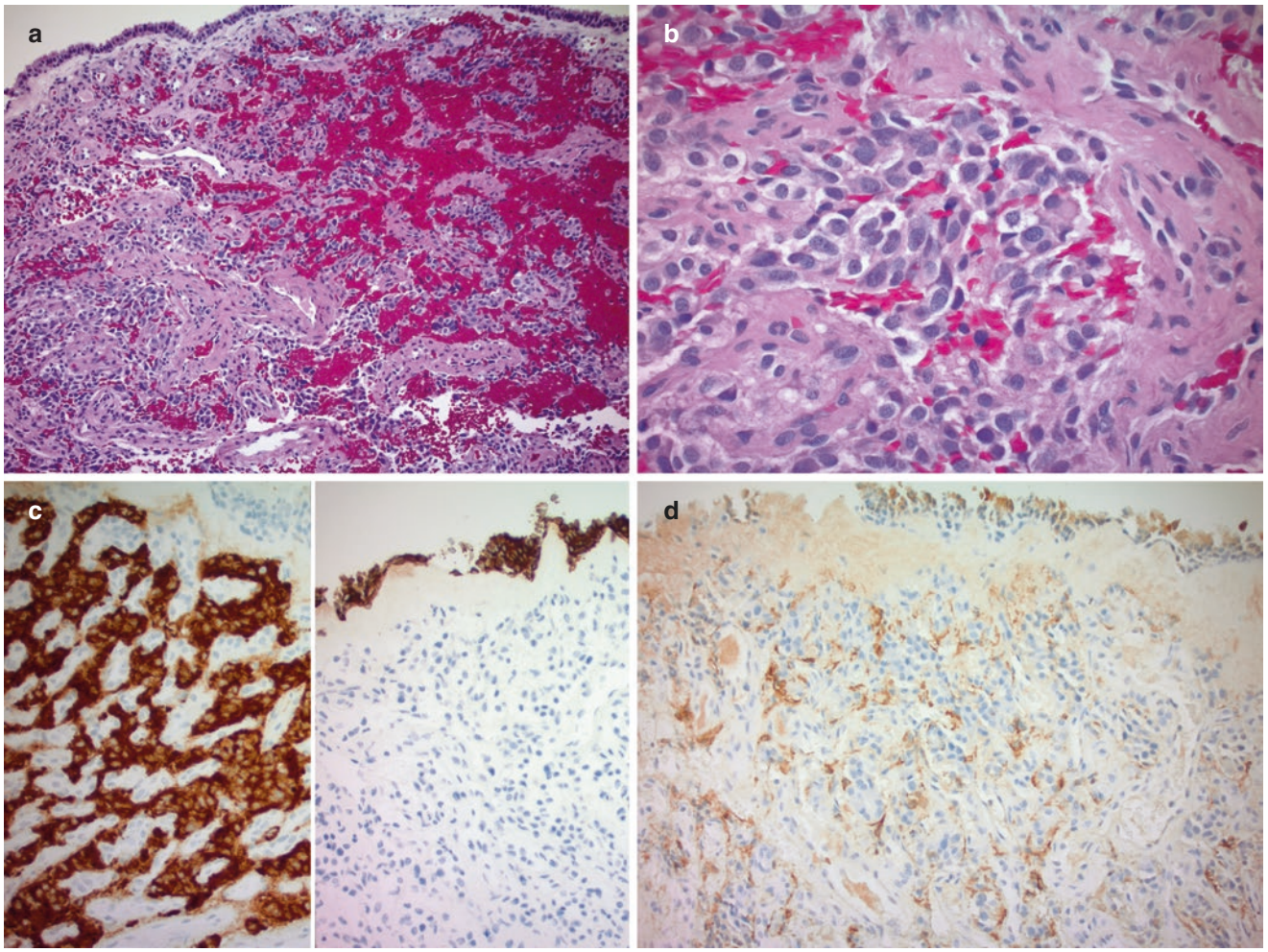


**Fig. 7.9** Case 1. (**a**) Nests of cells in the middle ear submucosa with a vascular stroma. (**b**) Monotonous, epithelioid cells with amphophilic cytoplasm, round nuclei, and salt and pepper chromatin. (**c**) The tumor cells are strongly positive for synaptophysin (left) and negative for pan-cytokeratin (right) which highlights the middle ear epithelium. (**d**) An S100 stain decorates the sustentacular cells

stain highlights sustentacular cells, a unique feature of paragangliomas.

3. Paragangliomas are the most common inherited tumors in humans. A patient with this diagnosis should be referred for genetic testing.
4. Bony erosion is not an indication of malignancy. There are no histologic features to predict malignancy in paragangliomas.

References: [47, 49, 78–80]

## Case 2

### Learning Objectives

1. To determine the differential diagnosis of skin lesions in the ear canal
2. To become familiar with the morphologic features of being and malignant squamous tumors of the ear canal

### Case History

A 73-year-old male presents with ear pain, pruritis and bloody discharge. Physical exam reveals a papillary tan-brown, keratotic lesion in the ear canal.

### Gross Findings

Lobulated, epidermal lesion with a "stuck on" appearance and roughened surface.

### Histologic Findings (Fig. 7.10)

A papillomatous proliferation of basal squamous cells with small, bland nuclei and a moderate amount of pink cytoplasm. Foci of hyperkeratosis are present.

### Differential Diagnosis

- Squamous papilloma
- Squamous cell carcinoma
- Seborrheic keratosis
- Basal cell carcinoma (BCC)

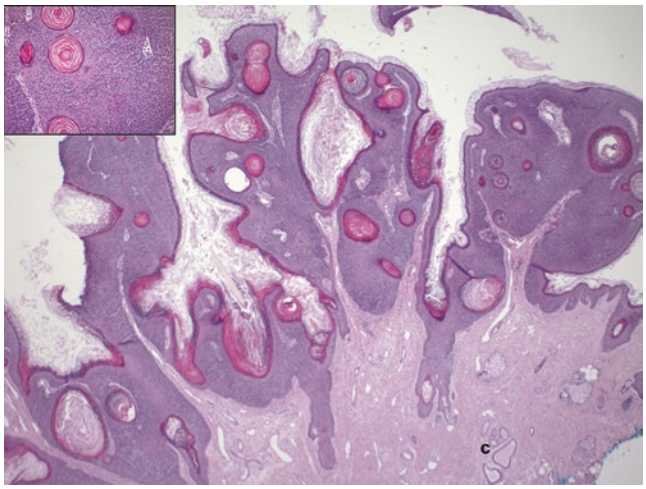

**Fig. 7.10** Case 2. A papillomatous squamous lesion with characteristic horn cysts filled with laminated keratin. A proliferation of (inset) basaloid squamous cells with bland nuclei forms the acanthomatous epidermis

### IHC and Other Ancillary Studies

None.

### Final Diagnosis *Seborrheic keratosis*

### Take-Home Messages

1. Seborrheic keratosis (SK) is a common benign, proliferative lesion of the skin that rarely occurs in the external auditory canal (EAC). Awareness of this entity is essential in avoiding a misdiagnosis of carcinoma on a small biopsy specimen.
2. Squamous cell carcinoma of the EAC has a poor prognosis and requires aggressive treatment. It must be confidently and carefully distinguished from benign squamous lesions of the EAC.
3. SK lacks atypia but may be pigmented. The downward growth of the basaloid proliferation should not be mistaken for BCC. BCC typically shows atypia, retraction artifact around the tumor nests, and a myxoid or mucoid stroma.

   References: [14, 15, 17, 19]

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# Thyroid Gland

8

Danielle Elliott Range and Michelle D. Williams

## List of Frequently Asked Questions

1. What are the histologic components of the thyroid gland, their normal variations and immunoprofile?
2. What are the inflammatory diseases of the thyroid gland?
3. What are the clinicopathologic features of Graves' disease?
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5. What are the criteria for the diagnosis of follicular thyroid carcinoma, and how is it classified?
6. Is Hurthle cell carcinoma a distinct clinicopathologic entity or a variant of follicular thyroid carcinoma?
7. How is poorly differentiated thyroid carcinoma characterized?
8. What is the significance of C-cell hyperplasia and how is it distinguished from medullary thyroid microcarcinoma?
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14. Are hyalinizing trabecular tumors really benign, and what entities are in the differential diagnosis?
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23. What are the most common hematolymphoid tumors of the thyroid gland?
24. What are the most common metastases to the thyroid gland?

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1. *What are the histologic components of the thyroid gland, their normal variations, and immunoprofile?*

The thyroid gland is involved in hereditary endocrine syndromes and is the site of developmental anomalies which can manifest in adulthood. Knowledge of thyroid development and its different cell types is important in

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the understanding of thyroid pathology. Table 8.1 summarizes the different cell types found in the thyroid gland.

- Grossly, the thyroid is a butterfly-shaped gland containing two lateral lobes (left and right) joined by a narrow portion of parenchyma called the isthmus. It is surrounded by a partial, thin fibrous capsule. Approximately 40% of patients have a pyramidal lobe that extends superiorly from the isthmus and represents a remnant of the thyroglossal duct. The normal thyroid gland weighs 15–25 g.
- Follicles are spherical-shaped structures (Fig. 8.1) that are the basic unit of the thyroid gland. Follicles are lined by follicular cells which produce thyroglobulin and thyroid hormones. Thyroglobulin is stored in colloid which is present in the follicles.
  - Thyroid hormones are released from the follicular cell into the rich vasculature that is native to the thyroid gland.
  - Normal follicles are round to oval with large variations in size but not shape.
  - Microfollicles are smaller than most normal follicles and are loosely defined as having less than 10–12 follicular cells on a tissue section.
- C-cells are responsible for calcium regulation; they are difficult to identify in the normal thyroid gland, though small aggregates may be noticeable.
  - C-cells are small epithelial cells with pale to clear cytoplasm and a central, round nucleus with a finely stippled chromatin. They are located in the parafollicular region and sit on the follicle basement membrane along with follicular cells.
  - C-cells are derived from endoderm of the ultimobranchial body.
  - The highest concentration of C-cells is located at the junction between the upper and middle thirds of the thyroid lobes, laterally.
- Solid cell nests (SCN) (Fig. 8.2) are remnants of the ultimobranchial body derived from the inferior branchial arch. They are seen in less than 10% of thyroidectomy specimens.
  - SCN are small clusters of cells averaging 0.1 mm.

**Table 8.1** Immunoprofile of the normal cellular components of the thyroid

| | Follicular cells | C-cells | Solid cell nests | Thymus epithelium | Parathyroid cells |
|---|---|---|---|---|---|
| Thyroglobulin | Positive | Negative | Negative | Negative | Negative |
| TTF-1 | Positive | Positive | Negative | Negative | Negative |
| Calcitonin | Negative | Positive | Negative | Negative | Negative |
| p63/p40 | Negative | Negative | Positive | Positive | Negative |
| PTH | Negative | Negative | Negative | Negative | Positive |
| Other positive IHC | PAX-8 | Synaptophysin<br>Chromogranin<br>CEA | CK19<br>±HBME-1<br>(n)Bcl-2 | HBME-1 | Synaptophysin<br>Chromogranin<br>GATA-3 |

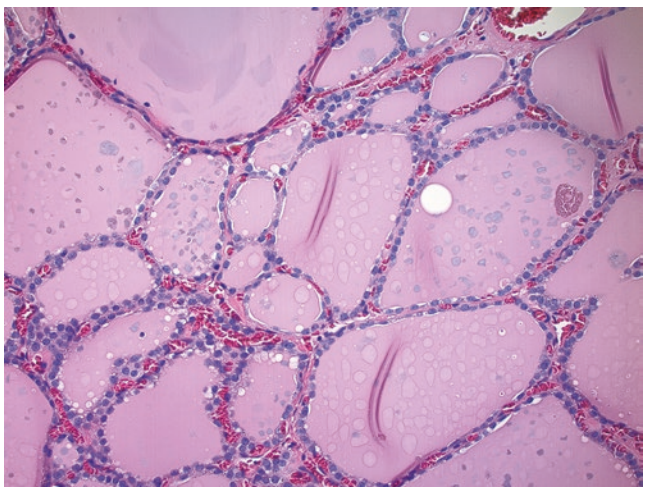

**Fig. 8.1** Normal thyroid shows varying sized follicles lined by low cuboidal cells with small round, mildly hyperchromatic nuclei. Pale pink, amorphous colloid is stored in the follicles, and each follicle is surrounded by a rich vascular network

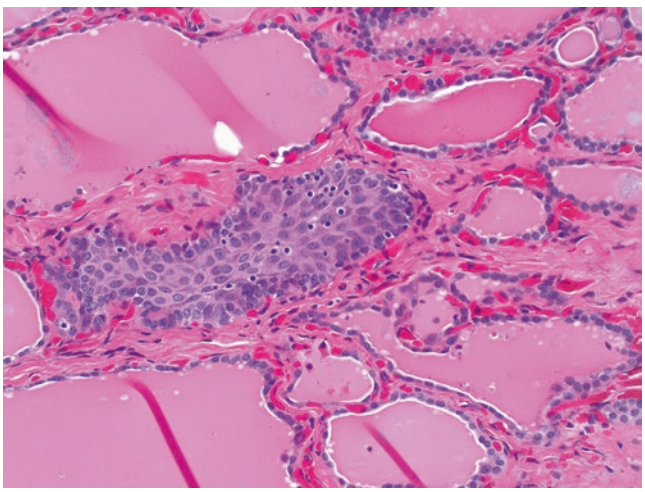

**Fig. 8.2** Solid cell nest. Squamoid epithelium with scant cytoplasm and pale, oval nuclei with small nucleoli

  - The main cell type in SCN is a transitional-type cell with an oval nucleus, fine chromatin, and longitudinal grooves. The cytoplasm is moderate in amount and eosinophilic.
  - C-cells are a minor component of SCN.
- Other tissue types can be found in the thyroid gland as normal variations and include (Fig. 8.3):

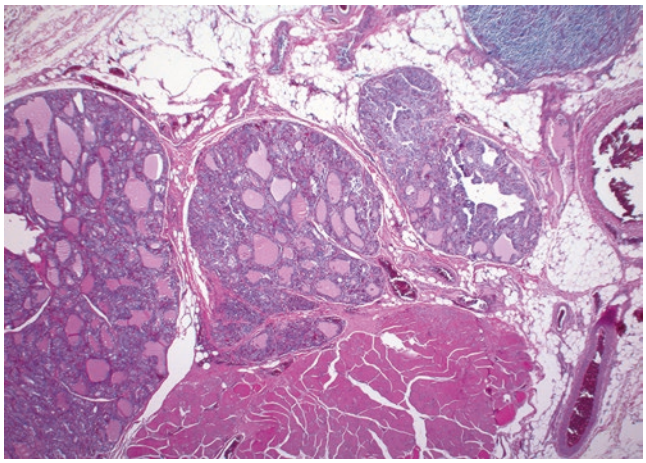

**Fig. 8.3** Nonneoplastic thyroid gland containing intracapsular fat, skeletal muscle, and lymphoid tissue as a normal variation

  - Adipose tissue
  - Skeletal muscle
  - Cartilage
  - Thymus
  - Parathyroid
- Metaplastic tissues include:
  - Bone with or without hematopoietic elements
  - Cartilage
  - Squamous epithelium with or without keratinization
  - Adipose tissue

References: [1–5]

2. *What are the inflammatory diseases of the thyroid gland?*

Inflammation of the thyroid gland is termed thyroiditis and is the result of infectious as well as autoimmune processes (most common). Table 8.2 compares the types of thyroiditis that are likely to be seen by pathologists.

- Hashimoto thyroiditis (Fig. 8.4) is the most common inflammatory disease of the thyroid.
  - A subset of Hashimoto thyroiditis may be part of the IgG4-related sclerosing diseases. These cases usually have:
    - A lower female predominance

**Table 8.2** Inflammatory diseases of the thyroid

| | Hashimoto thyroiditis | Riedel thyroiditis | Subacute thyroiditis |
|---|---|---|---|
| Annual incidence | 0.3–1.5/1000 | 1/100, 000 | 3/100,000 |
| Age, F:M ratio | 30–50 years, 8–9:1 | 30–50 years, 4:1 | 40–50 years, 4:1 |
| Etiology | Autoimmune | Unknown | Viral (Coxsackie, EBV, adenovirus, enterovirus) |
| Clinical | Enlarged thyroid, weight gain, paresthesias, fatigue, constipation, muscle weakness, cramps, hair loss, infertility | Firm, enlarged thyroid<br>Pressure related symptoms, supine-related dyspnea, dysphagia | Painful, enlarged thyroid<br>Fever, malaise, pharyngitis |
| Hormonal status | Hypothyroidism | Euthyroid<br>20–30% hypothyroid at presentation | Classic triphasic course:<br>3–6 week: thyrotoxicosis; 6 mn: hypothyroid; 12 mn: euthyroid |
| Laboratory findings | High titers: anti-Tg, anti-TPO Abs | Low titers: anti-Tg, anti-TPO Abs | High ESR, CRP<br>±Low titers anti-Tg, anti-TPO Abs in 25% cases |
| Gross | Diffuse, symmetrical thyroid enlargement<br>Pale, firm, vaguely nodular parenchyma | Firm, pale, white parenchyma | Rarely biopsied or removed |
| Morphology | Lymphocytic infiltration with germinal center formation<br>Variable plasma cells, macrophages, and giant cells<br>Oncocytic metaplasia of follicular epithelium, ±nuclear pallor, enlargement, pseudoinclusions<br>Fibrosis is minimal but may involve large portions of the gland in the fibrous variant<br>Nodular hyperplasia may be present | Extensive hyalinizing fibrosis extends beyond thyroid capsule<br>May involve adjacent structures: mediastinitis, SVC syndrome<br>Lymphocytic infiltrate with histiocytes, neutrophils, and eosinophils<br>Small and medium-sized vasculitis with lymphocytes and plasma cells | Granulomatous thyroiditis, epithelioid granulomas with multinucleated giant cells centered around disrupted follicles<br>Predominantly chronic infiltrate with lymphocytes, plasma cells, and neutrophils<br>May be misdiagnosed on biopsy as PTC or ATC |

*mn* months, *Tg* thyroglobulin, *TPO* thyroperoxidase, *Abs* antibodies, *SVC* superior vena cava, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PTC* papillary thyroid carcinoma, *ATC* anaplastic thyroid carcinoma

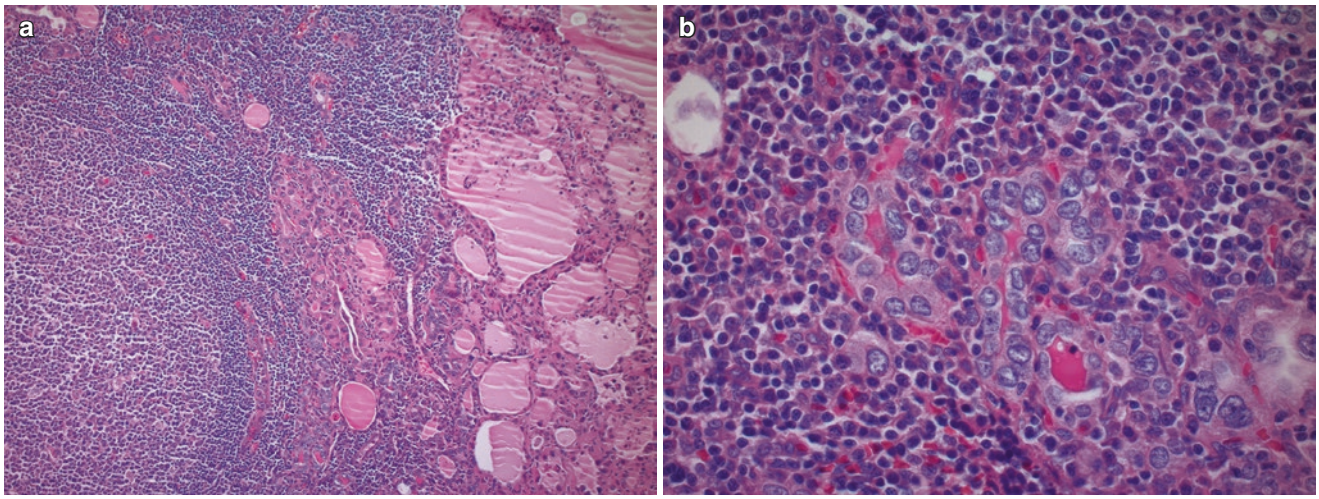


**Fig. 8.4** Hashimoto thyroiditis. (**a**) Oncocytic follicular epithelium (right) in a background of a dense lymphoplasmacytic infiltrate with reactive germinal centers. (**b**) Areas of Hashimoto thyroiditis may show atypical epithelium with enlarged, pale nuclei and occasional grooves; intranuclear pseudoinclusions (not pictured) may also be seen

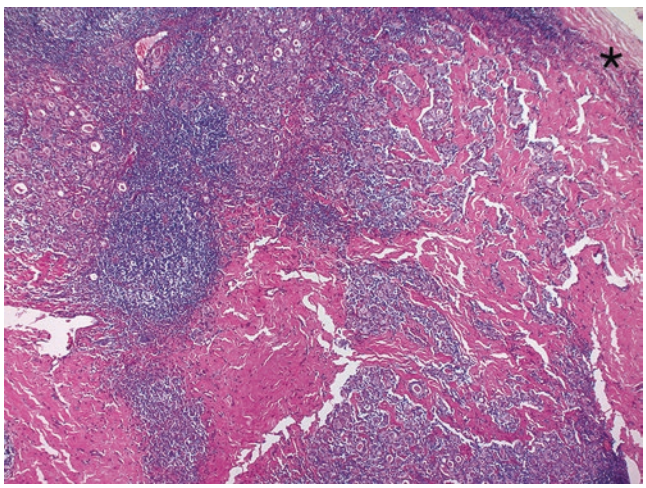

**Fig. 8.5** Fibrous variant of Hashimoto thyroiditis. Extensive sclerosis and associated chronic lymphocytic thyroiditis. The fibrosis is largely confined within the thyroid capsule (asterisk), unlike Riedel thyroiditis

    - More rapidly progressive clinical course
    - Subclinical hypothyroidism
    - Higher levels of anti-thyroperoxidase and anti-thyroglobulin antibodies
  - The fibrous variant of Hashimoto thyroiditis (Fig. 8.5) shows typical features but also includes dense sclerosis. Atrophic follicles and areas of squamous metaplasia are also seen.
- Subacute thyroiditis (Fig. 8.6) is known as granulomatous or de Quervain thyroiditis. It is the most common cause of thyroid pain.
- Riedel thyroiditis should be distinguished from the fibrous variant of Hashimoto thyroiditis by the use of specific criteria:
  - Fibroinflammatory process of all or part of the thyroid with extension into surrounding structures.
  - Chronic inflammation without lymphoid follicles, oncocytes, or granulomas.
  - Occlusive phlebitis.
  - Absence of neoplasm.
  - Entities in the differential diagnosis include fibrous variant of Hashimoto thyroiditis, anaplastic thyroid carcinoma, and sarcoma.
  - Disease associations: pancreatitis, sclerosing cholangitis, orbital pseudotumor, and retroperitoneal and mediastinal fibrosis.
- Suppurative thyroiditis is very rare and typically caused by bacterial infections; fungus and mycobacteria are infrequent causes.
  - Patients at risk include children with branchial fistulas/tracts involving the anterior neck (see Chap. 10), the immunocompromised, the elderly, and those with pre-existing thyroid disease.
- Palpation thyroiditis (Fig. 8.7) is caused by manipulation of the thyroid gland. It can result in elevated thyroid hormone levels, especially in cases of intraoperative manipulation. Typically, it is an incidental pathologic finding seen in glands removed for other reasons. Larger foci may be mistaken for papillary microcarcinomas or C-cell hyperplasia.
  - Microscopy shows scattered foci of follicles filled with foamy and epithelioid histiocytes, multinucleated giant cells, and lymphocytes.

References: [6–15]

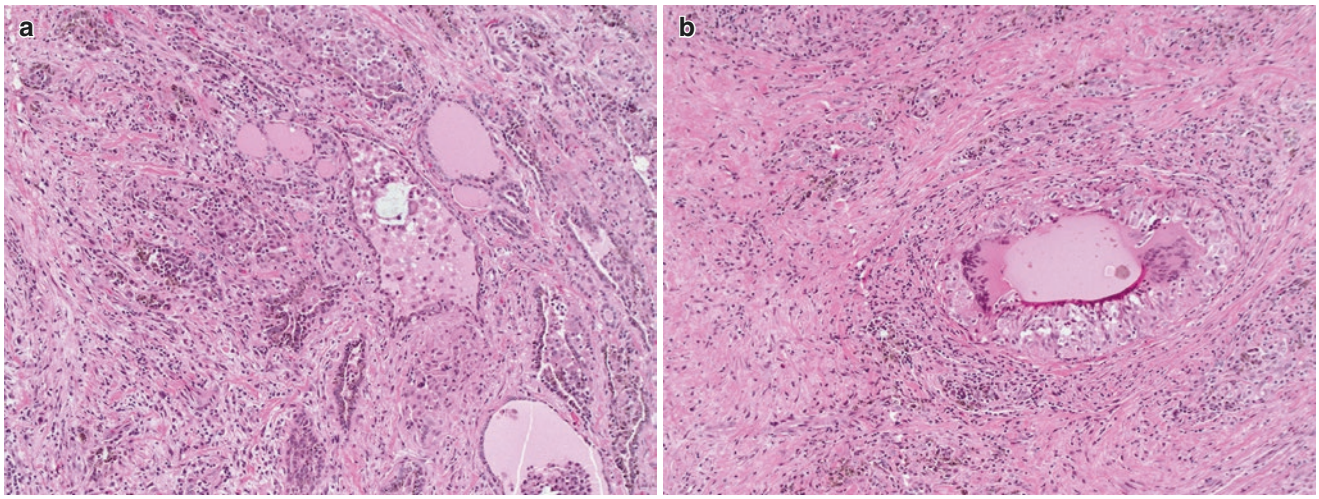


**Fig. 8.6** Subacute thyroiditis. (**a**) Atrophic follicles containing histiocytes and colloid in a background of fibrosis and chronic inflammation. (**b**) Destruction of a follicle with granulomatous inflammation, palisading epithelioid histiocytes, and multinucleated giant cells

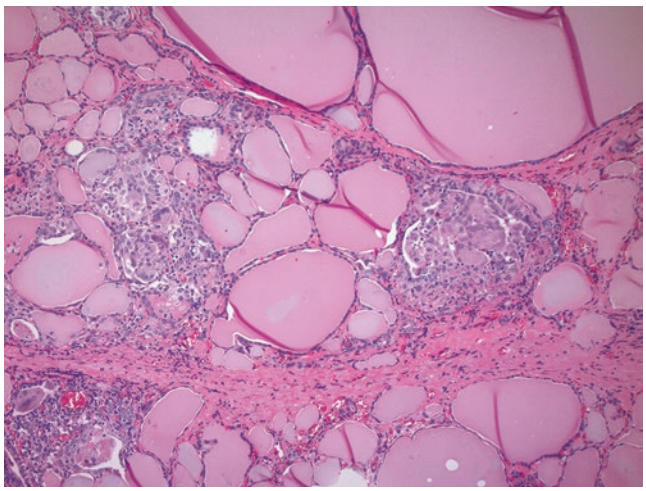

**Fig. 8.7** Palpation thyroiditis. Follicles are filled with chronic inflammation and a foreign body-type giant cell reaction to colloid

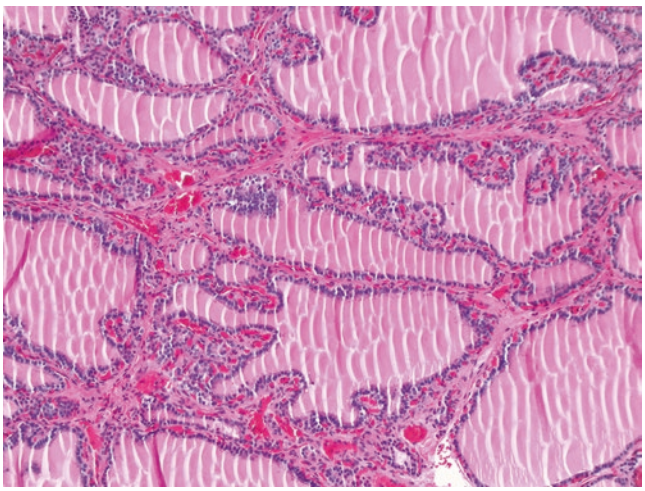

**Fig. 8.8** Graves' disease. Irregularly shaped follicles are separated by delicate fibrosis. The follicular epithelium is hyperplastic with multiple papillary infoldings

3. *What are the clinicopathologic features of Graves' disease?*

   Diffuse follicular hyperplasia is known as Graves' disease and is one of the principal forms of autoimmune thyroid disease. It is the most common cause of hyperthyroidism. Antibodies against the TSH receptor (thyroid stimulating hormone) are pathognomonic of Graves' disease. Patients range in age from 30 to 50 years old, and there is a 5:1 female predominance.

   - Patients present with an asymmetrically enlarged thyroid gland and symptoms related to hyperthyroidism:
     - Weight loss, fatigue, heat intolerance, tremors, and palpitations.
     - Diffuse enlargement is most common, but nodular hyperplasia also occurs.
   - Extraglandular manifestations include:
     - Exophthalmopathy: exophthalmos, proptosis, keratitis, double vision, optic neuropathy
     - Dermopathy
     - Acropachy
   - Histopathologic features (Fig. 8.8) may be marked or subtle depending on what kind of preoperative treatment the patient receives.
     - Gross findings include a pale, slightly firm gland.
     - Histologic findings include:
       - Fine fibrosis of interlobular septa
       - Variable chronic inflammation with or without germinal centers
       - Irregularly shaped follicles

- Hyperplastic epithelium with papillary infoldings
  - Cytologic atypia may be seen in the form of nuclear hyperchromasia or pale with vesicular chromatin. Nuclear membranes may be irregular, and pleomorphism can be seen but should be scattered.
- Cells can show pale, vacuolated cytoplasm or abundant, eosinophilic cytoplasm.
- Hyperplastic nodules may also be present in Graves' disease.
- Treatment includes radioactive iodine, antithyroidal drugs (e.g., methimazole), and subtotal or total thyroidectomy.

References: [16–18]

4. *How are benign nodules of the thyroid classified, and what are the criteria for their diagnosis?*

Thyroid nodules are relatively common abnormalities with an estimated prevalence in the United States of 4%. Thyroid nodules are encountered on physical exam or incidentally, as a result of imaging studies performed for other clinical reasons (Table 8.3). Thyroid nodules may be hyperplastic, benign, or malignant. Among palpable nodules, about 5–10% will be malignant. Regardless of pathogenesis, thyroid nodules may also be solitary or multiple. A general approach to the classification of thyroid nodules is depicted in Fig. 8.9. Among benign thyroid nodules, the nomenclature is not uniform or well-defined. Table 8.4 lists the various terms used to describe thyroid nodules.

- Goiter is the clinical term for an enlarged thyroid gland due to any etiology. Historically, a goiter typically refers to a gland with multiple nonneoplastic nodules. These nodules are usually a result of iodine deficiency in endemic areas or are sporadic in nonendemic areas.
  - Nodular hyperplasia (Fig. 8.10) is the term used to describe these nonneoplastic nodules. It can be seen in the setting of a multinodular goiter or in association with a variety of thyroid diseases (e.g., Graves' disease, thyroiditis).
- Adenomatous nodule is a term that is not well-defined. Generally, it refers to a nodule that is thought to be nonneoplastic and likely represents a hyperplastic process.

**Table 8.3** Demographics of thyroid nodules

| |
|---|
| *Thyroid nodule prevalence:* |
| On palpation 4% (increases with age) |
| On ultrasound 5.2–76% |
| At autopsy 50–65% |
| On PET 1–2% |
| *Thyroid nodule risk groups:* |
| Female gender (4× risk) |
| Ionizing radiation exposure in childhood |
| *Malignant thyroid nodule risk groups:* |
| History of H/N irradiation in childhood or at an advanced age (>70 years old) |
| Male gender |

**Table 8.4** Various terms used in the classification of benign thyroid nodules

| Multinodular gland | Solitary nodule | Histology |
|---|---|---|
| Nodular hyperplasia<br>Adenomatous hyperplasia<br>Adenomatous goiter<br>Multinodular adenomatous goiter | Follicular adenoma<br>Colloid nodule<br>Hyperplastic nodule<br>Adenomatous nodule | Macrofollicular |
| Adenomatous nodule<br>Follicular adenoma or dominant nodule[a] | Follicular adenoma<br>Benign thyroid nodule | Microfollicular |

[a]Encapsulated nodule distinct from background gland

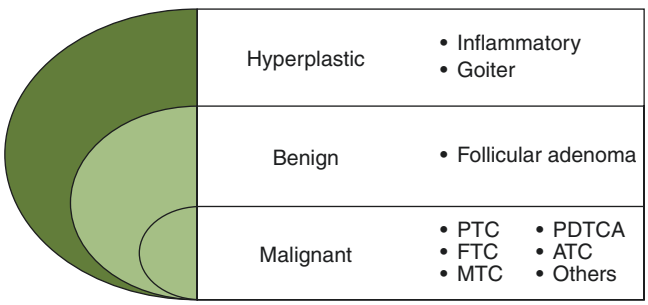


**Fig. 8.9** Classification of thyroid nodules. Malignant nodules include papillary (PTC), follicular (FTC), medullary (MTC), poorly differentiated (PDTC), and anaplastic thyroid carcinoma (ATC)

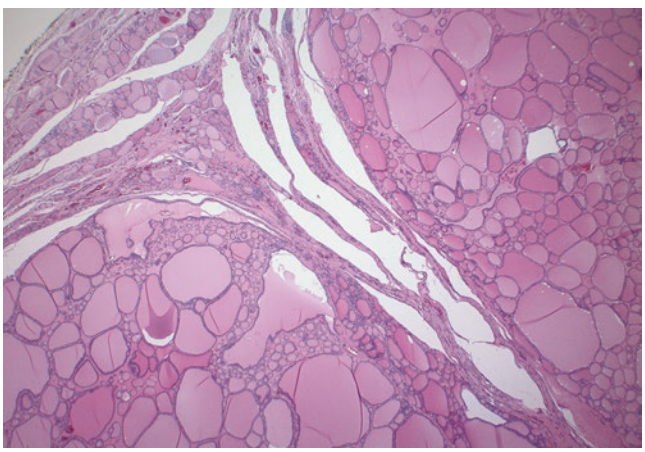

**Fig. 8.10** Multifocal nodular hyperplasia. Macrofollicular nodules are separated by compressed, intervening normal parenchyma. This gland had innumerable nodules of varying sizes

  - Some prefer to use this term for a solitary, follicular nodule that is benign and unencapsulated. In contrast nodular hyperplasia typically refers to a multifocal nodularity.
  - Others use the term to describe the dominant nodule in a multinodular gland or a nodule in an inflammatory process. In which case, the adenomatous nodule may be partially encapsulated, solid, or microfollicular.
  - Still, others use adenomatous nodules and nodular hyperplasia interchangeably.
  - We prefer to use nodular hyperplasia for both:
- A generalized process resulting in a multinodular gland
- Hyperplastic nodules that are a result of a generalized process such as thyroiditis (Fig. 8.11)
- A follicular adenoma (FA) is a benign, encapsulated neoplasm derived from follicular epithelial cells (Fig. 8.12). Follicular adenomas are thought to represent clonal tumors, but studies have shown some inconsistency in this parameter. As a result, histologic features are the principal method for diagnosing a FA.
  - Some pathologists reserve the diagnosis of FA only for solitary follicular lesions. Others require a distinct, complete capsule for the diagnosis, regardless of focality.
  - We use FA for a benign, solitary, follicular lesion of the thyroid as long as it is separate and distinct from the background gland.
- It is notable that some glands will have more than two adenomas. More than this is probably best classified as nodular hyperplasia, but a consensus definition does not exist.
- Of note, some refer to macrofollicular adenomas as adenomatous nodules, likely because this subtype is almost uniformly benign.
- Follicular adenomas may demonstrate a variety of patterns and cell types that have no clinical significance: microfollicular, macrofollicular, simple (normofollicular), solid/trabecular, fetal, embryonic, Hurthle cell (Fig. 8.13), spindle.
  - Toxic adenomas are hyperfunctioning adenomas with follicular hyperplasia, similar to that seen in Graves' disease.
- Clonality varies among lesions that are histologically classified as FA and nodular hyperplasia.

References: [5, 19–24]

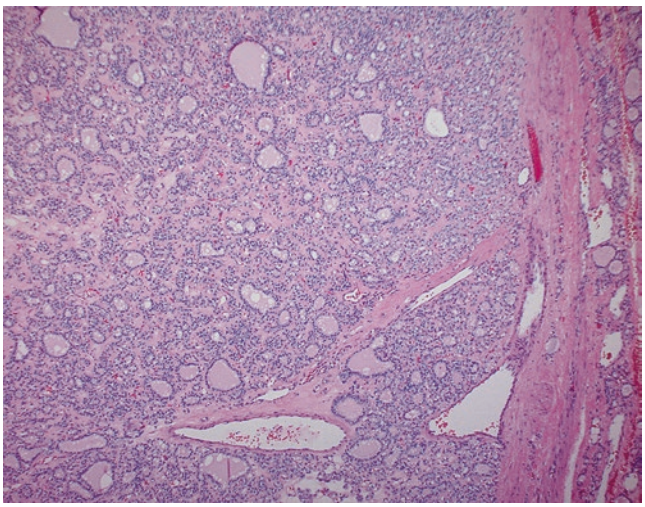

**Fig. 8.12** Follicular adenoma. An encapsulated, predominantly microfollicular proliferation comprising small, bland cells

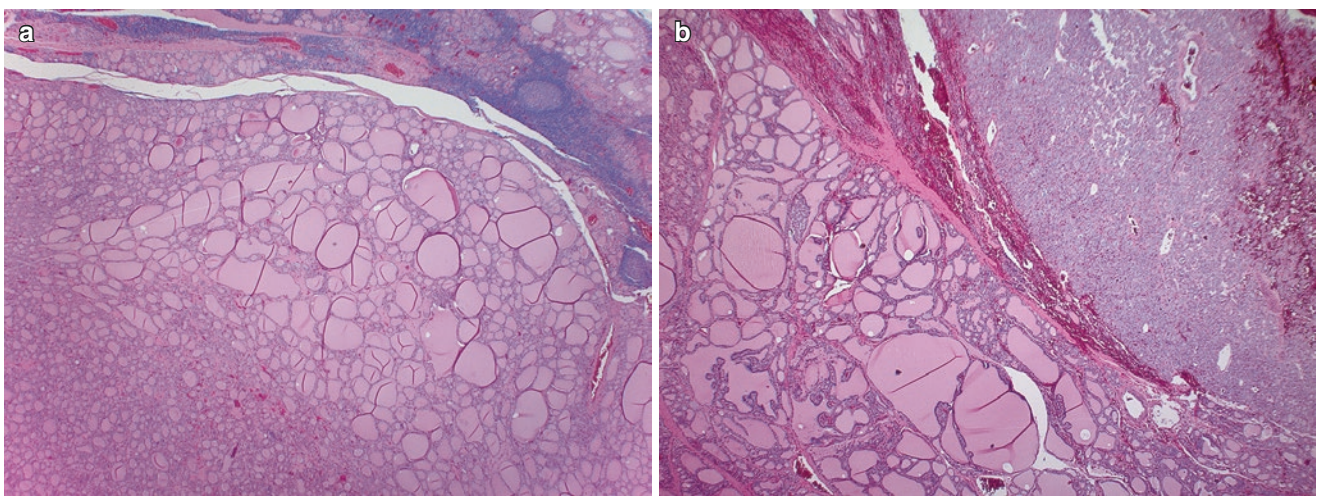


**Fig. 8.11** Nodular hyperplasia. (**a**) Hyperplastic nodule or nodular hyperplasia in a background of Hashimoto thyroiditis and (**b**) in Graves' disease. Some may consider the latter an adenoma

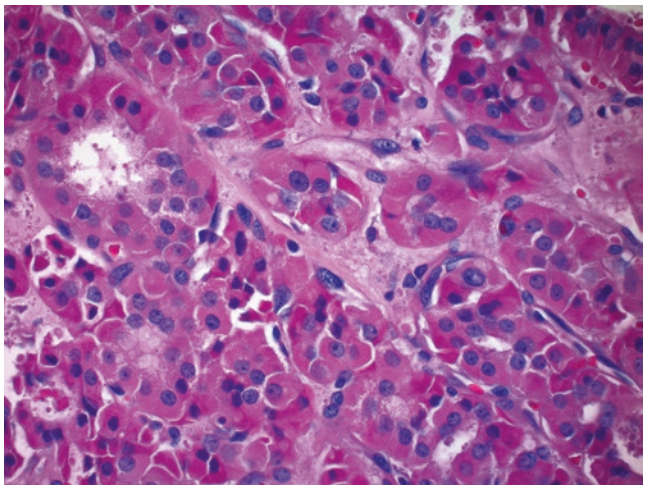

**Fig. 8.13** Hurthle cell (oncocytic) adenoma. This type of follicular adenoma is characterized by cells arranged in trabeculae, microfollicles, and nests. The cells are polygonal with abundant, granular eosinophilic cytoplasm; a central round, hyperchromatic nucleus; and a central prominent nucleolus

**Table 8.5** Relative frequency of thyroid carcinomas

| Differentiated | Histologic type | Incidence |
|---|---|---|
| Well-differentiated | Papillary thyroid carcinoma | 80–90% |
| | Medullary thyroid carcinoma | 4–8 |
| | Follicular thyroid carcinoma | 5–10 |
| | Hurthle cell carcinoma | 2–5 |
| Poorly differentiated | Poorly differentiated thyroid carcinoma | 6 |
| Undifferentiated | Anaplastic thyroid carcinoma | <1–5 |
| | Other | 1 |

5. *What are the criteria for the diagnosis of follicular thyroid carcinoma, and how is it classified?*

Follicular thyroid carcinoma (FTC) is a well-differentiated thyroid carcinoma and the second most common after papillary thyroid carcinoma (Table 8.5). It accounts for 5–10% of all thyroid carcinomas. FTC has a twofold female predominance and a mean age of 50 years.

- Follicular thyroid carcinoma is characterized by an encapsulated, purely follicular growth pattern. It is distinguished from follicular adenoma by demonstrating vascular or full-thickness capsular invasion.
- The 2017 World Health Organization (WHO) classification of FTC is summarized in Table 8.6. FTC is broadly divided into minimally invasive and widely invasive types.
  - Minimally invasive FTC (Fig. 8.14) comprises approximately 80% of all FTC and is further divided into subtypes with and without angioinvasion.
- Up to 50% of minimally invasive FTC are angioinvasive.
  - Widely invasive FTC (Fig. 8.15) is characterized by extensive thyroid parenchymal or soft tissue invasion. Extrathyroidal extension is not required. While vascular invasion may be present, it is not necessary for the diagnosis.
- Capsular invasion is well-defined (Table 8.6) but may be difficult to assess. The tumor capsule of any suspected FTC should be entirely sampled and histologically evaluated to exclude the presence of capsular and vascular invasion.
- Vascular invasion invariable takes the form of angioinvasion. Lymphovascular invasion is not typical and should raise concern for an alternate diagnosis such as papillary thyroid carcinoma.
  - The extent of vascular invasion has strong prognostic significance. Any case with capsular invasion should be fully evaluated for the presence of vascular invasion. Complete sampling of the tumor-to-normal thyroid interface is indicated.
  - Limited vascular invasion involves less than four vessels.
  - Extensive vascular invasion involves four or more vessels.
- Overall disease-specific survival at 5 and 10 years is 94% and 85%, respectively.
  - 5.8–14% of patients will have distant metastases (DM), and 3–5% will have lymph node metastases.
  - DM is the strongest prognostic indicator with 21–55% cancer-specific survival at 10 years (versus 99% for patients without DM).
  - There is a subset of patients that present with DM and low-risk histologic features (approximately 3–5%).
- Genetics: 45% RAS mutations, 35% PAX8/PPARγ rearrangements, 10% PTEN mutations.

References: [25–31]

6. *Is Hurthle cell carcinoma a distinct clinicopathologic entity or a variant of follicular thyroid carcinoma?*

Hurthle cell carcinoma (HCC) is a well-differentiated thyroid carcinoma derived from follicular cells with an oncocytic phenotype. The tumor cells are polygonal with abundant granular cytoplasm, a centrally located nucleus, and a conspicuous to prominent nucleolus. Tumors with greater than 75% Hurthle cells are included in this group. HCC accounts for about 15% of all follicular thyroid carcinomas and 3–5% of all thyroid carcinomas.

- The relatively low incidence of follicular and Hurthle cell carcinomas make generalizations difficult. HCC is viewed as a distinct entity from FTC by the WHO,

**Table 8.6** Diagnostic criteria and clinicopathologic features of follicular thyroid carcinoma

| | Diagnosis | Full-thickness Capsular invasion | Vascular invasion | Behavior |
|---|---|---|---|---|
| Minimally invasive FTC | Minimally invasive FTC | Present | Absent | DM are rare 2–6%<br>LN metastases 2%<br>DOD: 1% |
| | Encapsulated angioinvasive FTC | Present or absent | Present | |
| | | | Limited: <4 vessels | 10-year DFS 95% |
| | | | Extensive: ≥4 vessels | 10-year DFS: 80% |
| Widely invasive FTC | Widely invasive FTC | Present | Usually present but not required | DM 10–40%<br>DOD: 25%<br>10-year DSS: 44% |
| Criteria for FTC | | Penetration of tumor through the TC with minimal intervening stroma between tumor and normal thyroid<br>Invasive tongues may protrude through TC with a thin, attenuated rim of residual capsule<br>A nest of tumor in the normal thyroid, immediately outside of the TC | Involved vessel is usually large, must be in the TC or immediately outside of it, and have an endothelial lining<br>Intravascular tumor should be attached to the vessel wall and protrude into the lumen<br>An endothelium covering over the intravascular tumor or associated thrombus/fibrin should be present | |
| Does not meet criteria for FTC | Consider FT-UMP (see question 15) | Tumor nests in the capsule<br>Protrusion of tumor into the TC without penetration | Intravascular tumor without endothelial covering or thrombus/fibrin | |
| | Consider FA | | Floating tumor within a vascular space<br>Apparent intravascular tumor within the substance of the tumor does not qualify | |

*FTC* follicular thyroid carcinoma, *DM* distant metastases, *LN* lymph node, *DOD* dead of disease, *DFS* disease-free survival, *DSS* disease-specific survival, *UMP* uncertain malignant potential, *FA* follicular adenoma, *TC* tumor capsule

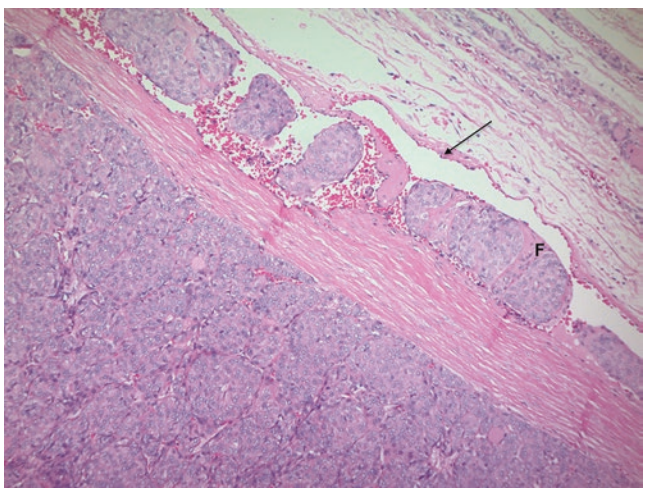


**Fig. 8.14** Angioinvasive follicular thyroid carcinoma. A solid, encapsulated tumor shows invasion in an intracapsular vessel. The intravascular tumor is associated with fibrin and focally attached to the vessel wall which is lined by endothelium (arrow)

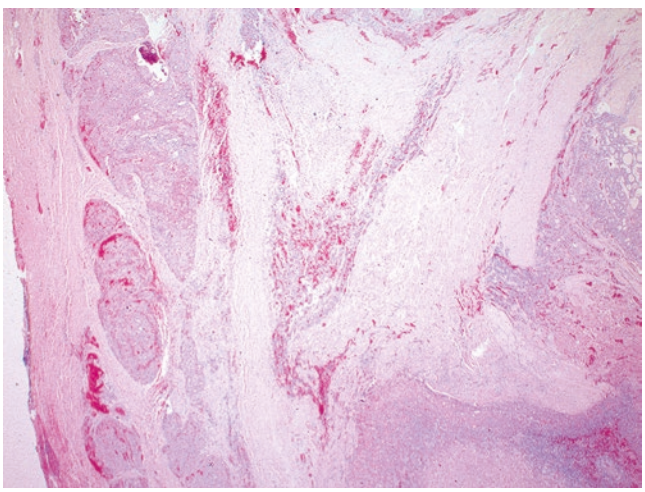

**Fig. 8.15** Widely invasive follicular carcinoma. Lobules and sheets of follicular cells haphazardly infiltrate the thyroid with broad bands of fibrosis. The tumor shows such extensive tissue invasion that the tumor capsule has been destroyed

though controversy regarding this viewpoint does exist.

- By most reports, there are some statistically significant differences between FTC and HCC. Hurthle cell carcinomas usually:

1. Are larger at presentation
2. Occur in a slightly older population
3. Are more likely to have distant metastases at presentation
   - In addition, when compared to FTC, HCC is more prevalent in males, though there is still a female predominance.
   - Despite all these differences, survival rates between the two groups have not consistently been proven to be statistically different.

- HCC is less avid to radioactive iodine, and this may contribute to some differences in outcomes.
- HCC genetic alterations are different from FTC, with lower rates of RAS mutations (16%) and PAX8-PPARγ rearrangement.

References: [32–37]

7. *How is poorly differentiated thyroid carcinoma characterized?*

Poorly differentiated thyroid carcinoma (PDTC) accounts for approximately 2% of all thyroid malignancies in the United States. The mean age of 60 years is slightly higher than in differentiated thyroid carcinoma, and there is a slight female predominance (2:1). The clinical behavior of PDTC is intermediate between differentiated thyroid carcinoma and anaplastic thyroid carcinoma with 10-year survivals of about 45–50%. Figure 8.16 outlines the histologic criteria for the diagnosis of PDTC (Fig. 8.17) based on the Turin proposal published in 2007.

- The Turin criteria:
  1. Do not specify how much of a given tumor should demonstrate the proposed features.
     - Subsequent studies show that tumors containing poorly differentiated components comprising as little as 10% of the tumor volume have a significantly worse prognosis.
     - Others have proposed using a cutoff of greater than or equal to 45% of the tumor volume in order to classify it as poorly differentiated.
  2. Do not require the presence of infiltrative growth and capsular or vascular invasion.
     - Most authors agree that the Turin criteria can be applied to oncocytic thyroid tumors yielding similar, if not worse, survival outcomes.
     - Positive IHC (immunohistochemistry): PAX8, TTF-1, thyroglobulin (may be weak or focal)

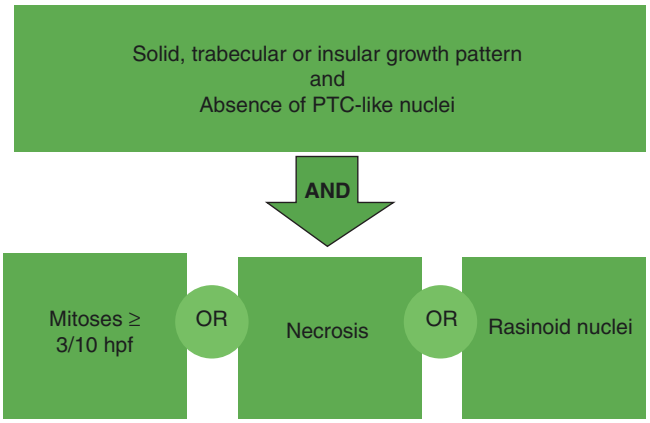


**Fig. 8.16** Turin criteria for the diagnosis of poorly differentiated thyroid carcinoma

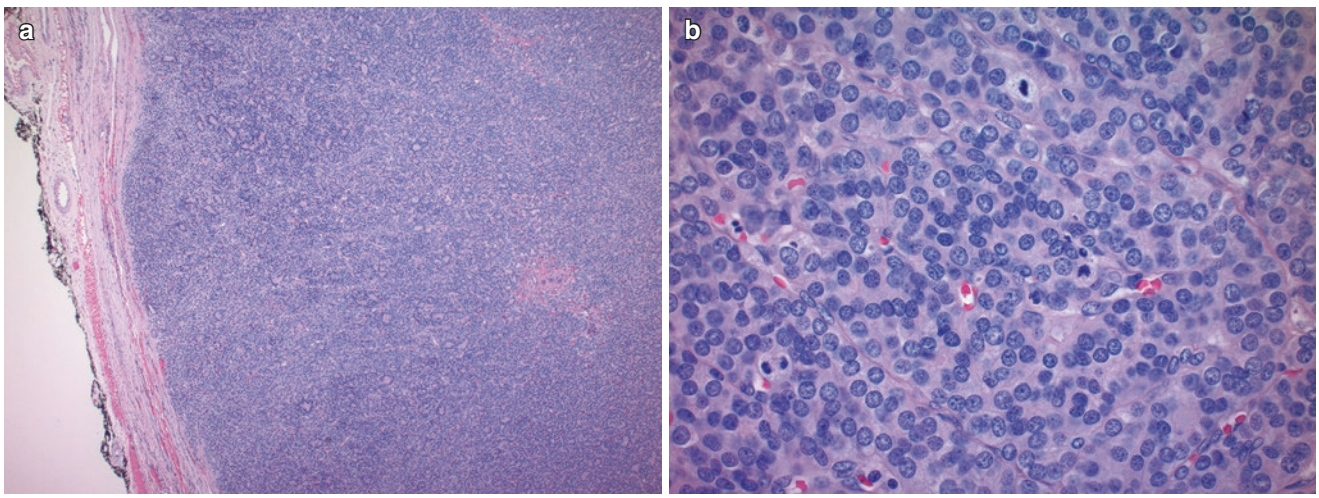


**Fig. 8.17** Poorly differentiated thyroid carcinoma. (**a**) A well-circumscribed, highly cellular tumor with a solid growth pattern. (**b**) Nuclear features of PTC are absent and mitoses are frequent, easily meeting criteria for the diagnosis

- Genetics: RAS mutations are the most common alteration (20–30%), with very few BRAF mutations. Twenty percent of cases will harbor TP53 mutations.

References: [38–45]

8. *What is the significance of C-cell hyperplasia, and how is it distinguished from medullary thyroid microcarcinoma?*

By definition, for the average middle-aged adult, C-cell hyperplasia (CCH) is an aggregate of 50 or more C-cells in 1 low-power field (10× objective). C-cells are normally increased in infants, children, and the elderly. The morphology of C-cells is described in question 1. C-cell hyperplasia (Fig. 8.18) can be seen in a variety of conditions as outlined in Table 8.7. Neoplastic CCH is related to medullary thyroid carcinoma (sporadic and familial), while reactive CCH is not.

- CCH is distinguished from medullary thyroid carcinoma by the presence of invasion.
  - Invasion can be identified by associated fibrosis between and within the aggregate of C-cells.
- Sporadic forms of MTC with and without RET mutations may rarely have C-cell hyperplasia.
  - CCH is not a definitive marker of inherited medullary thyroid carcinoma.
- MicroMTC – stromal fibrosis, amyloid, infiltrative architecture in stroma. There is no size threshold (Fig. 8.19).
- After MTC, CCH is the most common cause of hypercalcitoninemia.
  - CCH should be considered in any patient with increased calcitonin levels even without thyroid nodules by ultrasound.
  - Calcitonin levels in excess of 50 pg/mL are likely to represent CCH or MTC, but a normal calcitonin level does not exclude either diagnosis.

References: [46–50]

9. *What are the clinicopathologic features of medullary thyroid carcinoma?*

Medullary thyroid carcinoma (MTC) is a malignant epithelial neoplasm of C-cell origin. It accounts for only 4–8% of all thyroid malignancies but is responsible for approximately 15% of thyroid cancer deaths. The majority of MTC cases are sporadic (75%), but the proportion of cases attributed to the hereditary forms (25–30%) is one of the highest among hereditary cancer syndromes. Table 8.8 compares sporadic and hereditary MTCs.

- Hereditary MTC manifests as three different, autosomal dominant syndromes which are all caused by germline point mutations in the RET proto-oncogene: multiple endocrine neoplasia (MEN) types 2A and 2B and familial MTC (FMTC). A comparison of the clinicopathologic features of the three syndromes is summarized in Table 8.9.

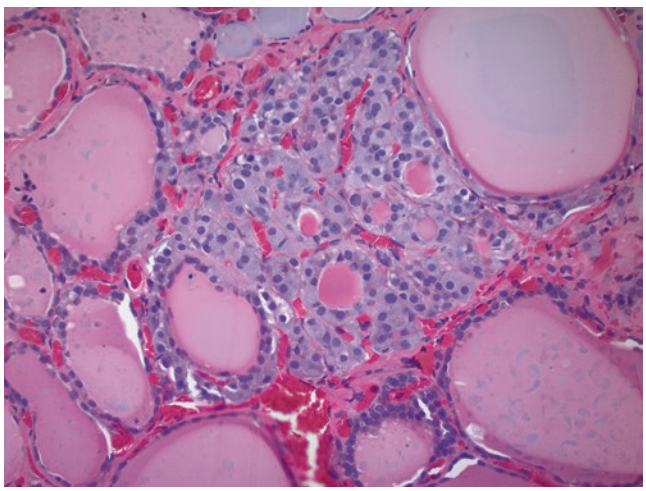

**Fig. 8.18** C-cell hyperplasia. Polygonal cells with clear to amphophilic cytoplasm and a central, round nucleus are present in a parafollicular location

**Table 8.7** Comparison of reactive and neoplastic C-cell hyperplasia

| Reactive/physiologic C-cell hyperplasia | Neoplastic C-cell hyperplasia |
|---|---|
| 50 normal-appearing C-cells in one low-power field (10x objective) | |
| Hashimoto thyroiditis<br>Primary and secondary hyperparathyroidism<br>Peri-tumoral<br>Drugs | Germline RET proto-oncogene mutation |
| Focal or diffuse | Nodular, focal, and/or diffuse |
| Unilateral | Bilateral |

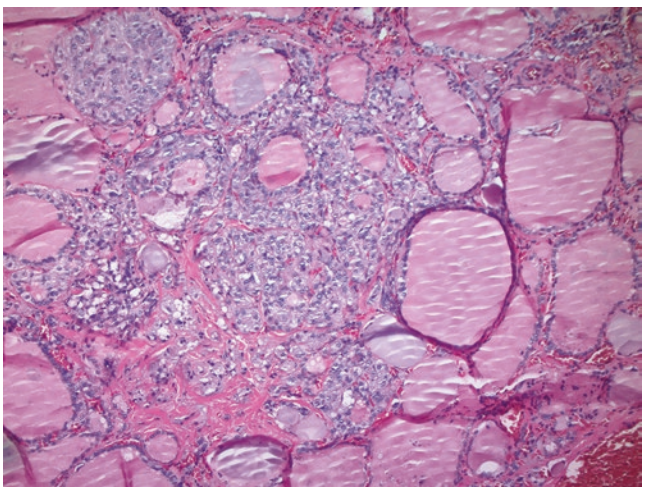

**Fig. 8.19** Medullary thyroid microcarcinoma. Large nests of pale cells appear to be in a parafollicular location, but areas of stromal infiltration at the lower left edge confirm the diagnosis of carcinoma in this MEN 2B patient

  - The genetics of hereditary MTC are complex, and the specific mutated codon within the RET genome (e.g., genotype) correlates with disease aggression and age at diagnosis.
- Almost 50% of sporadic MTCs harbor a somatic RET mutation.
  - 75–90% of the sporadic RET mutations are at codon M918T. This genotype is associated with aggressive behavior and is the same genotype seen in most MEN 2B patients.
  - RAS mutations are present in up to 80% of the RET-negative sporadic MTCs.
  - An estimated 5–10% of presumed sporadic cases will prove to be hereditary upon further investigation warranting genetic testing in all MTC patients.
- Grossly, medullary thyroid carcinoma is often well-circumscribed but unencapsulated with a tan-white, homogeneous, and slightly fleshy cut surface.
  - Sporadic cases tend to be unifocal, while familial cases are multifocal and bilateral.

**Table 8.8** Comparison of familial and sporadic forms of medullary thyroid carcinoma

| | Sporadic | Familial |
|---|---|---|
| Age, gender | 50–60 years, 2:1 = F:M | Young, <20 years, 1.5:1 = F:M |
| Clinical presentation | Neck mass 50% with LN metastases 10% with DM | Neck mass, symptoms of pheochromocytoma, elevated calcitonin |
| Tumor focality | Unifocal | Multifocal, bilateral |
| C-cell hyperplasia | Rare | 100% |
| Genetics | Tumor only RET mutation: ~50% RAS mutations: 10–45% of RET-negative cases | Germline RET mutation: 100% |
| Behavior | Often aggressive with lymph node metastases at diagnosis | Variable based on stage at diagnosis |

*LN* lymph node, *DM* distant metastases

  - MTC has an almost 100% penetrance in the familial forms. Prophylactic thyroidectomy is the treatment of choice for known familial cases.
  - Prophylactic thyroidectomy specimens may not have any gross abnormalities. The entire gland should be submitted for histologic evaluation to exclude a microcarcinoma.
- The histologic appearance of MTC does not vary between the sporadic and familial forms.
  - MTC cells are arranged in sheets, nests, and trabeculae with varying amounts of fibrous stroma (Fig. 8.20).
- Amyloid deposition in the stroma is present in most cases.
  - The cells are typically polygonal to slightly spindled with a moderate amount of eosinophilic to amphophilic cytoplasm. Fine, intracytoplasmic, basophilic granules may be evident.
  - Tumor nuclei are monotonous and round with a finely stippled chromatin and inconspicuous nucleoli. Binucleated forms and intranuclear pseudoinclusions can be seen.
  - Necrosis and mitoses are uncommon.
- Several histologic variants (see Fig. 8.20) of MTC have been described but have no clinical significance. Awareness of the different variants and their mimics is important in making the correct diagnosis. Table 8.10 lists the variants of MTC and their differential diagnosis.
  - Given its protean morphology and the significant clinical implications of the diagnosis, immunohistochemical confirmation is recommended for the diagnosis.
  - Positive IHC: CK7, TTF-1, calcitonin, synaptophysin, chromogranin, CD56, CEA, galectin-3 (variable).
  - Negative IHC: thyroglobulin, and CK20. PAX-8 is variable/weak.

References: [51–57]

10. *What are the diagnostic features of papillary thyroid carcinoma?*

**Table 8.9** Clinicopathologic features of inherited forms of medullary thyroid carcinoma

| Type | MEN 2A | MEN 2B | Familial MTC |
|---|---|---|---|
| Relative frequency | 70% | 5–10% | 22–25% |
| Age at presentation | 20–30 years | <10–20 years | 45–55 years |
| High-risk codons | 634 (80%) | 918 (90%) | 634 |
| Pheochromocytoma | 30–50% | 50% | – |
| Other clinical findings | Hyperparathyroidism Hirschsprung disease Cutaneous lichen amyloidosis | Neuromas, GI ganglioneuromas, Marfanoid habitus | None Considered a variant of MEN 2A |
| Behavior | Variable | Most aggressive | More indolent |

*MEN* multiple endocrine neoplasia, *GI* gastrointestinal

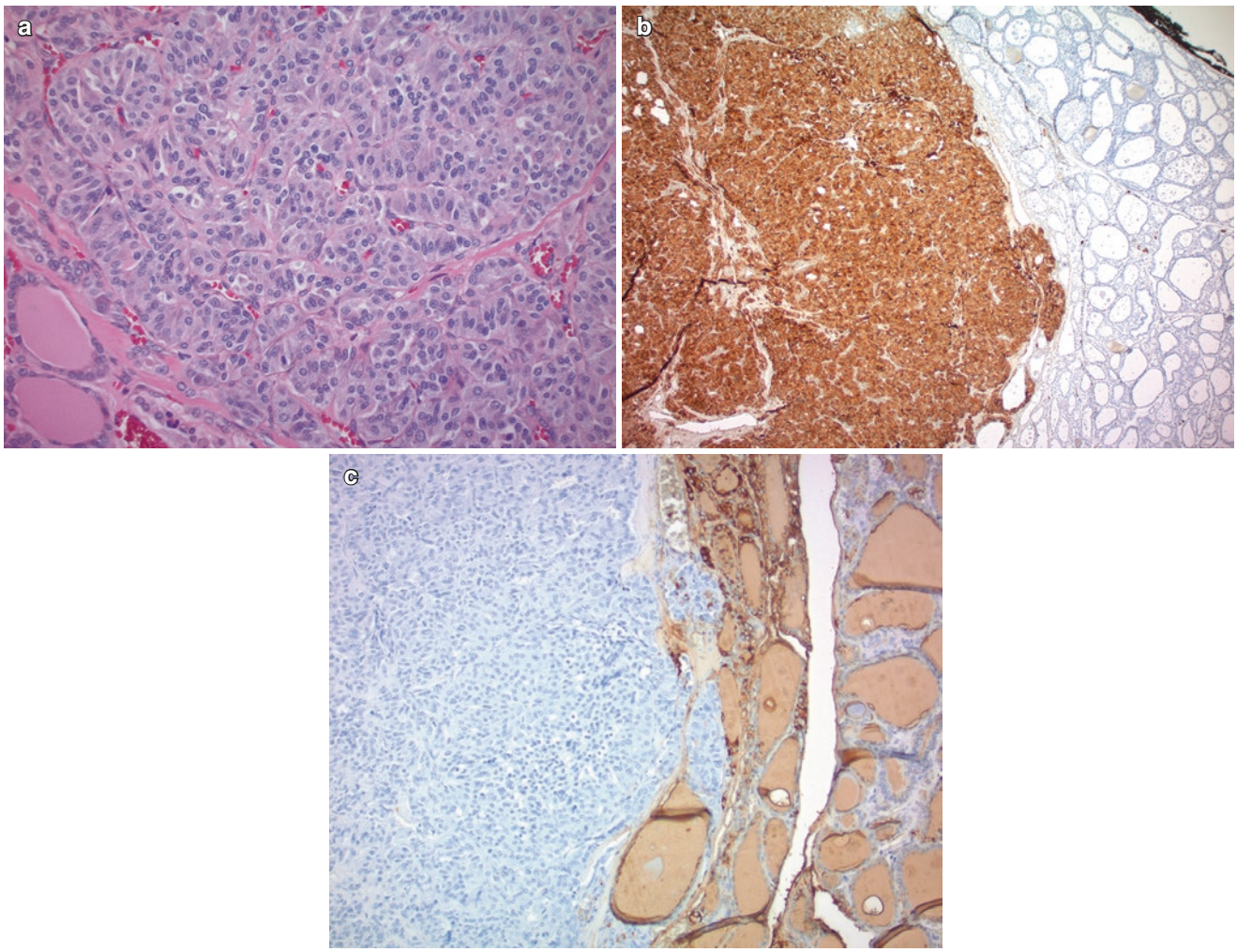


**Fig. 8.20** Medullary thyroid carcinoma. (**a**) Nests and ribbons of monotonous tumor cells with amphophilic cytoplasm and oval nuclei with a finely, stippled chromatin. The tumor cells are strongly positive for (**b**) calcitonin and negative for (**c**) thyroglobulin. The normal thyroid tissue (right) shows the inverse thyroglobulin staining pattern

**Table 8.10** Histologic variants of medullary thyroid carcinoma and their mimics

| Variant MTC | Mimic | Differential stains expressed in mimic |
|---|---|---|
| Spindle | Melanoma | HMB-45+, CK– |
| Small cell | Metastatic neuroendocrine carcinoma | IHC overlaps, clinical history required |
| Usual | Paraganglioma | CK–, TTF-1– |
| | Hyalinizing trabecular tumor, solid PTC | Tg+, calcitonin– |
| Oncocytic | Hurthle cell neoplasm | Tg+, calcitonin– |
| Follicular | Follicular neoplasm | Tg+, calcitonin– |
| Papillary | Papillary thyroid carcinoma | Tg+, calcitonin– |

*CK* cytokeratin, *Tg* thyroglobulin

Papillary thyroid carcinoma (PTC) is the most common malignancy of the thyroid gland accounting for over 85% of all thyroid carcinomas in the United States. Its incidence rate is one of the most rapidly increasing among all carcinomas worldwide. Part of this is attributed to increased detection and diagnosis. PTC is often an indolent tumor with 5-year survival rates approaching 98%. There is a striking female predominance, and the average age is 50 years. Papillary thyroid carcinoma (PTC) is divided into the classic/conventional type and several variants (Table 8.11).

- Classic PTC presents as a painless thyroid mass. About 30% of patients will present with lymph node metastases. Bilateral tumors occur in 20% of cases.

**Table 8.11** Relatively frequency of PTC variants

| Variant | Frequently |
|---|---|
| Classic | 30–40% |
| Microcarcinoma | 25–30 |
| Encapsulated follicular variant | 4 |
| Infiltrative follicular variant | 6 |
| (NIFTP) | 17 |
| Tall cell | 4–7 |
| Solid | 1–3 |
| Diffuse sclerosing | 2 |
| Columnar | <1 |

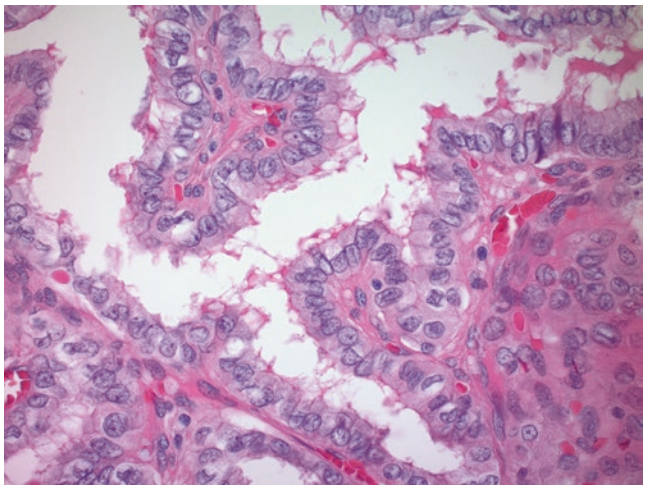

**Fig. 8.21** Papillary thyroid carcinoma. Classic PTC shows papillae with fibrovascular cores lined by atypical cells with enlarged, oval nuclei, pale chromatin, longitudinal grooves, and irregular nuclear membranes

- Grossly, classic PTC (cPTC) is ill-defined, tan-white, and firm. Cystic areas with gross papillae may be evident. Necrosis is rare and usually related to biopsy effect.
- Histologic evaluation (Fig. 8.21) shows a papillary architecture with varying amounts of follicular growth.
  - The cell cytoplasm ranges from eosinophilic to pale and clear.
  - The tumor is often associated with dense sclerosis at the advancing edge.
  - Psammoma bodies are rounded, stromal calcifications with concentric laminations arising from non-viable tumor cells. They may be present in varying amounts.
  - Diagnostic criteria for classic papillary thyroid carcinoma and most variants rely on nuclear features:
    - Enlargement with size variation
    - Oval, elongated nuclei
    - Clear, pale chromatin
    - Longitudinal nuclear grooves
    - Irregular nuclear membranes
    - Nuclear overlap
    - Intranuclear pseudoinclusions
    - Nuclear pseudoinclusions can have artefactual mimics, and strict criteria should be applied. They are not true nuclear inclusions but rather represent folding of the cytoplasm into the nucleus. As a result, nuclear pseudoinclusions should be:
      1. Surrounded by a membrane (i.e., the cytoplasmic membrane)
      2. The same tinctorial quality of the cytoplasm
- Positive IHC: TTF-1, thyroglobulin, PAX-8, CK19, LMWCK.
- Negative IHC: CK20, calcitonin, synaptophysin, chromogranin.
- Genetics: BRAF-V600E (40–80%), RET/PTC (5–25%), RAS (0–10%), TERT (5–10%).
- PTC typically is an indolent tumor with a 5-year survival rate of 98% and disease-specific survival approaching 99%.
  - Recurrence rates range from 10% to 30%.
  - Lymph node metastases: 40–50%.
  - Distant metastases: up to 5%, usually lung.
- Among the variants of PTC, 15 are recognized by the WHO. Recognition of these variants is important in order to exclude their benign mimics and to be aware of their clinical behavior. For the discussion here, we will focus on the more common variants and divide them into those with aggressive behavior (question 11) and those with a nonaggressive behavior (question 13).

References: [58–60]

11. *Which are the aggressive variants of papillary thyroid carcinoma, and what are their clinicopathologic features?*

Most variants of PTC exhibit the classic nuclear features, but there are some exceptions (Fig. 8.22). The biologically aggressive variants of PTC as a group account for less than 10% of all PTC (Table 8.12). For some in this group, overall survival rates don't differ from classic PTC, but they are included here because of more aggressive behavior in the form of recurrences, metastases, and disease-free survivals. A few notable points about some of the tumors in this category are discussed below. The amount of a given tumor that displays features of a particular variant is not well established. This is partly due to the scarcity of these variants. The criteria used in this section are based on WHO parameters. But the reader should be aware that the quantitation varies among authors.

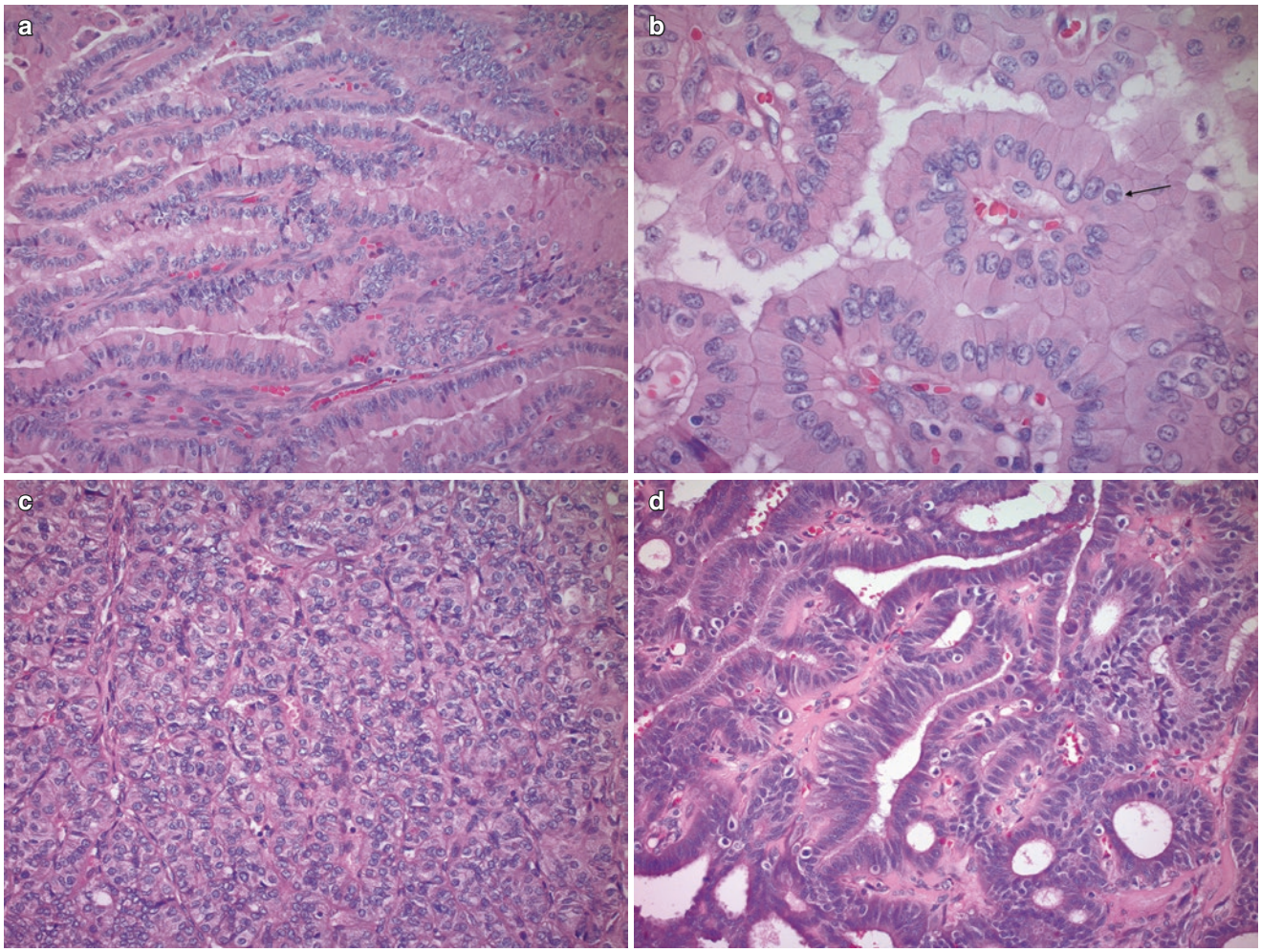


**Fig. 8.22** Papillary thyroid carcinoma variants. (**a**) Tall cell variant shows characteristic linear arrays of papillae, so-called tram tracks lined by (**b**) tall cells that are columnar three times as tall as wide, with abundant apical cytoplasm and robust, nuclear features of PTC including intranuclear pseudoinclusions (arrow). (**c**) Solid variant is largely devoid of follicles and has a trabecular pattern with pale, irregular nuclei. (**d**) Columnar variant shows follicles without colloid and lined by columnar cells with pseudostratification and minimal nuclear features of PTC

- Tall cell variant is the most common of the aggressive PTC variants.
- Solid variant is included among the more aggressive variants as there is literature to suggest this, especially in adults.
- Columnar variant as a histologic type alone does not convey a worse prognosis. But it is included here because columnar variants with extrathyroidal extension do convey a worse prognosis and should be considered among this group. In addition, this subtype is found more often found in older, male patients who tend to do worse overall among thyroid carcinoma groups.
- Hobnail variant – there is evidence to suggest that the hobnail phenotype may be related to subsequent development of poorly differentiated and undifferentiated thyroid carcinomas.

References: [60–90]

12. *What are the criteria used for the diagnosis of follicular variant of papillary thyroid carcinoma, and how is it related to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)?*

    Follicular variant of papillary thyroid carcinoma (FVPTC) accounts for 15–25% of all PTCs. The criteria for the diagnosis of FVPTC have evolved over the 40 years since its initial recognition, with regard to both nuclear and architectural features. This has resulted in significant inter- and intraobserver variability in the diagnosis of FVPTC, even among expert pathologists. Current criteria for the diagnosis of FVPTC include:

    1. An "almost exclusive" (99%) follicular architecture.
    2. At least focal nuclear features of PTC must be present. An actual amount has not been defined and is the source of much of the diagnostic variability.

**Table 8.12** Clinicopathologic features of aggressive variants of papillary thyroid carcinoma

| Variant | Tall cell | Solid | Columnar | Diffuse sclerosing | Hobnail |
|---|---|---|---|---|---|
| % all PTC | 1–19% | 1–3% | 0.2–0.4% | 0.7–6.6% | 0.2% |
| Demographics, mean age (years) | Older patients, 50 | More common in children, 35 | More often male, 64 | F:M = 5:1, 30 | F:M = 2:1, 53 |
| Clinical | Larger size, increased among males (25%) | Patients may have radiation exposure | Older, males have more aggressive disease | Neck mass with LAD at presentation | Neck mass and cervical LAD at presentation |
| Quantitative criteria | At least 30% tall cells | All or almost all solid (at least 70%) | At least 30–50% | None | At least 30% |
| Morphology | Tumor cells that are columnar and 2–3× tall as they are wide<br>Abundant eosinophilic cytoplasm with straight cell borders<br>Typical to exaggerated nuclear features of PTC<br>Numerous papillae forming linear arrays of tumor cells ("tram tracks") | Typically infiltrative<br>Nests of cells surrounded by a thin, fibrous stroma<br>Classic nuclear features of PTC and abundant cytoplasm<br>Minimal to absent papillae or follicles<br>Rare psammoma bodies<br>May show extensive fibrosis | Typically poorly circumscribed<br>Papillae and gland-like structures with cribriform areas<br>Columnar cells with pseudostratified, hyperchromatic nuclei<br>±subnuclear and supranuclear vacuoles<br>Rare pseudoinclusions and grooves<br>(m)ß-catenin+, CDX2+ | Diffuse gland involvement usually bilateral with extensive LVI<br>Numerous psammoma bodies<br>Solid, follicular, papillary<br>Cells with classic nuclear features of PTC<br>Squamous metaplasia<br>Extensive fibrosis<br>Chronic lymphocytic thyroiditis | Complex papillae, micropapillae, follicles without colloid<br>Cuboidal cells with dense eosinophilic cytoplasm, sharp cell borders, low N:C ratio, dyshesion<br>Apically located, pleomorphic, hyperchromatic nuclei<br>Focal classic PTC nuclei<br>2–3 mitoses/hpf, rare necrosis |
| Molecular | BRAF, TP53, TERT | RET/PTC3 > NTRK1/3 >> TERT | 30% BRAF | RET/PTC1 > RET/PTC3<br>Rare BRAF | 70% BRAF<br>7% RET/PTC1 |
| Adverse behavior | RAI-refractory<br>ETE, LN metastases | Increased ETE and LVI<br>High association with lung DM | Large tumor size, ETE, LN disease, infiltrative growth | Frequent LN metastases, LVI, ETE (70%) | Frequent LVI, LN, and DM<br>Refractory to RAI |
| Recurrence rates | Recurrence rate: 27% | Recurrence rate: 15–20%<br>Higher DM rate | LN metastases: 49% | Recurrence rate: 22%<br>LN metastases: >80%<br>DM: 12% | Recurrence rate: 25%<br>LN metastases: 70%<br>DM: 36% |
| Survival | 5-year OS: 82% | 10-year OS: 90% | 10-year DSS: 93%, DOD: 30% | 5-year survival: 90% | DOD: 21% |

*LAD* lymphadenopathy, *LVI* lymphovascular invasion, *RAI* radioactive iodine, *LN* lymph node, *(m)* membranous, *ETE* extrathyroidal extension, *DM* distant metastases, *OS* overall survival, *DOD* dead of disease

3. The tumor must show evidence of invasion, either of the adjacent normal thyroid parenchyma, the tumor capsule, or vasculature.

Follicular variant is currently divided into infiltrative and encapsulated subtypes.

- Infiltrative follicular variant of PTC (IFVPTC) is a distinct entity with morphologic, clinical, and molecular characteristics that closely resemble classic PTC. In particular, IFVPTC typically shows robust, well-developed nuclear features of PTC (Fig. 8.23).
- Encapsulated FVPTC (EFVPTC) is predominantly encapsulated with foci of vascular or capsular invasion. It typically has only scattered or less developed nuclear features of PTC. EFVPTC is a controversial entity for a few reasons:

1. There are no clear, well-defined criteria for exactly how much of the tumor must show nuclear features of PTC.
2. Some authors believe that this entity is best classified as follicular carcinoma since it demonstrates molecular, clinical, and architectural (capsular or vascular invasion) features that more closely resemble follicular thyroid carcinoma.

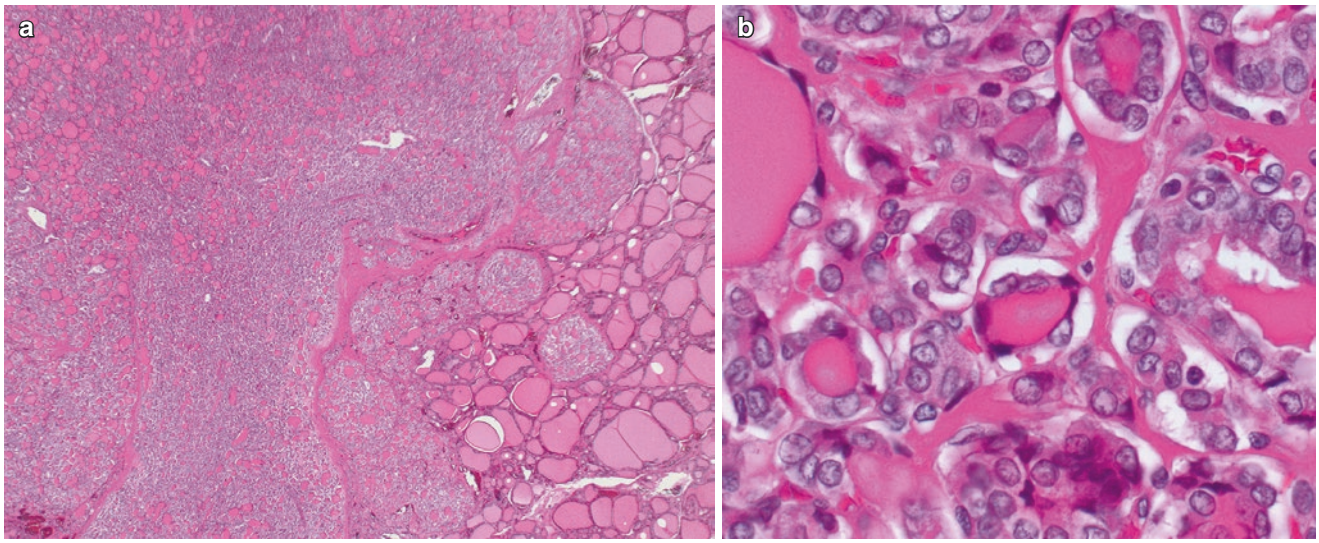


**Fig. 8.23** Infiltrative follicular variant of PTC. (**a**) Infiltrative follicles of tumor percolate into normal thyroid tissue. (**b**) High magnification shows classic PTC nuclei

- Genetics: RAS mutations and PAX8/PPARγ rearrangements.
- Hematogenous metastases are more common than lymphatic metastases.
- Our knowledge of the clinical behavior of IFVPTC and EFVPTC is based on studies before 2006, and after 2016.
  - Before 2006, FVPTC was not routinely studied or divided into IFVPTC and EFVPTC. Instead it was more commonly viewed as a single entity which behaved similarly to cPTC based on statistical significance, usually related to survival and mortality. Though rates of LN metastases were higher in the cPTC group.
  - After 2006 and before 2016, FVPTC was touted as having a better prognosis than cPTC. Though this was not uniformly confirmed by all studies, likely because of variability in diagnostic criteria. During this time, studies began to separate FVPTC into the infiltrative and encapsulated subtypes in an attempt to better understand the behavior and genetics of each.
  - In 2016 the noninvasive, EFVPTC was reclassified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) by a panel of experts. And by default, the invasive forms of EFVPTC retained its name and by definition its invasive growth pattern. Table 8.13 highlights the criteria required for the diagnosis of NIFTP (Fig. 8.24).
- This reclassification effectively removed a subset of indolent tumors from the FVPTC category. As a result, the better prognosis typically associated with FVPTC has changed. Table 8.14 compares the two types of FVPTC with NIFTP.
- It is now known that anywhere from 20% to 60% of previously diagnosed FVPTCs actually represent noninvasive EFVPTC, now reclassified as NITFP.

**Table 8.13** Updated diagnostic criteria used for the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

| Inclusion criteria | Exclusion criteria |
|---|---|
| Follicular architecture<br>Encapsulated or well-demarcated<br>Focal or diffuse nuclear features of PTC, no specified amount *and* a nuclear score of 2–3. One point for each of three categories:<br>– Nuclear enlargement, elongation, overlap, crowding<br>– Nuclear membrane irregularities<br>– Chromatin clearing, glassy nuclei | Presence of true papillae formation (with fibrovascular cores)[a]<br>Psammoma bodies<br>Capsular invasion<br>Vascular invasion<br>3 or more mitoses per 10 high-power fields<br>Tumor necrosis<br>More than 30% solid or trabecular growth |

Adapted from reference [115]
[a]Revised from original criteria reference [119]

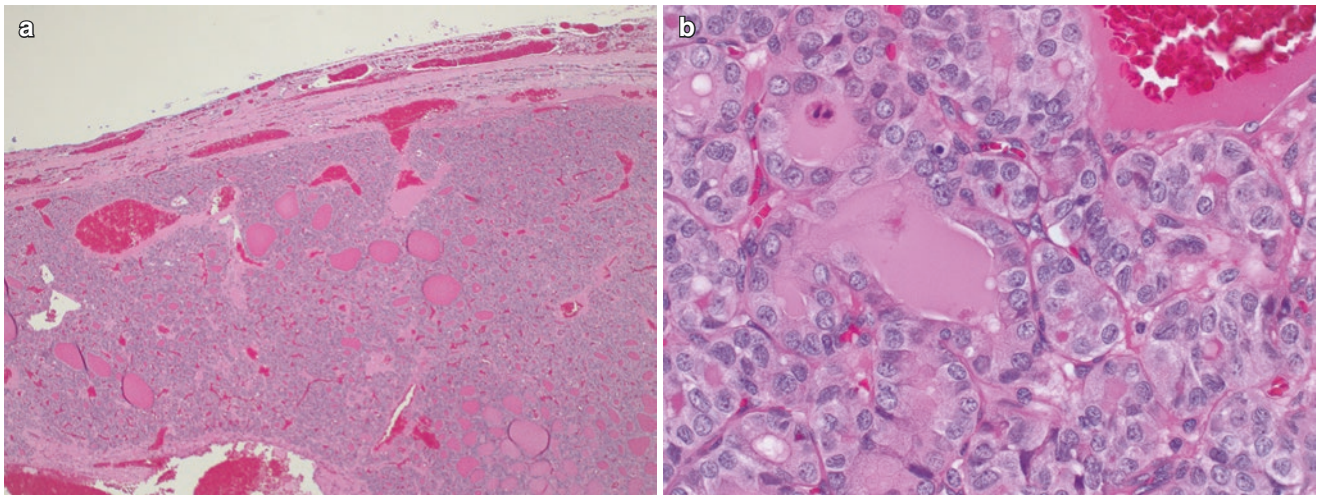


**Fig. 8.24** NIFTP. (**a**) An encapsulated, follicular tumor without invasion and with (**b**) focal, poorly developed PTC nuclei

**Table 8.14** Comparison of follicular-patterned tumors with papillary-type nuclei

| | Infiltrative FVPTC | Encapsulated FVPTC | NIFTP |
|---|---|---|---|
| % of all FVPTC | 20% | 15% | 60% |
| Papillae | Rare to none | Rare to none | None |
| PTC nuclear features | Classic, well-developed | Poorly developed | Poorly developed |
| Pseudoinclusions | Yes | Very rare | Very rare |
| Invasion | Yes | Yes (capsular and/or vascular) | No |
| Cytologic diagnosis | Suspicious or positive for malignancy | Atypical or follicular neoplasm | Atypical or follicular neoplasm |
| Molecular | BRAF (30%), RET/PTC | RAS, PAX8-PPARγ | RAS (50%), PAX8/PPARγ (rare) |
| LN metastases rate | 65% | 5% | <1% |
| Behavior | Lymph node metastases | Hematogenous metastases: lung, bone | Indolent, benign behavior |
| Treatment | Lobectomy or total thyroidectomy ±RAI | Lobectomy or total thyroidectomy ±RAI | Lobectomy alone |

- More recent studies confirm that FVPTC, having excluded the noninvasive EFVPTC, behaves more like cPTC and does not have a better prognosis.
  - This finding mirrors the diagnostic environment of pre-2006 and suggests a possible overdiagnosis of EFVPTC in the ensuing years between 2006 and 2016.
  - However, few recent studies, after the 2016 advent of NIFTP, have done a side-by-side comparison of infiltrative FVPTC with the now pared down, remaining subset of EFVPTC.
- As the literature on NIFTP expands, there are a few caveats to the diagnosis that are worth mentioning (Table 8.15).
  - In 2018, Seethala et al. along with others from the original paper recommended that tumors qualified as NIFTP, not have any papillae.
  - The defining article only studied tumors greater than 1 cm, but tumors less than 1 cm were not explicitly excluded in the criteria. We believe that, if a sub-centimeter lesion represents the index nodule for which the surgery was indicated, then it can be diagnosed as NIFTP. Some authors advocate for the diagnosis of NIFTP regardless of size or surgical indication. This topic is not well studied to date.
- NIFTP is regarded as a low-risk, indolent thyroid neoplasm requiring limited surgery (lobectomy alone) and no postoperative radioactive iodine. Nonetheless,

**Table 8.15** Caveats to be considered in the diagnosis of NIFTP

| Feature | Explanation | Suggested actions or diagnosis |
|---|---|---|
| Well-developed, diffuse nuclear features of PTC | This is an unusual finding for NIFTP; FVPTC should be excluded | Sample the entire tumor<br>Consider deeper sections into the tissue<br>Consider molecular testing for BRAF |
| Amount of nuclear PTC features | 30% PTC nuclei is a rule of thumb suggested for NIFTP, but it is not well studied and only loosely endorsed. Cases with the sprinkling sign may not meet this threshold but should be diagnosed as NIFTP if all other criteria are met | Consider a diagnosis of follicular adenoma |
| Papillae formation | Presence of any papillae should exclude the diagnosis of NIFTP | Diagnose as EFVPTC with focal papillae formation (if no invasion) |
| Sub-centimeter nodule | Consider NIFTP criteria if the nodule represents the index lesion for which the surgery was indicated | Diagnose as NIFTP if diagnostic criteria are met |
| Aberrant molecular findings | BRAF, TERT, RET/PTC, or ALK | The presence of any of these alterations should preclude a diagnosis of NIFTP<br>Diagnose as EFVPTC with high-risk molecular profile |

*FVPTC* follicular variant papillary thyroid carcinoma, *EFVPTC* encapsulated FVPTC

the panel of authors of the defining paper are careful to point out that it is not a benign tumor.

- Most studies of NIFTP confirm an indolent clinical course.
- There are rare reports of lymph node metastases associated with NIFTP (0.5%). But these studies are plagued with limitations around how well-sampled the tumors are and whether one can definitively diagnosis NIFTP without histologically evaluating the entire tumor for all exclusion criteria, especially the presence of papillae.

References: [91–120]

13. *Which are the nonaggressive variants of papillary thyroid carcinoma, and what are their clinicopathologic features?*

The PTC variants which have similar clinical behavior to classic PTC show a wide morphologic spectrum (Fig. 8.25). Some must be distinguished from benign mimics, while others are important for their exceedingly indolent behavior or clinical associations. Some of the more common nonaggressive variants of PTC are summarized in Table 8.16.

- Papillary thyroid microcarcinoma (mPTC) is not a homogeneous group.
  - Intratumoral fibrosis, multifocality, and tall cell features are related to tumor aggression, including lymph node and distant metastases.
  - Patients diagnosed with mPTC preoperatively have higher rates of lymph node metastases (30% versus 3%) and recurrence rates (8% versus 0%) when compared to those diagnosed after histologic examination (i.e. incidental).
  - mPTC patients with BRAF-V600E mutations are twice as likely to recur.

References: [59, 91–100, 121–134]

14. *Are hyalinizing trabecular tumors really benign, and what entities are in the differential diagnosis?*

Hyalinizing trabecular tumor (HTT), formerly termed hyalinizing trabecular adenoma, is an encapsulated, noninvasive follicular neoplasm with a trabecular growth pattern, distinct hyalinization, and PTC-like nuclei.

- HTTs are rare and deserve special attention because of its many mimics, including papillary thyroid carcinoma, paraganglioma, and medullary thyroid carcinoma.
- Microscopic findings (Fig. 8.26) show conspicuous intracellular and intratrabecular hyalinization which may vary in quantity.
  - Tumor cells are arranged in ribbons and nests with minimal to absent follicle formation.
  - Nuclei are round to oval with fine to hyperchromatic chromatin.
- Grooves, prominent pseudoinclusions, and perinuclear vacuoles are present.
- Nuclear overlap and pallor are not typical.
  - The cytoplasm is eosinophilic, moderate to abundant with an elongated shape that may spindle in areas, and have distinct cell borders.

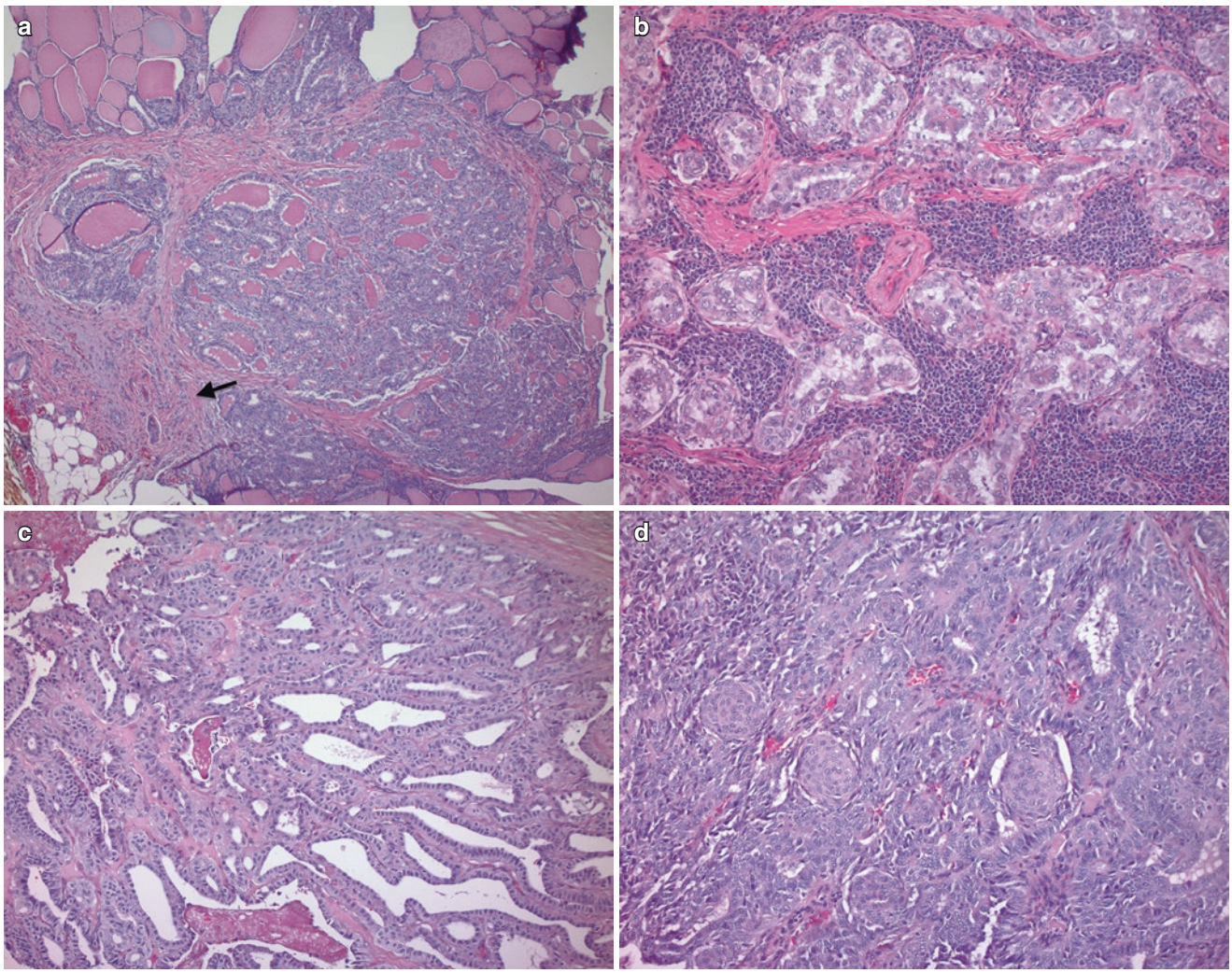


**Fig. 8.25** Papillary thyroid carcinoma variants. (**a**) This microcarcinoma has an infiltrative growth with single tumors cells (arrow). (**b**) Warthin-like variant has papillae lined by oncocytic epithelium with classic nuclear features and a dense lymphoplasmacytic infiltrate in the stroma. (**c**) Cribriform-morula variant contains punched out follicular spaces devoid of colloid and lined by cuboidal to columnar cells with occasional grooves and pseudoinclusions. (**d**) Areas of the cribriform variant show solid, squamoid morules

- Rounded, refractile, perinuclear, intracytoplasmic "yellow bodies" are common and may show cytoplasmic retraction creating a halo effect.
  - Psammoma bodies may be present.
- HTTs are largely benign tumors with a very low malignant potential.
  - There are exceedingly rare cases of metastatic HTT in the literature, and some examples are not well documented.
- The principal differential diagnosis of HTT includes papillary thyroid carcinoma and medullary thyroid carcinoma (MTC).
  - The trabecular architecture and amyloid deposition that may be seen in MTC can mimic the hyalinization of HTT. Immunohistochemical stains for calcitonin and neuroendocrine markers will confirm a diagnosis of MTC.
  - PTCs with a trabecular pattern may mimic HTT, but classic nuclear features with pallor, overlap, and variable growth patterns may help distinguish PTC from HTT. In addition PTC lacks the intratrabecular hyalinization of HTT.
- Positive IHC: TTF-1, PAX8, membranous Ki-67 with MIB-1 antibody, variable galectin-3, neuron-specific enolase.
- Negative IHC: CK19 (weak, focal), chromogranin, synaptophysin, high molecular weight keratin.

**Table 8.16** Clinicopathologic features of nonaggressive variants of papillary thyroid carcinoma

| Variant | MicroPTC | Encapsulated Classical PTC | Follicular variant | | Warthin | Cribriform-morula |
|---|---|---|---|---|---|---|
| | | | Infiltrative FV 6% | Encapsulated FV 4% | | |
| % of all PTC | 25–30% | 10% | 15% | | Rare, <1% | Rare, < 1% |
| Gender, age | 3–4:1 = F:M, mean 48 years | 3:1 = F:M, median 45 years | 2–3:1 = F:M, mean 44 years | 3:1 = F:M, mean 45 years | 90% female, 45 years | Young, females, mean 28 years |
| Clinical | Incidentally found via imaging for non-thyroidal causes or on pathologic review | 30% multifocal | Similar to classic PTC | Noninvasive subset reclassified as NIFTP | Hashimoto thyroiditis in almost all cases (85%) | 50% are associated with familial adenomatous polyposis |
| Minimum diagnostic criteria | Size less than or equal to 1 cm | Classic PTC with full encapsulation, 26% with capsular invasion, 15–20% with LVI | Not well-defined but almost exclusively follicular pattern (99–100%)<br>By definition must have invasion | | None | None, but may see minor components of other types |
| Morphology | Papillary, follicular with may show classic nuclear features of PTC<br>Morphology with sclerosis or encapsulation may vary | Papillae with or without follicles<br>Classic nuclear features of PTC<br>Densely fibrotic capsule | Unencapsulated, follicular architecture with infiltration of normal tissue<br>Classic nuclear features of PTC<br>Neoplastic follicles may be scattered among normal creating the "sprinkling sign" | Fully encapsulated or well-circumscribed, follicular architecture<br>By definition must have either capsular or vascular invasion<br>Usually poorly developed nuclear features of PTC<br>DM more likely parenchymal | Papillary architecture ±cyst formation lymphocytes and plasma cells in papillary cores<br>Tumor cells have granular, eosinophilic cytoplasm and classic nuclear features of PTC | Solitary nodule in sporadic cases<br>Solid, follicular, papillary, cribriform patterns with no colloid<br>Scattered squamoid morules with whorls of cells with pale nuclei<br>Cuboidal to columnar cells with oval, ±clear nuclei, rare grooves, frequent pseudoinclusions, ±psammoma bodies, ±TTF-1+, ±Tg, (n) ß-catenin+ |
| Molecular | BRAF (50%) | – | BRAF, RET/PTC | RAS, PAX8/PPARγ | BRAF (75%) | APC alterations, RET/PTC, CTNNB1 |
| Recurrences | LN metastases: 24%<br>DM: 0.8% | Recurrence rate: 28%<br>LN metastases: 50%<br>DM: 3% | LN metastases: 65% | LN metastases: 5% | LN metastases: 27% | Recurrence rates: 9%<br>LN metastases: 12%<br>DM 3% |

*IFV* infiltrative follicular variant, *EFV* encapsulated follicular variant, *NIFTP* noninvasive follicular thyroid neoplasm with papillary-like nuclear features, *LVI* lymphovascular invasion, *DM* distant metastases, *LN* lymph node, *(n)* nuclear

- Genetics: PAX8-GLIS3 and rare PAX8-GLIS1 translocations define this entity. RET/PTC-1 has also been documented. BRAF-V600E and RAS mutations are not present.

References: [135–143]

15. *What are the criteria used for the diagnosis of thyroid tumors of uncertain malignant potential?*

Thyroid tumors of uncertain malignant potential (TT-UMP) are follicular-patterned tumors with equivocal capsular or vascular invasion. They are divided into well-differentiated tumor of uncertain malignant potential (WDT-UMP) and follicular tumor of uncertain malignant potential (FT-UMP). The former will have some nuclear features of papillary thyroid carcinoma. Table 8.17 compares the two tumor types.

- NIFTP is not included in this category of tumors because it has an *unequivocal* absence of capsular or vascular invasion. If there is equivocal invasion,

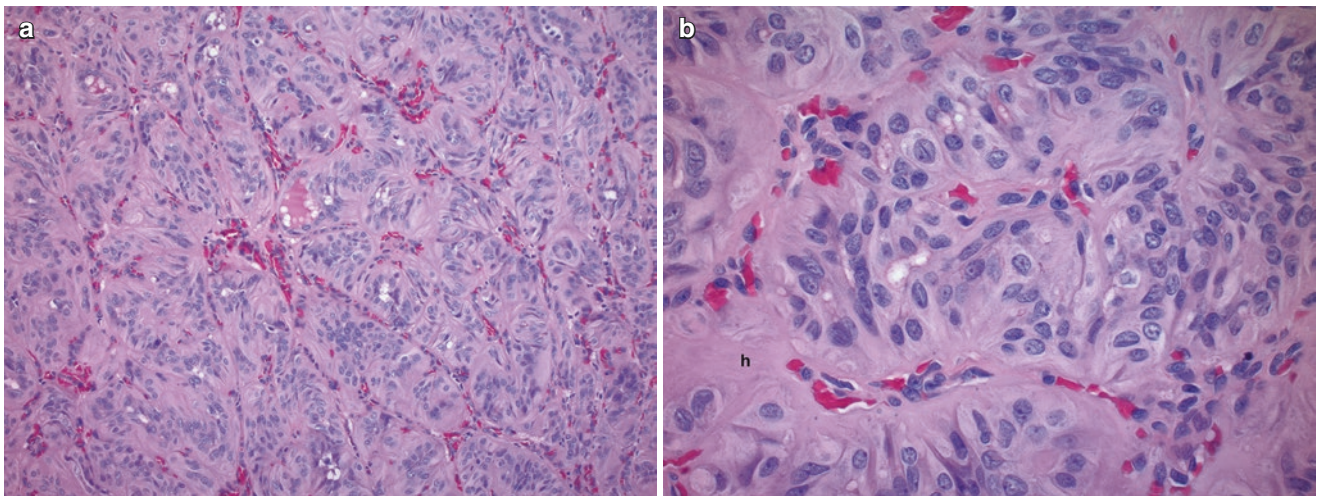


**Fig. 8.26** Hyalinizing trabecular tumor. (**a**) Trabeculae of cells with pale pink cytoplasm and bland, pale, oval nuclei. (**b**) Occasional grooves and nuclear membrane irregularities are present. Intratrabecular hyalinization (h) is present

**Table 8.17** Comparison of thyroid tumors of uncertain malignant potential

| | WDT-UMP | FT-UMP |
|---|---|---|
| Invasion | Equivocal capsular and/or vascular invasion:<br>• Tumor extends into but not through the tumor capsule<br>• Tumor cell nests are present within the capsule stroma<br>and/or<br>• Intravascular tumor without endothelial covering, fibrin, or thrombus | |
| PTC-like nuclei | Equivocal | Absent |
| HBME-1 | 40–70% | 25–62% |
| Galectin-3 | 40–80% | 37–50% |
| CK19 | 30–60% | nd |
| Molecular alterations | 6.7% RET/PTC<br>19% RAS | 6% PAX8/PPARγ<br>20% RAS |

*nd* no data

NIFTP is excluded, and a diagnosis of WDT-UMP should be considered.

  - Figure 8.27 illustrates the relationship of thyroid tumors of uncertain malignant potential with their benign and malignant counterparts.

- WDT-UMP and FT-UMP both show nuclear enlargement.
  - WDT-UMP demonstrates focal or poorly developed features of PTC. Grooves and nuclear pallor are typical, but pseudoinclusions and nuclear overlap are exceedingly rare.
  - FT-UMP shows no equivocal *or* unequivocal PTC nuclear features but does demonstrate equivocal capsular or vascular invasion (Fig. 8.28).
- The molecular alterations and immunohistochemical profile of TT-UMP show significant overlap with follicular adenomas. Morphologic features are the mainstay of the diagnosis.
- Mimics of capsular invasion include:
  1. Fine-needle aspiration (FNA) biopsy tracks through the capsule which may be associated with hemosiderin and fibrosis.
  2. Tangential cuts of tissue sections may artificially displace tumor outside of the capsule.
- Mimics of vascular invasion include:
  1. Tumor nests pushing or herniating into a vessel from underneath the endothelium.
  2. Artefactual retraction of stroma around tumor cells. Careful examination will show an absence of endothelium.
  3. Detached tumor fragments lodged into vascular spaces from tissue handling or cutting.

References: [60, 115, 119, 144–149]

16. *What are the morphologic features of anaplastic thyroid carcinoma?*

Anaplastic thyroid carcinoma (ATC) accounts for less than 5% of thyroid malignancies but is responsible for up to half of the deaths related to thyroid cancer. It is an undifferentiated carcinoma with a mortality rate above 90% and a median survival of less than 1 year.

Patients are typically elderly with a slight female predominance. The classic clinical presentation is a rapidly enlarging neck mass.

- There are three predominant morphologic patterns of ATC: spindle (Fig. 8.29), giant cell (Fig. 8.30), and squamous/epithelioid. They have no clinical significance but are important for the differential diagnosis (Table 8.18).
- A given tumor may show more than one pattern.

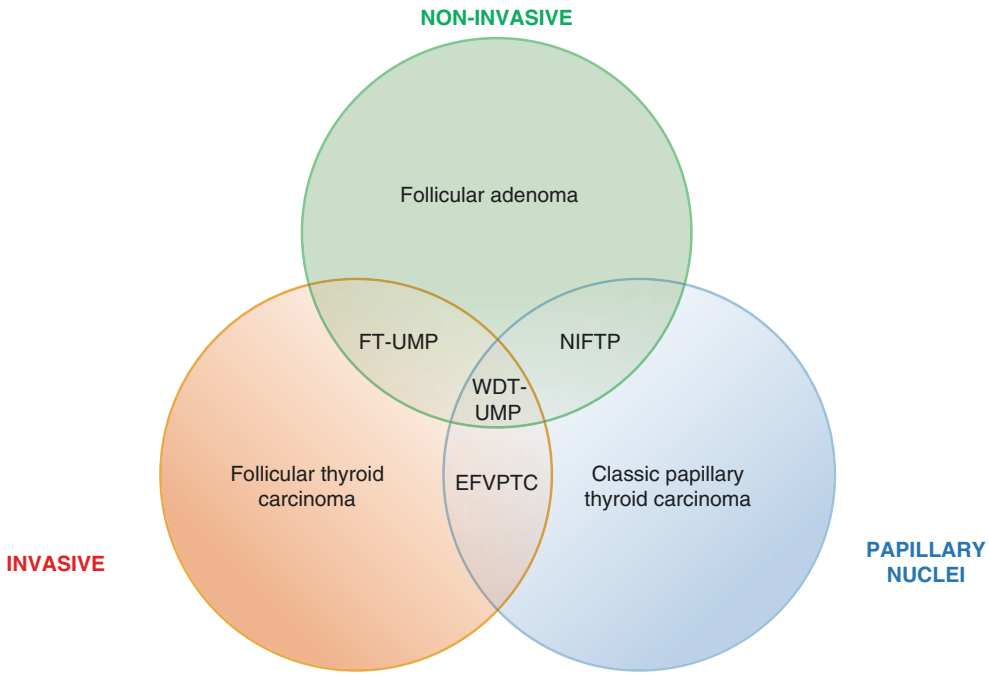


**Fig. 8.27** Thyroid tumors of uncertain malignant potential, by definition, have equivocal features of invasion and are represented here at the intersection of invasive and noninvasive thyroid tumors, with and without PTC nuclei. WDT-UMP is distinguished from FT-UMP by the presence of PTC-like nuclei. NIFTP, like WDT-UMP, demonstrates poorly-developed PTC nuclei but is unequivocally noninvasive

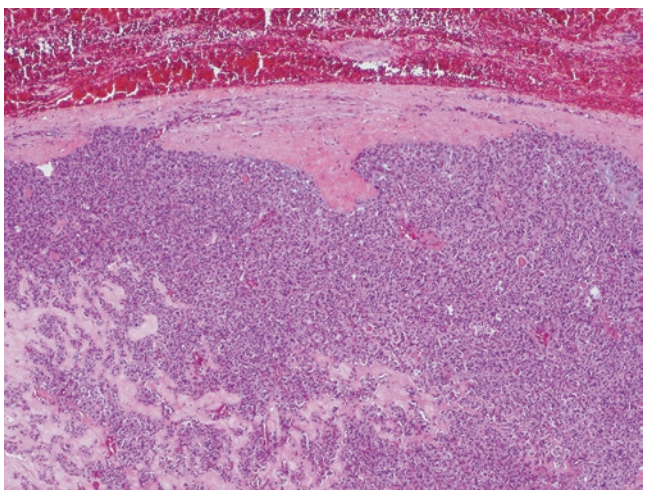

**Fig. 8.28** Follicular tumor of uncertain malignant potential. A focus of tumor pushes into the tumor capsule but does not transgress it and is equivocal for capsular invasion. Deeper tissue sections in cases like this may reveal complete transcapsular invasion

- ATCs typically show necrosis, extensive soft tissue invasion, vascular invasion and infiltration, and high mitotic activity.
- ATC may arise de novo or from high-grade transformation of a well-differentiated thyroid carcinoma, usually papillary thyroid carcinoma.
- Immunohistochemical stains show a wide variation of expression across studies and within a given tumor. The greatest challenge is in establishing both an epithelial and thyroid origin.
  - Positive IHC: PAX8, low molecular weight cytokeratin
  - Negative IHC: TTF-1(negative or weak/focal), thyroglobulin, high molecular weight cytokeratin
  - Genetics: BRAF-V600E(30–40%), TP53(70%), TERT promoter mutations (70%), PTEN, ALK
- Rarely, a well-differentiated thyroid carcinoma will have anaplastic foci. Overall, these patients have better survival.
  - There is no consensus regarding what amount of anaplastic thyroid carcinoma is clinically significant. Some studies have proposed 10% of the entire tumor volume.
  - It is recommended that any amount of ATC be documented in the pathology report.

References: [150–154]

17. *What are the primary spindle cell lesions of the thyroid gland?*

Spindle cell lesions of the thyroid are rare and include a variety of neoplastic, metaplastic, and reactive processes. Table 8.19 highlights the different entities in the differential diagnosis of spindle lesions of the thyroid and their immunoprofile. Most of the epithelial tumors have been discussed earlier, but spindle epithelial tumor with thymus-like elements (SETTLE) will be discussed here separately.

- Spindle epithelial tumor with thymus-like elements (SETTLE) of the thyroid is a malignant epithelial tumor with a biphasic pattern of spindled and epithelioid cells. It is rare, with less than 100 cases reported in

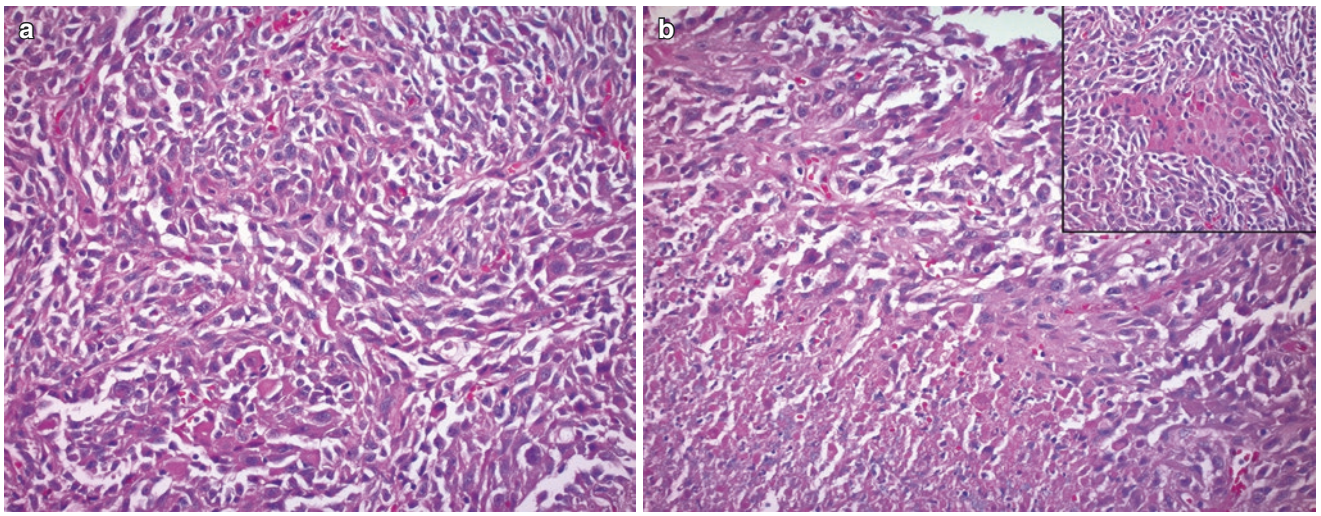


**Fig. 8.29** Anaplastic thyroid carcinoma. (**a**) Spindle cell tumor with a storiform pattern. (**b**) Large areas of necrosis are present (lower left corner), and residual foci of Hurthle cell carcinoma were identified (inset)

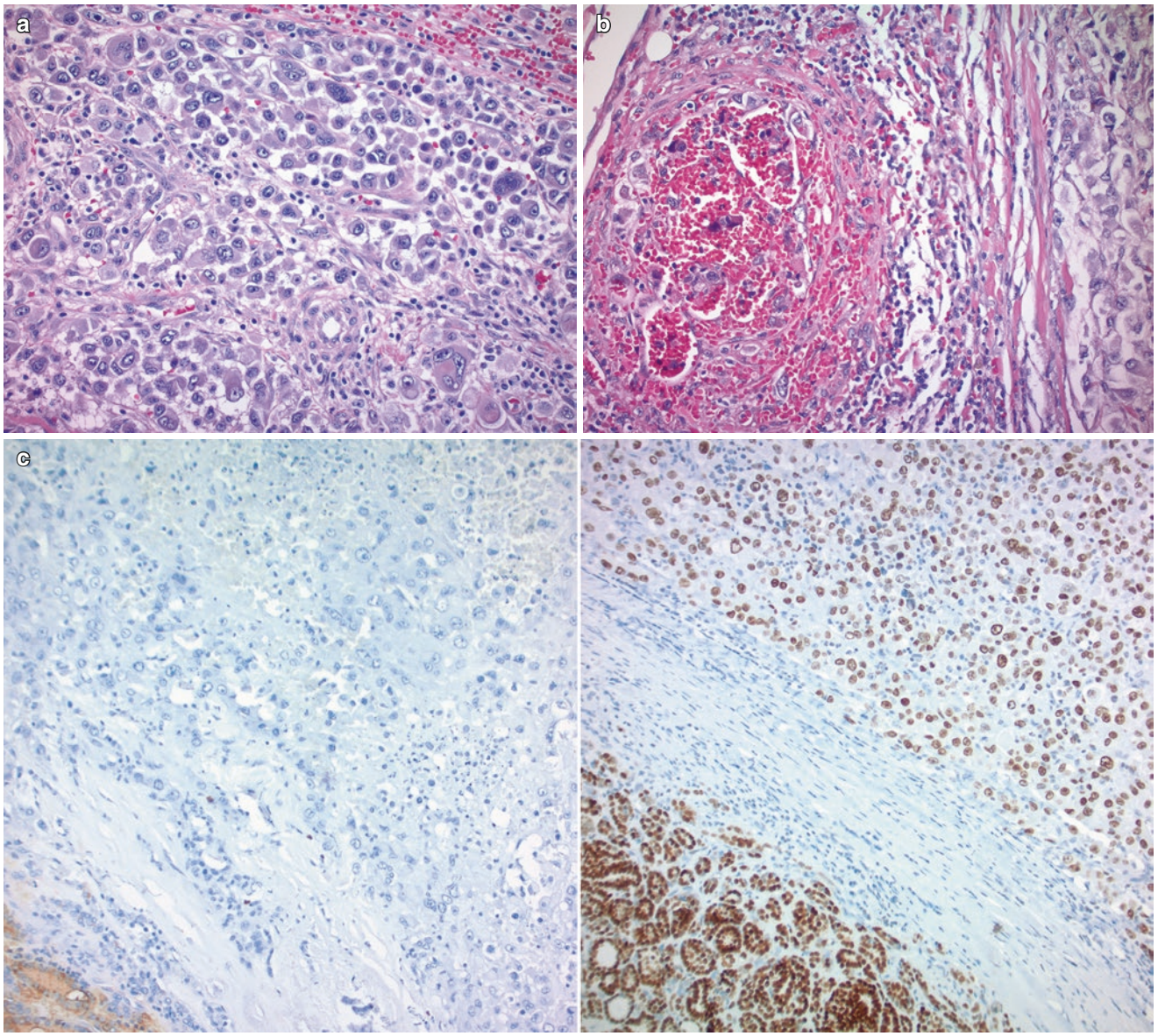


**Fig. 8.30** Anaplastic thyroid carcinoma. (**a**) Giant cell type comprises large epithelioid cells with abundant cytoplasm and pleomorphic nuclei. (**b**) Tumor cells infiltrate a vessel wall. (**c**) The tumor cells are negative for thyroglobulin (left) and positive for TTF-1 (right)

**Table 8.18** Morphologic features and differential diagnosis of variants of anaplastic thyroid carcinoma

| | Variant | Morphology | Differential diagnosis | Features of entities in the differential diagnosis |
|---|---|---|---|---|
| Sarcomatoid | Spindled | Cellular tumor with fascicular or storiform pattern<br>May show marked pleomorphism with necrosis and mitoses<br>±Giant tumor cells, inflammation with neutrophils and lymphocytes<br>Staghorn-like vascular pattern with infiltration of vessel walls by tumor cells<br>The paucicellular variant has extensive hyalinization and more bland cytology. But focal areas of necrosis, atypia, and vascular invasion are seen<br>Heterologous elements may be present: cartilage, bone, skeletal muscle | Sarcoma | CK–<br>Clinical history of sarcoma |
| | | | SETTLE | Young patients<br>Slow growing |
| | | | Solitary fibrous tumor | Blandcytology,CD34+,CK– |
| | | | Riedel thyroiditis | Bland cytology, no necrosis |
| | Giant cell | Sheets of pleomorphic cells with abundant, pink cytoplasm, osteoclast-like giant cells with multinucleation may be present<br>Nuclei are hyperchromatic and vesicular<br>Dyshesive cells form alveolar-like pattern and pseudoglandular spaces<br>Mitoses and necrosis are common | Spindle cell metaplasia in PTC, MTC, FA | Tg+, TTF-1+, bland morphology |
| Epithelial/ squamoid | Squamous | Sheets and infiltrative nests of polygonal epithelial cells with moderate amounts of eosinophilic cytoplasm<br>Nuclear pleomorphism is less pronounced than in the sarcomatoid tumors<br>Keratinization may be present<br>Spindled areas and lymphoepithelial-like variants can be seen<br>Necrosis and frequent mitoses | Primary thyroid SCC | Purely squamous with no other cell types |
| | | | H/N SCC | Clinical and radiographic evidence of a mucosal H/N primary |
| | | | Metastatic SCC | PAX8– |
| | | | Mucoepidermoid carcinoma | Mucous cells, bland cytology<br>Eosinophils and CLT in sclerosing variant |
| | | | Squamous metaplasia in WDTC | Tg+, TTF-1+, bland morphology |
| | | | CASTLE/Thymic carcinoma | CK5/6+, CD5+, lymphocytic infiltrate |

*CK* cytokeratin, *SETTLE* spindle epithelial tumor with thymus-like differentiation, *Tg* thyroglobulin, *PTC* papillary thyroid carcinoma, *MTC* medullary thyroid carcinoma, *FA* follicular carcinoma, *SCC* squamous cell carcinoma, *H/N* head and neck, *CLT* chronic lymphocytic thyroiditis, *WDTC* well-differentiated thyroid carcinoma, *CASTLE* carcinoma showing thymus-like element

**Table 8.19** Spindle cell lesions of the thyroid gland

| | Spindle cell lesions | Tg/TTF-1 | Epithelial markers | Mesenchymal markers |
|---|---|---|---|---|
| Epithelial | PTC variants | +/+ | ±CK | Negative: SMA– |
| | MTC with spindle metaplasia | –/+ | Positive, calcitonin+ | Negative |
| | FA, HTT with spindle metaplasia | +/– | CK+, HMWCK– | Negative: SMA–, desmin– |
| | ATC | –/– (Rare+ ) | ±CK,±EMA | Negative |
| Mesenchymal | Spindle cell nodule | –/- | Negative | SMA+ CD68+ |
| | Smooth muscle tumors | –/- | Negative | Positive: SMA, vimentin, MSA, desmin |
| | PNST | –/- | Negative | Positive: S100, vimentin |
| | SETTLE | –/- | Positive | Positive: vimentin, ±SMA |

*Tg* thyroglobulin, *PTC* papillary thyroid carcinoma, *CK* cytokeratin, *HMWCK* high molecular weight cytokeratin, *SMA* smooth muscle actin, *FA* follicular adenoma, *HTT* hyalinizing trabecular tumor, *MSA* muscle-specific actin, *PNST* peripheral nerve sheath tumor, *SETTLE* spindle epithelial tumor with thymus-like differentiation

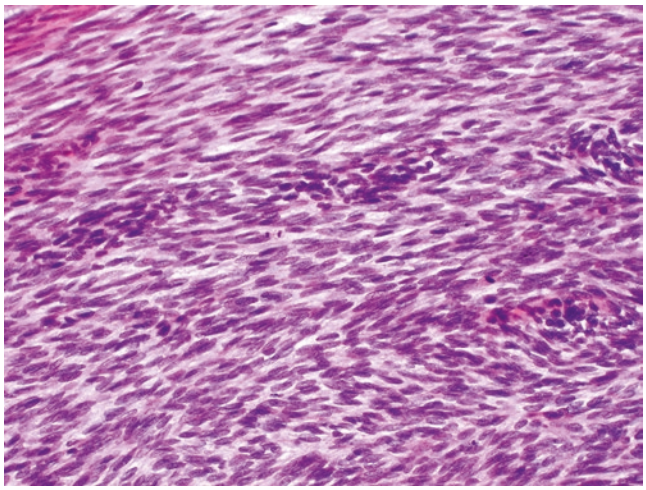

**Fig. 8.31** SETTLE. Bland spindle cells arranged in sweeping fascicles with scant cytoplasm

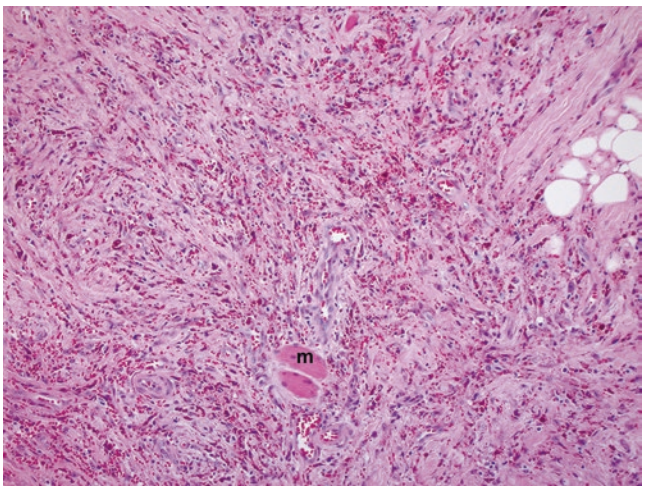


**Fig. 8.32** Biopsy changes. A bland, low cellularity, spindle cell proliferation with hemorrhage, a sparse inflammatory infiltrate, and fibrosis. Entrapped skeletal muscle (m) and fat are evident

the literature. It occurs primarily in children and young adults, though the age ranges from 4 to 59 years old.
  - SETTLE is an encapsulated, circumscribed tumor that invades the adjacent thyroid parenchyma. The tumor comprises cellular lobules of predominantly bland spindle cells separated by thin, irregular, fibrous septa (Fig. 8.31).
- The lobules may be cystic or demonstrate clefting from the surrounding stroma.
  - The epithelial cells may be glandular, squamous, or ciliated and arranged in tubulopapillary structures.
- Mucinous, columnar, and cuboidal cells are present.
- The spindle cells are monotonous with oval nuclei, fine chromatin, and bipolar, elongated, eosinophilic cytoplasm.
  - Immunohistochemical findings do not support a thymic origin, as the epithelium is negative for CD20 and CD5.
- Positive IHC: CK, EMA, MSA, SMA, vimentin
- Negative IHC: Thyroglobulin, TTF-1, S100, calcitonin
  - SETTLE is often indolent. But metastatic rates to lymph nodes and lung, in small case series, average 30% over 5 years.
- Primary mesenchymal tumors of the thyroid are rare and represent less than 1% of all thyroid tumors. They include leiomyoma, solitary fibrous tumor, and peripheral nerve sheath tumors. All are similar in morphology to their soft tissue counterparts, and descriptions for individual entities can be found in Chap. 10.
- Reactive processes with spindled morphology are generally myofibroblastic in origin:
  - Post-biopsy spindle cell nodules (Fig. 8.32)
  - Spindle cell proliferations associated with thyroiditis (e.g., Riedel thyroiditis)
- Other, more common epithelial tumors of the thyroid may contain foci of spindle cells or even spindle cell differentiation. These will typically express some broad spectrum cytokeratins but usually not CK19 or the high molecular weight cytokeratins. They include:
  - Metaplastic spindle cells seen in papillary thyroid carcinoma, medullary thyroid carcinoma, and follicular adenomas (Fig. 8.33).
- Cribriform-morula and nodular fasciitis-like variants of PTC are notable for their spindled morphology.
  - Anaplastic thyroid carcinoma has a spindle cell variant (see question 16).
  - Sclerosing mucoepidermoid carcinoma with eosinophilia (see question 18).

References: [155–158]

18. *Which are the squamoid lesions seen in the thyroid gland?*

Squamous lesions of the thyroid include primary squamous tumors (Figs. 8.34 and 8.35), variants of other thyroid carcinomas, and metaplasia. Primary squamous tumors of the thyroid are rare and summarized in Table 8.20.

- Primary thyroid squamous cell carcinoma (Fig. 8.36) by definition is composed exclusively of squamous cells with no other cell types; this helps to distinguish it from anaplastic thyroid carcinoma or well-differentiated thyroid carcinomas with squamous metaplasia. A thorough clinical evaluation with pan-endoscopy of the upper aerodigestive tract is recommended to exclude a metastatic primary head and neck squamous cell carcinoma. Its distinction from anaplastic thyroid carcinoma is somewhat academic as the prognosis is poor for both tumors.
- Squamous metaplasia can be seen in a variety of thyroid entities and lacks atypia. It should be distinguished from squamous *differentiation* which shows malignant squamous features and represents high-

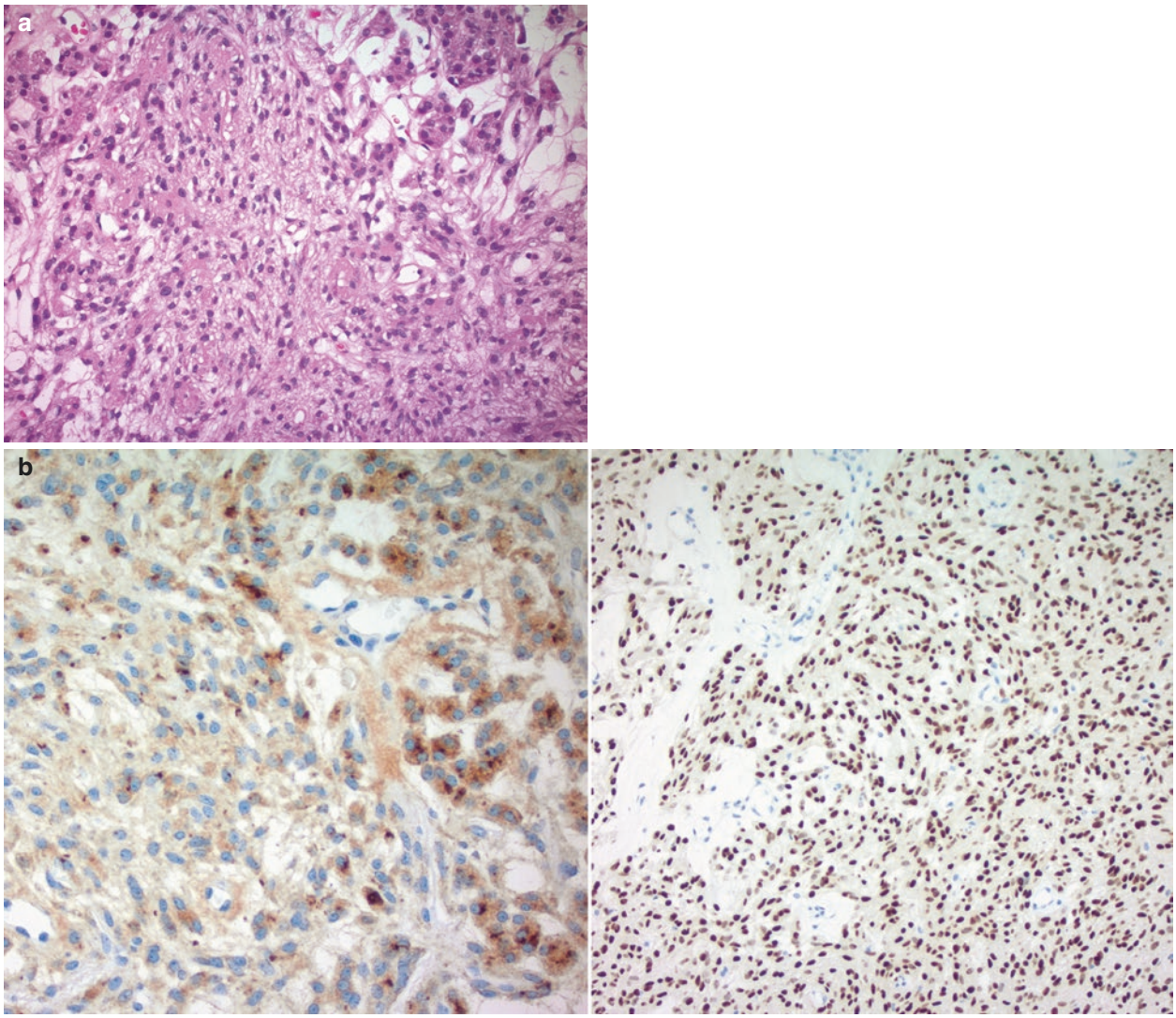


**Fig. 8.33** Follicular adenoma with spindle cell metaplasia. (**a**) Short-spindled cells with abundant cytoplasm merge with more typical microfollicular areas (upper right). (**b**) The spindle areas are weakly positive for thyroglobulin (left) and TTF-1 (right)

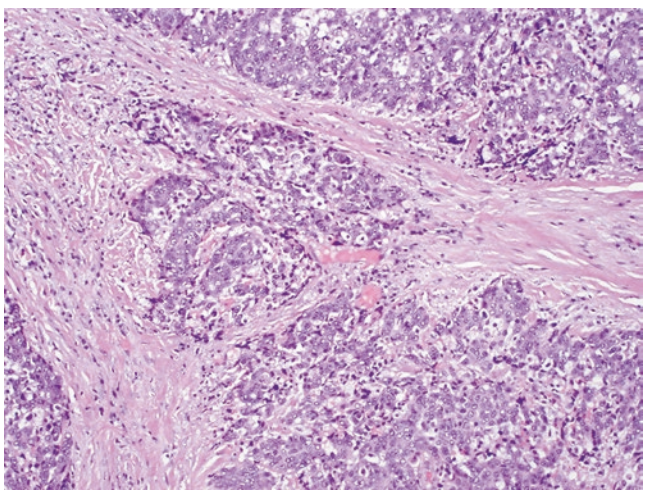

**Fig. 8.34** CASTLE. Intrathyroidal thymic carcinoma shows sheets of squamoid cells with nuclear pleomorphism and a sparse chronic inflammatory infiltrate, resembling lymphoepithelial carcinoma

grade/anaplastic transformation of a pre-existing well-differentiated thyroid carcinoma.

– Tumors that may show squamous metaplasia include:
  - Papillary thyroid carcinoma – squamous metaplasia can be seen in 20–40% of cases (Fig. 8.37).
  - Follicular adenomas and carcinomas rarely show squamous metaplasia.
  - Medullary thyroid carcinoma.
  - Hashimoto thyroiditis – squamous metaplasia is especially common in the fibrous variant.
– Thyroid tumors that have squamous differentiation or variants include:
  - Anaplastic thyroid carcinoma (see question 16)

References: [5, 159–170]

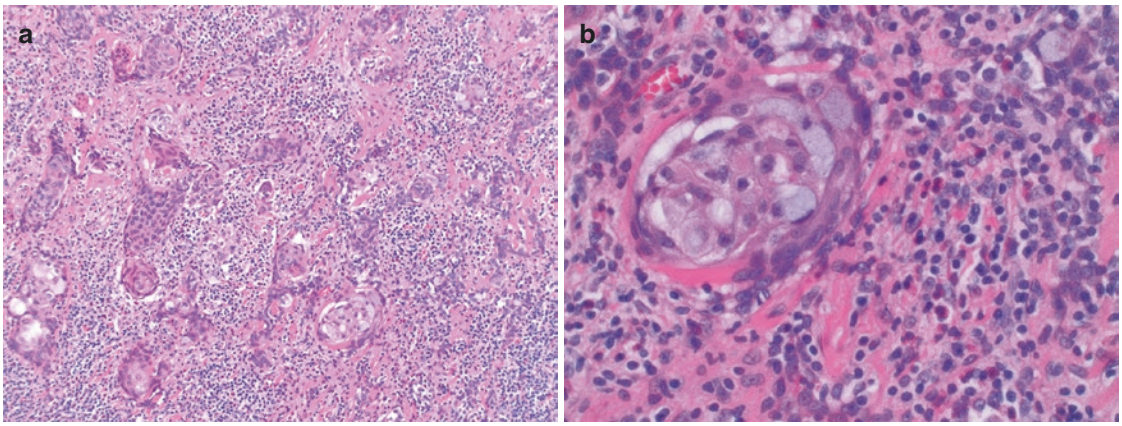


**Fig. 8.35** Sclerosing mucoepidermoid carcinoma with eosinophilia. (**a**) Islands of squamous cells with keratin pearl formation in a dense inflammatory infiltrate. (**b**) Scattered groups of mucous cells are intimately associated with squamous cells. Scattered eosinophils and delicate fibrosis are present

**Table 8.20** Clinicopathologic features of squamoid lesions of thyroid

| | Mucoepidermoid carcinoma | Sclerosing mucoepidermoid carcinoma with eosinophilia | Carcinoma showing thymus-like differentiation/Thymic carcinoma | Primary squamous cell carcinoma |
|---|---|---|---|---|
| % of thyroid malignancies | <0.5% | Very rare | 0.08–0.15% | Very rare |
| Mean age, gender | 47 years, F:M = 2:1 | 55 years, F:M = 7:1 | 48 years, F > M = 1.2:1 | Median 64 years, F:M = 2–3:1 |
| Clinical presentation | Painless neck mass | Slow-growing neck mass | Slow-growing mass, lower lobes, hoarseness, dyspnea | Large neck mass |
| Morphology | Circumscribed, unencapsulated tumor with cystic change<br>Intimate association of sheets of squamous cells with pearl formation and duct-like structures with ±ciliated cells<br>Scattered mucus cells and psammoma bodies are present<br>Cells have oval, pale nuclei ±Grooves and pseudoinclusions<br>Fibrotic stroma, rare mitoses, and necrosis<br>50% associated with PTC, ±HT | Circumscribed but infiltrative mass with small nests and strands of cells in a fibrotic stroma<br>Tumor cells are polygonal with eosinophilic cytoplasm and foci of keratinization, moderate pleomorphism<br>Mucous cells line cystic spaces and admixed with squamous nests<br>Stroma has mixed inflammation with predominance of eosinophils<br>Frequent PNI and LVI<br>Background HT (96%), rare association with PTC | Well-circumscribed, lobular, or nodular pattern with areas of infiltrative growth<br>Tumor cells arranged in nests and ribbons in a fibrous stroma with lymphoplasmacytic infiltrate<br>Cells are polygonal or spindled with abundant, pale pink cytoplasm, vesicular nuclei, and prominent nucleoli<br>Varying amounts of keratinization and Hassall corpuscles<br>Rare mitoses | By definition, must be purely composed of squamous cells without coexisting PTC, ATC, or FTC<br>Identical to SCC at other body sites<br>Usually poorly differentiated or undifferentiated<br>Extensive PNI, LVI, ETE |
| Positive IHC | TTF-1, Tg, PAX8, p63, E-cadherin | p63, CK, CD10, galectin-3, CK19 | CD5, CD117, p63, HMCK, EGFR, GLUT-1, E-cadherin, Bcl-2, PAX8, CK19 | PAX-8, CK19, CK7, CK5/6, CK18 |
| Negative IHC | Calcitonin, synaptophysin, chromogranin | Tg, PAX-8, calcitonin, S100, ±TTF-1 (neg or weak) | TTF-1, Tg, calcitonin, vimentin, calretinin | Tg, TTF-1, CK20, p53 |
| Outcomes | LN metastases: 40%<br>DM: 10%<br>Rare deaths<br>Possible anaplastic transformation unclear: 10% | LN metastases: 45%<br>DM: 30%<br>Rare deaths | Generally indolent<br>Recurrence rate: 18%<br>5, 10-year CSS: 90, 82% | Poor prognosis<br>DOD at 1 year: 80%<br>Median survival: 9 months |

*SCC* squamous cell carcinoma, *PTC* papillary thyroid carcinoma, *HT* Hashimoto thyroiditis, *PNI* perineural invasion, *LVI* lymphovascular invasion, *ETE* extrathyroidal extension, *Tg* thyroglobulin, *LN* lymph node, *DM* distant metastases, *CSS* cancer-specific survival, *DOD* dead od disease

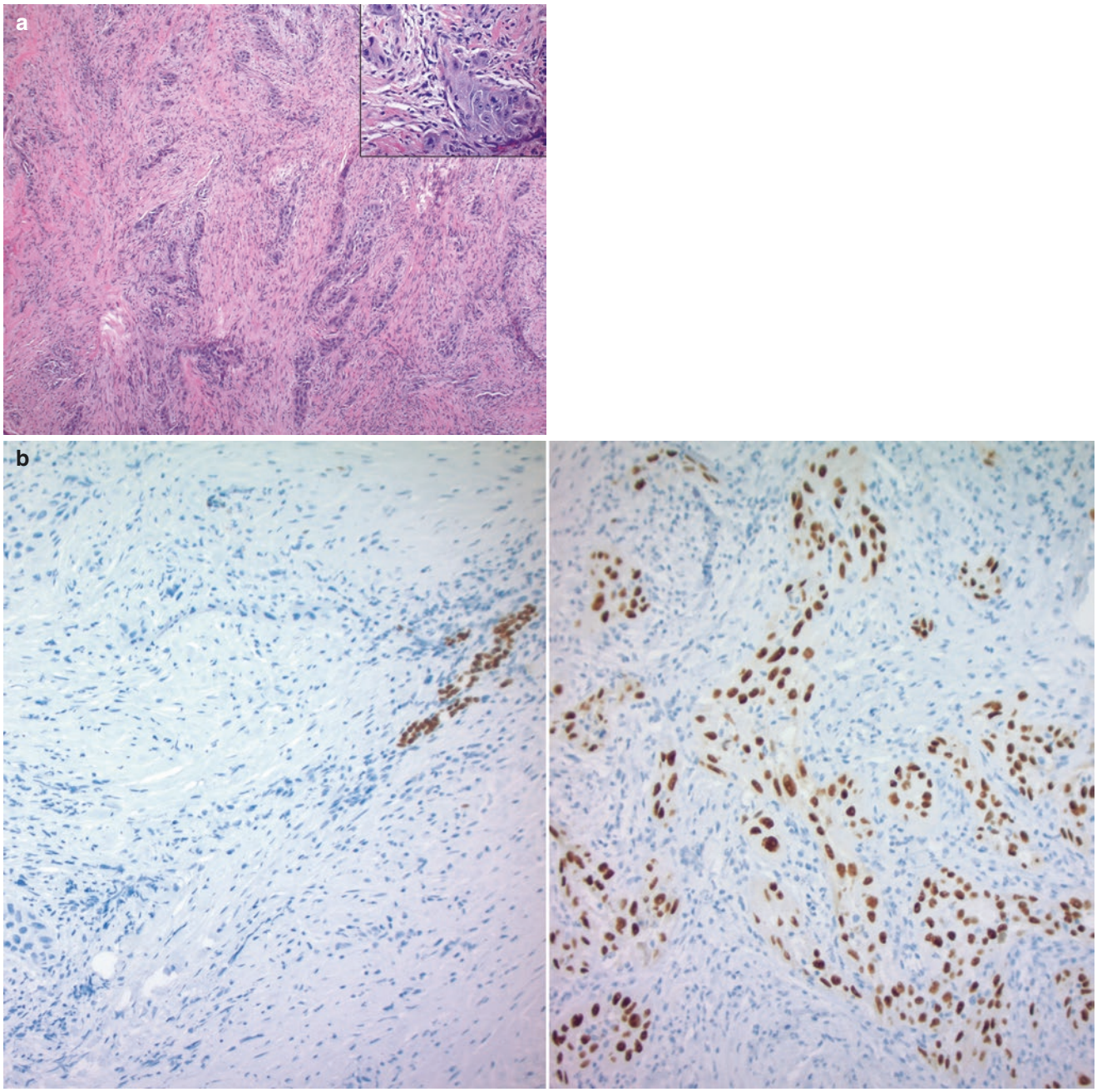


**Fig. 8.36** Primary squamous cell carcinoma. (**a**) Nests of squamous cells in a desmoplastic stroma. Clear squamous differentiation is evident (inset). (**b**) TTF-1 stains residual benign thyroid epithelium and the tumor cells are negative (left). The tumor cells are strongly positive for p63 supporting squamous differentiation (right)

19. *How is thyroid tissue in the lateral neck characterized?*

The presence of thyroid tissue in the lateral neck is somewhat controversial based on embryology. The lateral lobes of the thyroid are derived from the fourth pharyngeal pouch endoderm, the ultimobranchial body, and its derivatives. Dysembryogenesis of these structures may explain the presence of thyroid tissue in the lateral neck.

- Thyroid ectopia can occur anywhere along the path of descent of the thyroid gland from the tongue base to the normal gland location in the pre-tracheal region (tracheal rings 2–5). Lingual thyroid accounts for 90% of ectopic thyroid tissue and is discussed in more detail in Chap. 1.

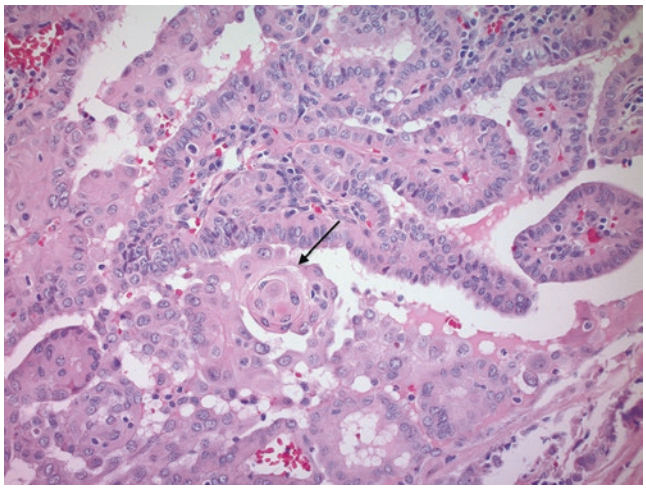

**Fig. 8.37** Squamous metaplasia in a papillary thyroid carcinoma is cytologically bland

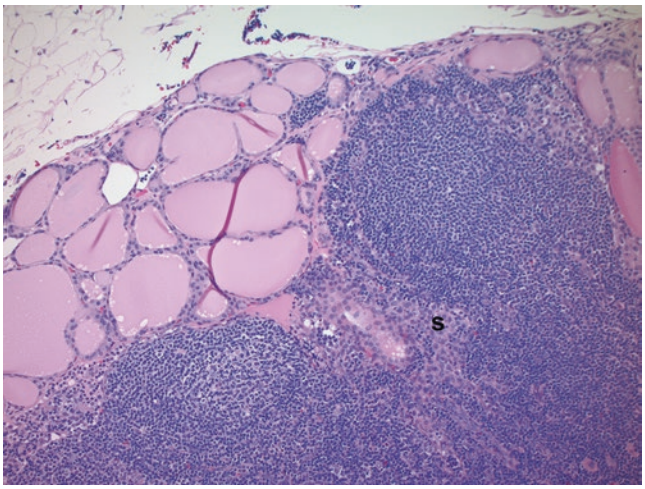


**Fig. 8.38** Thyroid inclusion in a lymph node. A Wedge-shaped aggregate of benign-appearing follicular epithelium is present in a subcapsular location. Sinus histiocytes (S) are easily identified, confirming lymph node tissue

- Benign-appearing thyroid tissue in the lateral neck can be seen in the following scenarios:
  1. Incidental thyroid tissue found in cervical lymph nodes after node dissection for a head and neck malignancy, usually at levels 3 or 4.
  2. Parasitic nodules – detached fragments of thyroid tissue in the lateral neck usually as a result of inflammatory and hyperplastic thyroid diseases. Parasitic nodules can also be found in the mediastinum and central neck.
- Incidental, benign-appearing follicular thyroid tissue in cervical lymph nodes is a diagnostic dilemma for physicians. Controversy exists as to whether they represent benign inclusions or metastases:
  - Embryologic evidence to support the idea of lateral ectopic thyroid is only theoretical.
  - The absence of a documented primary thyroid carcinoma does not exclude the possibility of a metastasis or prove benignity:
- Patients may not undergo thyroidectomy given their more concerning head and neck malignancy.
- Complete histologic evaluation of the thyroid gland may not detect a microcarcinoma.
- It is well known that PTC lymph node metastases don't uniformly show nuclear features of PTC. Therefore, the absence of atypia does not necessarily exclude the presence of a primary thyroid carcinoma.
  - The estimated prevalence of thyroid tissue in a LN among patients undergoing cervical lymph node dissection or at autopsy is less than 5%.

**Table 8.21** Criteria for the diagnosis of benign thyroid inclusions in lymph nodes

| |
|---|
| Involvement of no more than two lymph nodes |
| Lymph node size ≤5 mm (reported range 0.2–1.5 mm) |
| Thyroid follicles with no papillae or nuclear atypia |
| - Wedge-shaped |
| - Capsular or subcapsular (no nodal parenchymal involvement) |
| Involvement of less than 1/3 of the lymph node parenchyma |
| No psammoma bodies |
| No desmoplasia |
| Negative IHC or molecular results supporting a carcinoma diagnosis |

  - Some studies report approximately 25% of thyroidectomies will not yield a primary carcinoma, while those that do may yield a primary on the contralateral side.
  - Table 8.21 provides a list of criteria to classify benign-appearing, incidental, intranodal thyroid tissue as an inclusion (Fig. 8.38). In Triantafyllou et al., a multidisciplinary group of experts put forth management options for incidentally encountered thyroid tissue in lymph nodes; Fig. 8.39 outlines the proposed course of action.
- Parasitic nodules are portions of nodular thyroid tissue which become detached from the main gland. This is typically seen in the setting of nodular hyperplasia, Graves' disease, or Hashimoto thyroiditis. It may be encountered intraoperatively and presented to the pathologist as a possible cervical lymph node, or a mediastinal or neck mass.

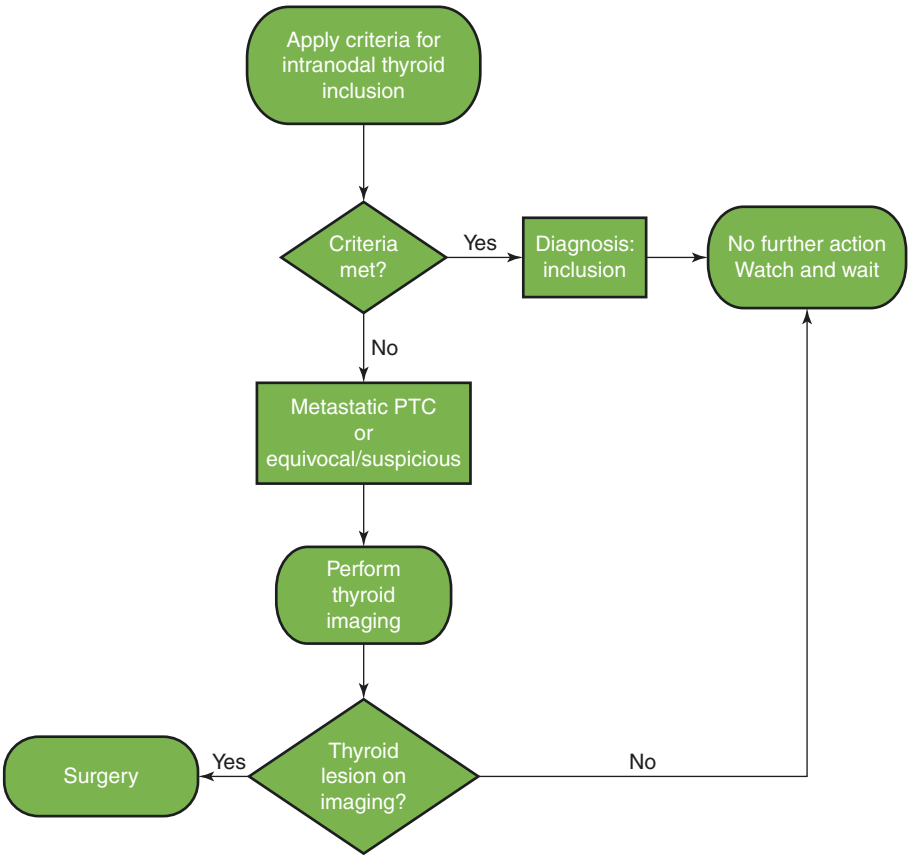


**Fig. 8.39** Proposed strategy for the management of incidental thyroid tissue in a lymph node. (Adapted from [172])

  - Parasitic nodules are thought to represent nodular hyperplasia of extracapsular thyroid tissue.
  - Their frequency is likely underreported in the literature and may be misdiagnosed as metastatic papillary thyroid carcinoma.
  - There should be no true lymph node parenchyma, capsule, or nuclear features of papillary thyroid carcinoma.
  - Parasitic nodules in the setting of Hashimoto thyroiditis can be especially difficult to distinguish from metastasis because of the associated lymphoid proliferation and focal nuclear atypia and pallor, mimicking PTC.
- Identifying lymph node structures can help distinguish parasitic nodules from lymph node metastases: the presence of subcapsular or medullary sinuses that may contain sinusoidal histiocytes is helpful.
- The distribution and quality of the epithelium may favor a diagnosis of thyroiditis with evenly distributed foci of oncocytic epithelium (Fig. 8.40).

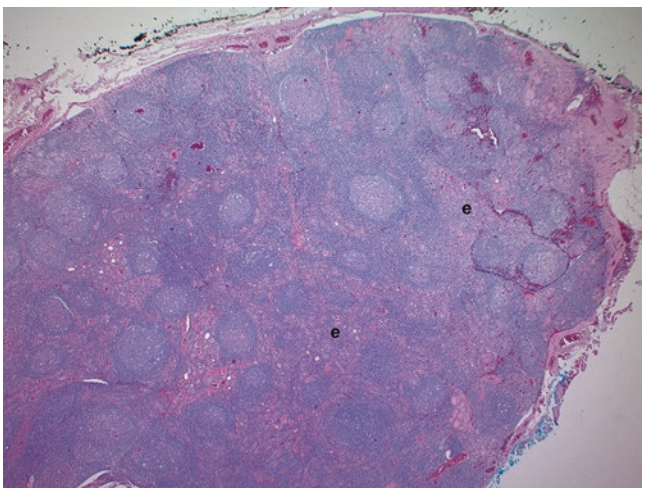


**Fig. 8.40** Parasitic nodule. A circumscribed fragment of thyroid tissue in a patient with a Hashimoto thyroiditis. Germinal centers are separated by evenly distributed aggregates of oncocytic epithelium (e). This low power view gives the impression of nodal sinus histiocytes where the epithelium is located, but true sinuses and a subcapsular sinus are absent

**Table 8.22** Molecular alterations and clinical correlates in thyroid tumors

| Genetic alteration | Type | Tumor | Clinicopathologic associations |
|---|---|---|---|
| RET | Mutation | MTC | Germline mutations cause MEN type 2 (100%)<br>Point mutations at codon 918: MEN 2B, more aggressive disease<br>Point mutation at codon 634: MEN 2A, intermediate risk for aggressive disease |
| RET/PTC | Rearrangement | PTC | Associated with radiation exposure and classic PTC<br>RET/PTC1 (67%) and RET/PTC3 (33%): account for 90% of all rearrangements in PTC<br>Seen in PTC of children and young patients<br>No correlation with outcomes |
| BRAF-V600E | Mutation | PTC, IFVPTC, ATC, PDTC | Associated with RAI-refractory tumors<br>Rare in radiation-associated tumors<br>Aggressive behavior, poor outcome, ±decreased survival |
| NTRK1, 3 | Rearrangement | PTC | NTRK1: PTC<br>NTRK3: Radiation-associated PTC and follicular architecture |
| ALK | Rearrangement, mutation | PTC, ATC | High frequency in radiation-induced PTC<br>Rearrangement in PTC, PDTC, ATC<br>Mutation in ATC<br>Rearrangement not seen in FA, FTC, MTC, HCA, HCC |
| TERT | Mutation | PTC, FTC, PDTC, ATC | Associated with poor prognostic parameters: older age, large tumor size, high stage, DM<br>Advanced stage disease and poor prognosis |
| TP53 | Mutation | PDTC, ATC | Primarily limited to high-grade carcinomas<br>More aggressive behavior in conjunction with BRAF mutations |

*MTC* medullary thyroid carcinoma, *PTC* papillary thyroid carcinoma, *MEN* multiple endocrine neoplasia, *IFVPTC* infiltrative follicular variant PTC, *ATC* anaplastic thyroid carcinoma, *FA* follicular adenoma, *PDTC* poorly differentiated thyroid carcinoma, *FTC* follicular thyroid carcinoma, *DM* distant metastases

**Table 8.23** Relative frequency of molecular alterations in thyroid tumorigenesis

| | FA | FTC | EFVPTC | PTC | MTC (H/S) | PDTC | ATC |
|---|---|---|---|---|---|---|---|
| RAS (N > H > K) | 20–40% | 40–50% | 25–45% | 0–10% | 80% of RET-neg MTC | 20–50% | 10–50% |
| PAX8-PPARγ | 5–20 | 20–40% | 0–30% | – | – | 5% | – |
| BRAF-V600E | – | – | 0–10% | 45–80% | – | 5–35% | 25% (10–50%) |
| RET | – | | 0–10% | 10–25% | 100/30–70% | 10% | |
| ALK(fusion) | – | – | | 6% | | 0–10% | 0–10% |
| TP53 | – | – | – | – | – | 10–35% | 40–80% |
| TERT | – | 10–35% | 5–15% | 5–25% | – | 20–50% | 30–75% |

*ATC* anaplastic thyroid carcinoma, *FA* follicular adenoma, *FTC* follicular carcinoma, *MTC* medullary thyroid carcinoma, *PDTC* poorly differentiated thyroid carcinoma, *PTC* papillary thyroid carcinoma, *FV* follicular variant, *H* hereditary, *S* sporadic

- Knowledge of the patient's clinical thyroid history (e.g., thyroiditis, goiter, Graves' disease) may be a clue to the possibility of a parasitic nodule.

References: [60, 171–178]

20. *What are the common genetic alterations associated with thyroid tumorigenesis?*

A number of genetic alterations are associated with benign and malignant thyroid tumors. Some of these alterations are related to specific clinical scenarios. Table 8.22 summarizes some of the genetic alterations identified in thyroid tumors and their clinical significance. Approximately 75% of thyroid carcinomas harbor a known genetic alteration. Table 8.23 provides the relative frequencies of the different alterations.

- An important point should be made here. Much of the reported data for molecular alterations found in follicular variant of papillary thyroid carcinoma (FVPTC) is somewhat misleading as it includes cohorts with infiltrative FVPTC, encapsulated FVPTC, and the newly defined NIFTP (see question 12).
  - So reported rates of molecular alterations for FVPTC include a substantial number of NIFTPs, a tumor that is known to harbor genetic alterations more commonly seen in follicular carcinomas and adeno-

mas. This accounts for the reported rates of RAS and PAX8/PPAR-gamma mutations in FVPTC.
  - Conversely, the infiltrative subtype of FVPTC, which behaves, looks like, and harbors mutations typically seen in classic PTC accounts for the reported rates of BRAF-V600E and RET rearrangements in FVPTC.
- Some genetic alterations have particular importance because of their correlation with clinical behavior and malignancy and are helpful when evaluating biopsy specimens.

References: [60, 179–183]

21. *Which hereditary and genetic syndromes are associated with thyroid tumors?*

A number of hereditary disorders include thyroid tumors as part of their phenotype (Table 8.24).

- Multiple endocrine neoplasia is the most common hereditary thyroid syndrome (MEN-2A and MEN-2B) contributing to 20–30% of hereditary medullary thyroid carcinomas.
- Familial non-medullary thyroid carcinomas (FNMTC) account for about 10% of all follicular cell-derived thyroid neoplasms. FNMTC syndromes include a family of largely autosomal dominant disorders: familial PTC, FNMTC type 1 syndrome, familial PTC with renal papillary neoplasia, and familial multinodular goiter syndrome.
  - By definition, non-medullary thyroid carcinoma must be present in three or more first-degree relatives.
  - Patients tend to have more aggressive disease with multifocal carcinomas, extrathyroidal extension, locoregional recurrence, and metastases.
- Other genetic syndromes are associated with thyroid tumors but are not the primary manifestation of the disorder. The thyroid tumors associated with Cowden syndrome and familial adenomatous polyposis (FAP) have a unique appearance and should prompt the pathologist to consider a syndromic disorder.
  - Figure 8.41 shows the unusual multinodular thyroid in a patient with a PTEN mutation. Unlike a typically multinodular gland, the nodules in these patients have a strikingly similar appearance.

References: [53, 184–187]

22. *Which pathologic features have prognostic significance in thyroid carcinomas?*

Several factors are important in the assessment of patient outcomes for thyroid carcinoma. Table 8.25 summarizes the pathologic parameters that should be included in any pathology report of thyroid carcinoma. Some parameters are specifically addressed within the American Joint Committee on Cancer (AJCC) staging system including tumor size, extent, and patient age.

**Table 8.24** Genetic syndromes associated with thyroid tumorigenesis

| Syndrome (frequency of thyroid carcinoma) | Mutation | Thyroid carcinoma | Other thyroid findings | Extrathyroidal findings |
|---|---|---|---|---|
| MEN-2A, 2B (>95%) | RET | Medullary thyroid carcinoma | CCH | 2A: pheochromocytoma, hyperparathyroidism<br>2B: pheochromocytoma, mucosal neuromas, GI ganglioneuromas |
| FMTC (>95%) | RET | Medullary thyroid carcinoma | CCH | – |
| Cowden syndrome (35%) | PTEN | Multicentric FTC (10–15%), FVPTC | Multiple FAs: solid, microfollicular, typically identical and devoid of colloid<br>Background CCH or CT | Hamartomas and carcinomas of breast, uterus |
| FAP (2–12%) | APC, ß-catenin | Cribriform-morula variant PTC | – | Multiple colorectal adenomas |
| Carney (15%) | PRKAR1α | PTC, FTC, FA | Adenomatous nodules | Triad: spotty pigmentation, endocrine tumors, myomas |
| Werner syndrome (18%) | WRN | PTC, FTC, ATC | – | Premature aging disorder, cardiac disease |
| Familial non-MTC syndromes | Not well characterized | PTC | Adenomatous nodules | Renal tumors |

*TC* thyroid carcinoma, *CCH* C-cell hyperplasia, *GI* gastrointestinal, *FTC* follicular thyroid carcinoma, *FVPTC* follicular variant papillary thyroid carcinoma, *CT* chronic thyroiditis, *PTC* papillary thyroid carcinoma, *FA* follicular adenoma, *ATC* anaplastic thyroid carcinoma, *FNMTC* familial non-medullary thyroid carcinomas

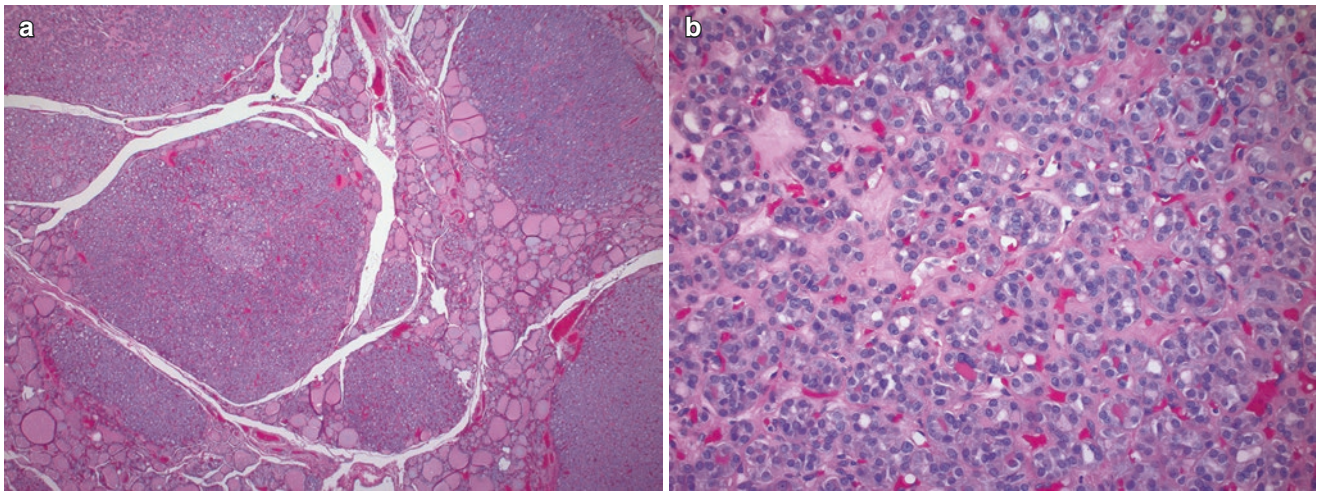


**Fig. 8.41** Thyroid gland in a patient with PTEN mutation. (**a**) Multiple follicular nodules of varying size all have a similar histologic appearance. The highly cellular nodules create clefting as they retract from the surrounding normal parenchyma. (**b**) The nodules are microfollicular but devoid of colloid and solid in areas

**Table 8.25** Pathologic features used in thyroid carcinoma risk assessment[a]

| Histologic feature | Criteria | High-risk parameter | Impact | Comments |
|---|---|---|---|---|
| Extrathyroidal extension (ETE) | Tumor extension beyond the thyroid capsule | Gross ETE into muscle, subcutaneous tissue, or adjacent structures | Increased recurrence rates (23–40%) | Microscopic ETE eliminated from AJCC system due to low recurrence rates 2–9%<br>Also poor interobserver agreement |
| Margin status | Tumor cells at inked border of specimen | Macroscopic, gross involvement (R2) | Increased recurrence rates with a positive posterior margin | Microscopic (R1) positive margin not independent predictor of recurrence or DFS |
| Lymph node (LN) status | Number of involved LNs, size of LN, size of metastasis, location of positive LNs | Macroscopic, gross positive LN | Correlates with recurrence and disease-free survival | Small volume LN metastases have low recurrence risk (<5%) and survival impact |
| Extranodal extension | Involvement of perinodal adipose tissue | Present | Persistent, recurrent disease | Not established as an independent prognosticator of survival |
| Vascular invasion | Tumor in vessel space, attached to wall (see question 5) | Extent is most important: ≥4 foci of vascular invasion | 45% risk of DM | |
| Capsular invasion (CI) | Tumor present outside of the tumor capsule | Widely invasive carcinomas have high risk of DM | Minimally invasive CI is not used in risk stratification, regardless of quantity | |

[a]Most data based on papillary thyroid carcinoma
*LN* lymph node, *DFS* disease-free survival, *DM* distant metastases

Other pathologic parameters are reflected in the American Thyroid Association modified 2009 risk stratification system (Table 8.26). Both systems are used together to assess the patient's risk for recurrent disease, survival and to guide pre- and postoperative management. Important prognostic features are discussed in Table 8.27.

- Tumors are risk stratified within the ATA system according to a three-tier system. In general, high-risk tumors require total thyroidectomy and postoperative radioactive iodine ablation. The intermediate-risk tumors have more varied management, while the management of low-risk tumors is geared toward more conservative treatments. Table 8.26 highlights the pathologic features used in the ATA risk stratification system.
- The AJCC staging takes various combinations of primary tumor characteristics (T) and metastatic status (N-nodal, M-distant disease) to create different stage groups which correlate with survival outcomes.

**Table 8.26** Pathologic features used in the ATA risk assessment of thyroid carcinoma

| Low risk | Intermediate risk | High risk |
|---|---|---|
| Papillary thyroid carcinoma with:<br>– Non-aggressive histology<br>– No LN metastases or ≤5 LN metastases less than 0.2 cm in size<br>– Complete resection<br>– No vascular invasion<br>– No ETE<br>EFVPTC without ETE<br>FTC with capsular invasion, no ETE, and <4 foci of VI<br>MicroPTC with no ETE | Microscopic ETE<br>Aggressive histology<br>PTC with VI<br>>5 LN metastases, all less than 3 cm<br>Multifocal microPTC with ETE and BRAF-V600E | Macroscopic ETE<br>Incomplete resection<br>DM<br>Any LN metastases ≥3 cm<br>FTC with ≥4 foci of VI |

Adapted from Ref. [181]
*ETE* extrathyroidal extension, *LN* lymph node, *PTC* papillary thyroid carcinoma, *VI* vascular invasion, *EFVPTC* encapsulated follicular variant PTC, *FTC* follicular thyroid carcinoma

**Table 8.27** Poor prognostic features in thyroid carcinoma

| |
|---|
| Age >55 |
| Male gender |
| Necrosis |
| Mitoses |
| Histologic type (ATC, PDTC, MTC, HCC) |
| High stage |
| Genetic alterations: TERT, RET-M918T, TP53 |

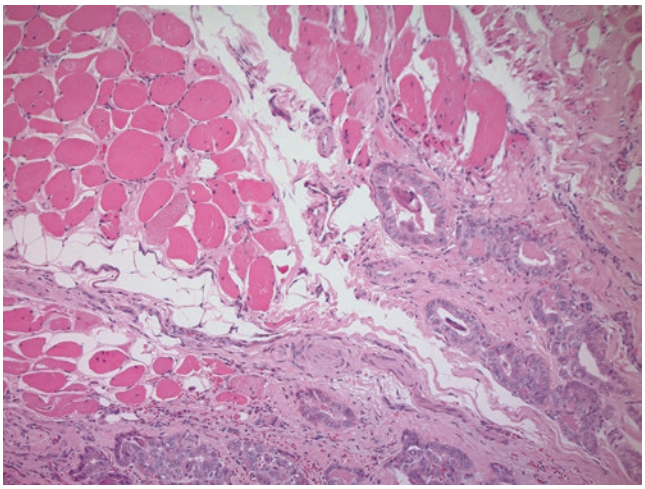

**Fig. 8.42** Extrathyroidal extension of papillary thyroid carcinoma into skeletal muscle no longer affects T staging in the AJCC system if it is only microscopic invasion

  - T stage: tumor size and extent of invasion (e.g., extrathyroidal extension, invasion of adjacent structures)
  - N stage: presence and site of nodal involvement (lateral neck, central neck disease)
  - M stage: presence of distant metastases
- The 8th edition of the AJCC TNM staging system published in 2017, overall serves to downstage patients when compared to the previous 7th edition (2007). The changes better reflect patient survival, and a few points are worth highlighting.
  - Histologic subtype is no longer considered in AJCC pathologic T staging (pT). Differentiated and anaplastic thyroid carcinomas all use the same criteria for assigning a pathologic T stage.
  - However, all anaplastic thyroid carcinomas, regardless of pT assignment, are in the stage IV prognostic group.
  - Microscopic extrathyroidal extension (ETE) is no longer part of the AJCC staging (Fig. 8.41) but should be documented for risk stratification. Only gross ETE as determined by clinical and/or radiographic evidence is considered (T3b or T4).
  - The 8th ed. AJCC raises the age at diagnosis to 55 years or older (from 45 years) in considering the final prognostic stage groupings, recognizing that younger patients demonstrate better survival rates.
- The percentage of a tall cell component within a tumor impacts prognosis, but the quantitative cutoff varies among authors (see question 11). It is recommended that the amount is quantified and reported.
- The presence of psammoma bodies within a lymph node without epithelium should be mentioned in the pathology report.
  - Psammoma bodies are thought to represent old, calcified tumor.

References: [181, 188–190]

23. *What are the most common hematolymphoid tumors of the thyroid gland?*

Hematopoietic tumors may be primary to the thyroid gland or involved secondarily. Primary lymphomas of thyroid constitute less than 2% of all extranodal lymphomas and less than 5% of all thyroid malignancies. Morphologic features of the different lymphomas are discussed in detail in Chap. 10.

- Primary thyroid lymphomas have a 3:1 female predilection and an average age of 65 years.
- Patients present with a rapidly enlarging mass, dysphagia, or symptoms related to mass effect.
  - Over 90% of primary thyroid lymphomas are non-Hodgkin lymphomas.

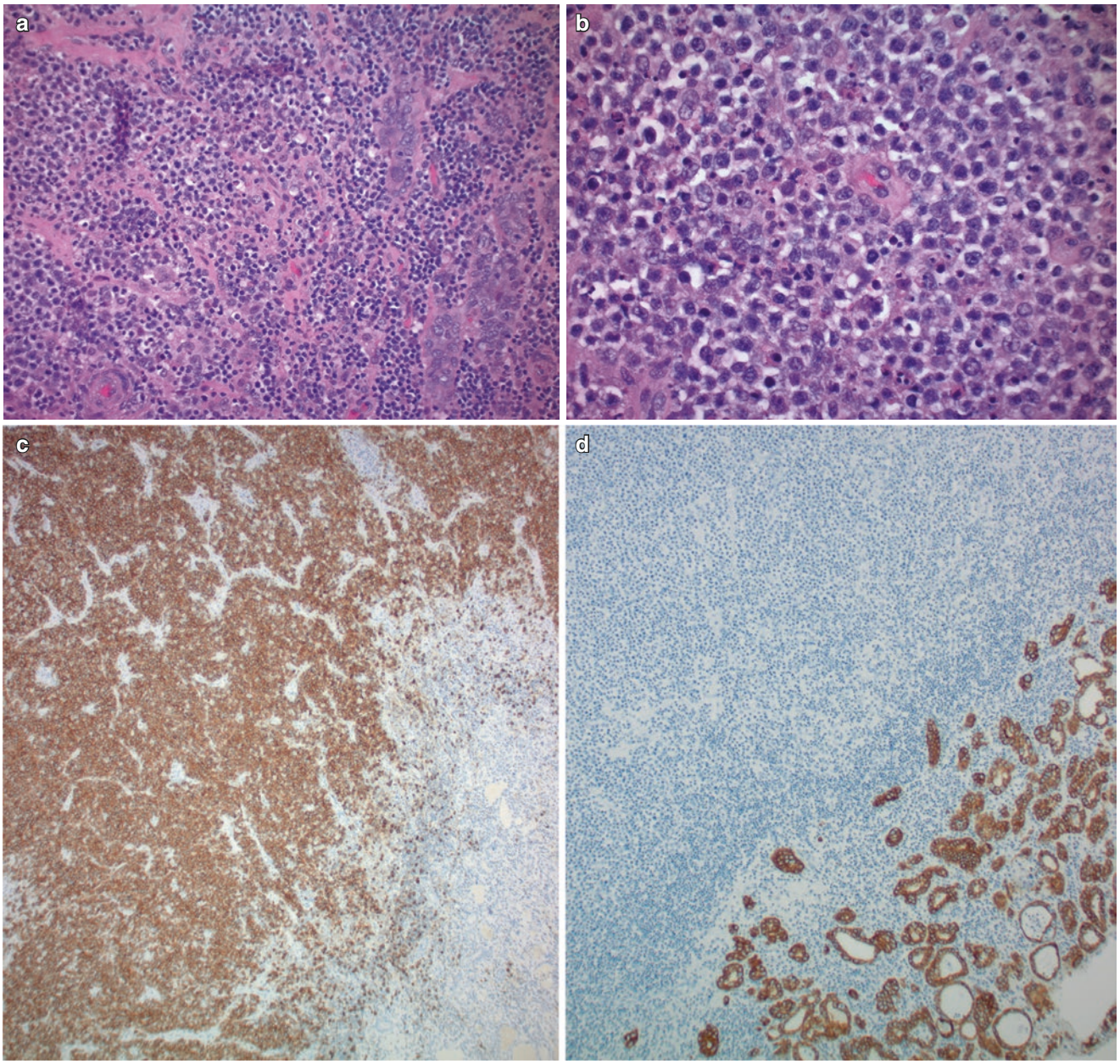


**Fig. 8.43** Primary diffuse large B-cell lymphoma of thyroid. (**a**) Sheets of lymphocytes obliterate most of the normal thyroid architecture leaving a focus of residual chronic thyroiditis (lower right). (**b**) The lymphoid cells are large with vesicular nuclei, prominent nucleoli, and brisk apoptosis. The tumor cells are (**c**) positive for CD20 and (**d**) negative for cytokeratin

- Diffuse large B-cell is the most common subtype (43–87%) (Fig. 8.43).
- Extranodal marginal zone B-cell lymphoma of mucosal-associated lymphoid tissue (MALT) and follicular lymphomas follow in decreasing frequency.
- It is thought that a subset of primary thyroid DLBCLs is derived from MALT lymphomas.
  - Up to 50% of patients with primary thyroid lymphoma have a history of Hashimoto thyroiditis.
  - Over 90% of patients present with early-stage disease, and the disease-specific survival is about 80% at 5 years.
- 5-year survival rates for DLBCL are slightly worse (75%) than for MALT lymphomas (90%).
- Primary Hodgkin lymphoma of the thyroid is very rare with only a handful of cases reported in the literature. Patients tend to be younger than those with non-Hodgkin lymphomas.
- Other lymphomas of the thyroid include Burkitt lymphoma and T-cell lymphomas.

Other hematopoietic tumors that may involve the thyroid are relatively rare. Most present as a painless thyroid mass. The reader is again referred to Chap. 10 for further details of tumors seen in the thyroid gland, like Rosai-Dorfman disease, follicular dendritic cell sarcoma, and plasmacytomas. Langerhans cell his-

tiocytosis will be discussed here as it has particular significance to the endocrine system.

Langerhans cell histiocytosis (eosinophilic granuloma) has long been thought to be a monoclonal proliferation of Langerhans dendritic cells. Recent evidence suggests that it may actually represent an inflammatory myeloid neoplasm. It typically affects children and can present with unifocal, single-organ disease or as disseminated disease. The former is more common in adults and presents with bone disease. Thyroid involvement is rare in Langerhans cell histiocytosis (LCH) in either form (<1% of patients); awareness is important to avoid misdiagnosis.

- Patients with LCH of the thyroid present with an enlarged thyroid or a mass. The median age is 28 years, and there is a slight female predominance. Approximately 65% of patients will have multiorgan disease.
  - Bone and lung involvement are most common.
  - Patients may be hypothyroid (20%) or euthyroid (40%) at presentation.
  - Patients with LCH of the thyroid demonstrate a higher rate of diabetes insipidus when compared to those with other sites of organ involvement.
- Histologic sections show sheets of cells that obliterate the normal follicular architecture. Scattered residual follicles may be present.
  - LCH cells have a moderate amount of eosinophilic cytoplasm and a characteristic eccentrically placed, bean-shaped nucleus with longitudinal grooves.
  - Cell membranes may be indistinct, creating a syncytial-like growth pattern.
  - LCH is associated with a mixed inflammatory infiltrate containing varying amounts of eosinophils and lymphocytes. Concurrent chronic thyroiditis may be present.
  - LCH growth may extend beyond the thyroid capsule into adjacent soft tissues.
  - Positive IHC: CD1a, S100, CD207, CD68.
  - Negative IHC: Cytokeratin, thyroglobulin, EMA, CD20, CD3, CD5.
- Genetics: BRAF-V600E in half of cases and MAP 2K1 in the remaining 30–50% of cases.
- Overall mortality rate is 3%, though patients with isolated thyroid involvement have a better prognosis.
- The differential diagnosis includes papillary thyroid carcinoma, follicular adenoma, lymphoma, melanoma, and myeloid sarcoma.

References: [191–198]

24. *What are the most common metastases to the thyroid gland?*

Metastases comprise 2% of all thyroid malignancies and are identified in less than 0.2% of thyroidectomy specimens. The incidence ranges from 1.25% to 24.2% in autopsy and case series. Straccia et al. performed a meta-analysis of intrathyroidal metastases of 25 references and 514 patients. The frequency of intrathyroidal metastases by site of origin is summarized in Table 8.28.

Metastases to the thyroid are indicative of late-stage disease and carry a poor prognosis.

Almost 70% of cases are metachronous with latency periods ranging from 7 to 120 months.

This statistic highlights the difficulty in arriving at the correct diagnosis for patients that have a remote history of a primary malignancy.

In addition, far more cases are diagnosed on fine-needle aspiration biopsy than on thyroidectomy. Limited diagnostic material adds to the difficulty in the diagnosis.

More than 50% originate from an infra-diaphragmatic primary.

Average survival after thyroidectomy was 32 months with an upper limit of 10 years.

Taken together, renal cell carcinoma is the most likely metastasis to the thyroid (Fig. 8.44).

References: [199–204]

**Table 8.28** Frequency of metastases to the thyroid and their immunoprofiles

| | Site | Frequency (%) | Contrasting IHC | Identical IHC |
|---|---|---|---|---|
| Known primary | Kidney | 37 | CD10+ | PAX-8+ |
| | Lung | 24 | NapsinA+ | CK7+, TTF-1+ |
| | Breast | 14 | Gata-3+ | CK7+ |
| | Colon | 9 | CDX-2+, CK20+ | – |
| Unknown primary 27% | Unknown | 2 | – | – |

Adapted from reference [199]

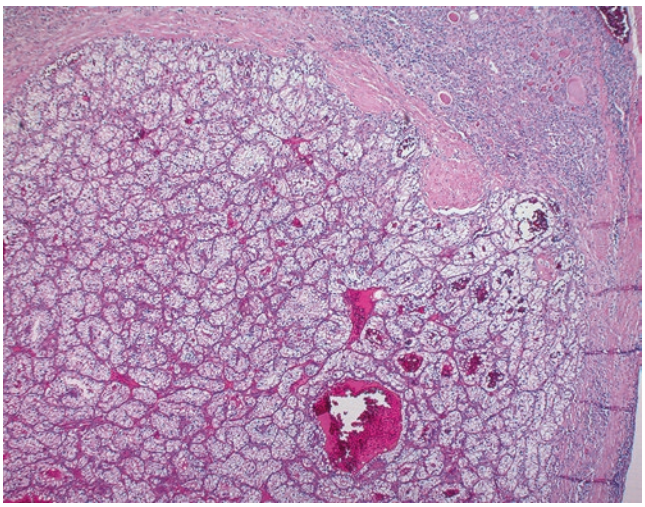

**Fig. 8.44** Metastatic renal cell carcinoma in the thyroid gland of a patient with chronic thyroiditis

## Case Presentations

### Case 1

#### Learning Objectives

1. To generate the differential diagnosis for cystic neck masses
2. To recognize the need to thoroughly submit cyst wall for histologic examination
3. To utilize ancillary studies as required for definitive diagnosis

#### Case History

A 36-year-old female with cystic lateral neck mass (Fig. 8.45a). Fine-needle aspiration (FNA) biopsy was nondiagnostic.

#### Gross Findings

Collapsed cyst with thin wall. A solid component was not appreciated. The cyst lining was smooth without excrescences. Histologic review of the entire cyst wall was performed.

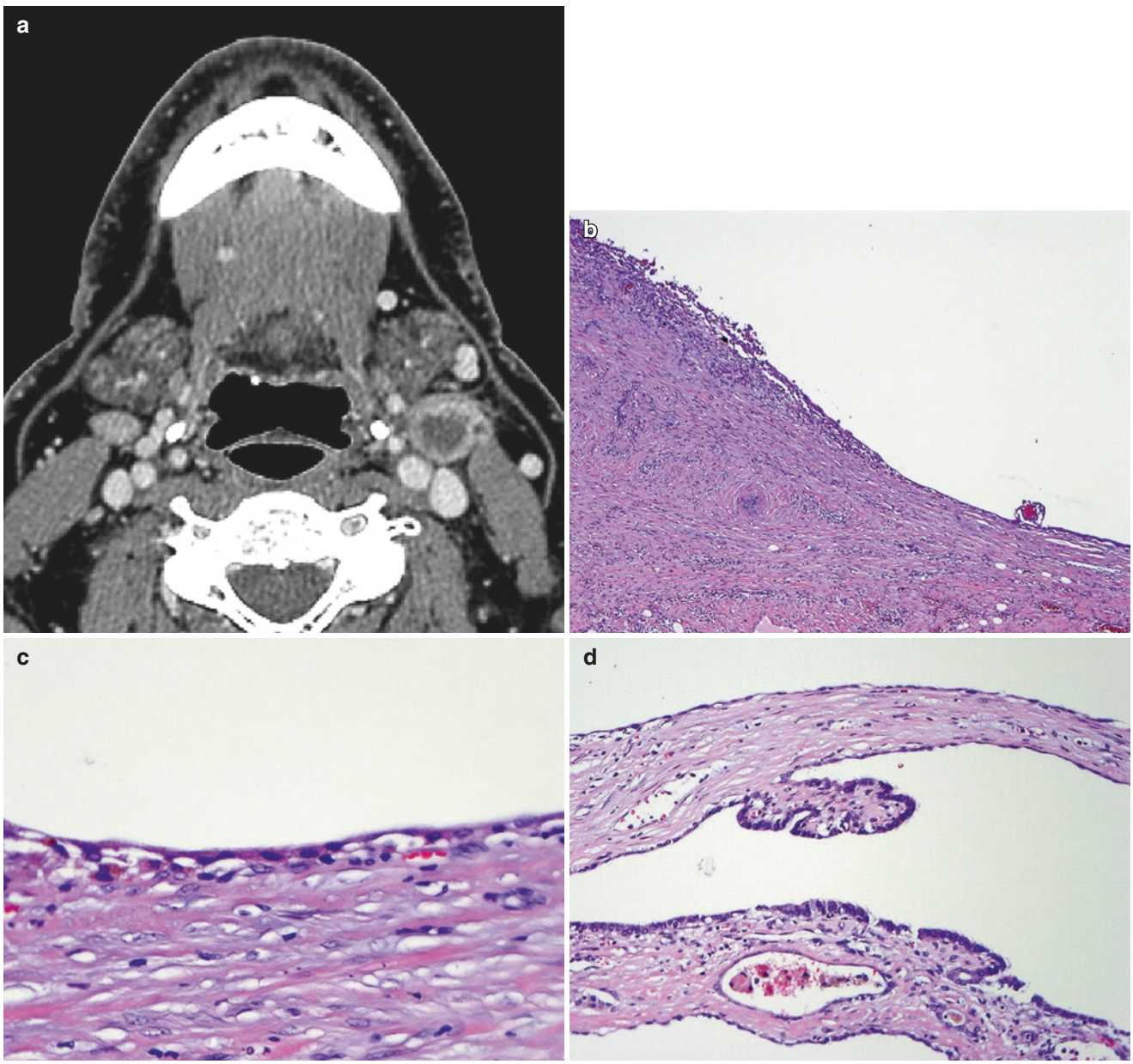


**Fig. 8.45** Case 1. (**a**) A CT scan shows a cystic mass in the left lateral neck. (**b**) The cyst wall is fibrotic with (**c**) an attenuated lining. (**d**) Focal areas show papillae lined by atypical, elongated nuclei with fine chromatin and nuclear overlap

**Histologic Findings** (Fig. 8.45b–d)
- A largely denuded cyst wall with a flattened lining in areas and limited nuclear visualization. Foci of focal papillae formation are present.
- Scattered enlarged, clear nuclei that may are may not be diagnostic of papillary thyroid carcinoma.

**Differential Diagnosis**
- Branchial cleft cyst
- Papillary thyroid carcinoma, cystic
- Squamous cell carcinoma, cystic
- Dermoid cyst
- Thyroglossal duct cyst

**Ancillary Studies**
- In the lateral neck, FNA fluid may be tested for thyroglobulin in the chemistry lab.
- TTF1 and PAX-8 are nuclear markers that will highlight thyroid cells.

**Final Diagnosis** *Metastatic papillary thyroid carcinoma presenting as lateral neck cyst*

**Take-Home Messages**
1. Cystic neck nodules may represent malignancy in all ages.
2. Lateral neck cysts are of particular concern since the handful of midline cystic lesions tend to be benign. These include thyroglossal duct cyst and dermoid cyst.
3. Papillary thyroid carcinoma cells may be distended in macrofollicles and large cysts, obscuring the nuclear features. Thorough sampling of the entire cyst wall is critical in confirming the diagnosis.
4. Confirmation of thyroid tissue by immunohistochemical studies can verify the tissue type, but diagnosis relies on the morphologic features of PTC.
   References: [205–208]

## Case 2

**Learning Objectives**

1. To recognize gross and histologic features of a diffusely enlarged thyroid gland
2. To generate the differential diagnosis of lesions with squamous metaplasia

**Case History**
A 19-year-old female with enlarged goiter and hypothyroidism by examination. Ultrasound suggests diffuse calcifications and enlargement bilaterally.

**Gross Findings**
Markedly enlarged thyroid bilaterally. Cut surface is pale with vague nodularity with scattered, punctate foci of yellow discoloration (Fig. 8.46a). Vague nodularity is noted on the left, superiorly. Lymph nodes in the isthmus region are palpable.

**Histologic Findings** (Fig. 8.46b–d)
- Background thyroid with thyroiditis, consistent with Hashimoto thyroiditis.
- Variable degree of sclerosis with diffuse psammoma bodies associated with solid epithelial proliferation.
- Areas with papillary architecture, nuclear enlargement, and clearing consistent with papillary thyroid carcinoma nuclei. Solid clusters of cells show bland, squamous metaplasia.

**Differential Diagnosis**
- Papillary thyroid carcinoma, conventional type
- Squamous carcinoma involving thyroid (either primary or spread from the upper aerodigestive tract)
- Papillary thyroid carcinoma, diffuse sclerosing variant
- Mucoepidermoid carcinoma
- Sclerosing Hashimoto thyroiditis (Fig. 8.47)

**Ancillary Studies**
- Not necessary for the diagnosis but the tumor cells are positive for TTF-1, PAX-8, and thyroglobulin.

**Final Diagnosis** *Papillary thyroid carcinoma, diffuse sclerosing variant*

**Take-Home Messages**
1. This variant of PTC is most common in pediatric and young adults and may involve one or both thyroid lobes diffusely.
2. Squamous metaplasia may be prominent but lacks the atypia and pleomorphism of squamous cell carcinoma.
3. The triad of chronic lymphocytic thyroiditis often with sclerosis, psammoma bodies, and papillary thyroid carcinoma with diffuse lymphatic spread is a hallmark of this variant.
4. Patients are at higher risk for lung metastases at the time of presentation and surgery may be difficult secondary to the fibrosis.
   References: [82, 83, 209]

## Case 3

**Learning Objectives**
1. To thoroughly evaluate the gross thyroidectomy specimen for correlative findings for this tumor

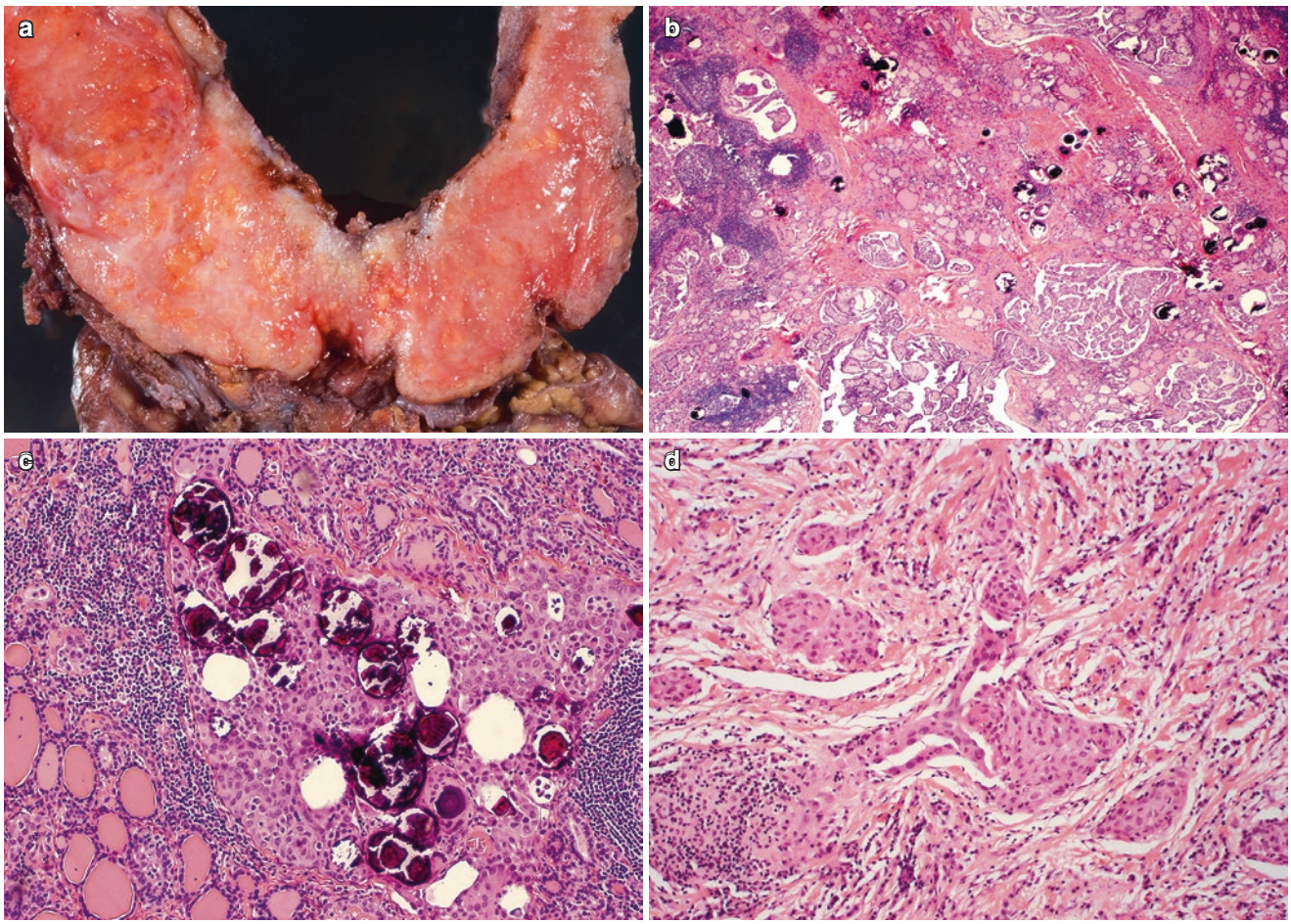


**Fig. 8.46** Case 2. (**a**) The total thyroidectomy specimen is diffusely enlarged with a pale, focally fibrotic cut surface. (**b**) Prominent background lymphocytic thyroiditis is present with a papillary proliferation, sclerosis, and (**c**) numerous psammoma bodies admixed with solid, atypical, squamoid tumor nests. (**d**) Other areas show bland squamous metaplasia

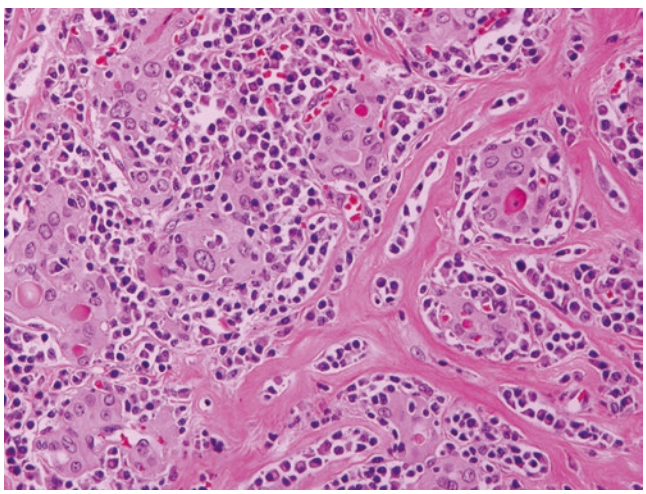

**Fig. 8.47** Case 2. Hashimoto thyroiditis with sclerosis and thyroid follicles with oncocytic change may have a squamoid appearance

2. To be aware of the differential diagnosis based on the morphologic spectrum
3. To utilize immunohistochemistry for diagnostic classification

### Case History

A 40-year-old female with left-sided thyroid nodule on palpation. The patient has previously been evaluated for chronic diarrhea. She has no known family history of thyroid disease and has two children.

### Gross Findings

Circumscribed, thyroid nodules are present in the upper half of both thyroid lobes. Sections show a solid, fleshy, tan-white cut surface (Fig. 8.48a).

### Histologic Findings (Fig. 8.48b)

- The tumor is arranged in small irregular nests with infiltration into adjacent thyroid follicles.

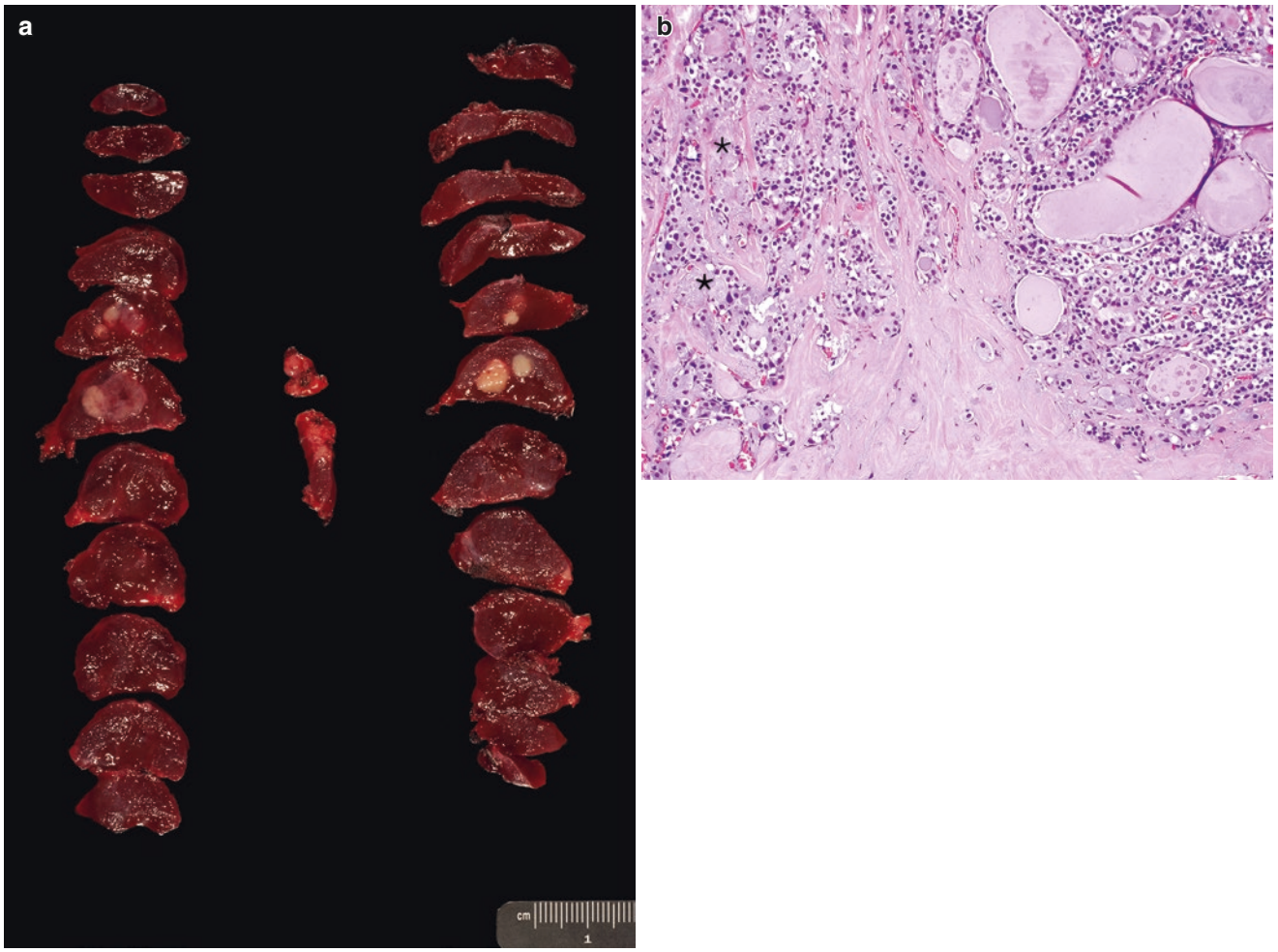


**Fig. 8.48** Case 3. (**a**) Careful sectioning of the thyroid reveals bilateral, tan-white nodules. (**b**) The tumor cells are arranged in nests and have an amphophilic to clear cytoplasm. Amorphous, waxy extracellular material is present (asterisk) consistent with amyloid

- The tumor cells show plump oncocytic to clear cells within an amorphous stroma.

**Differential Diagnosis**
- Poorly differentiated thyroid carcinoma
- Medullary thyroid carcinoma
- Paraganglioma
- Hyalinizing trabecular tumor
- Papillary thyroid carcinoma
- Metastasis to thyroid

**Ancillary Studies**
- Positive IHC: cytokeratin, TTF-1, synaptophysin, chromogranin, calcitonin, CEA, ±PAX-8
- Negative IHC: thyroglobulin

**Final Diagnosis** *Medullary thyroid carcinoma. Hereditary MTC is likely, given the bilateral nature of the tumor. This patient's genetic testing was positive for multiple endocrine neoplasia type 2A.*

**Take-Home Messages**
1. Histologic evaluation of the thyroid gland in patients with a biopsy diagnosis of MTC or positive genetic testing should focus on the upper two-thirds of bilateral lobes.
2. In the absence of gross abnormalities, the entire thyroid gland should be evaluated histologically.
3. C-cell hyperplasia must be differentiated from lymphovascular invasion which is a common feature in this tumor.
4. Guidelines encourage all patients with medullary thyroid carcinoma to undergo genetic screening regardless of age at presentation.

References: [53, 210]

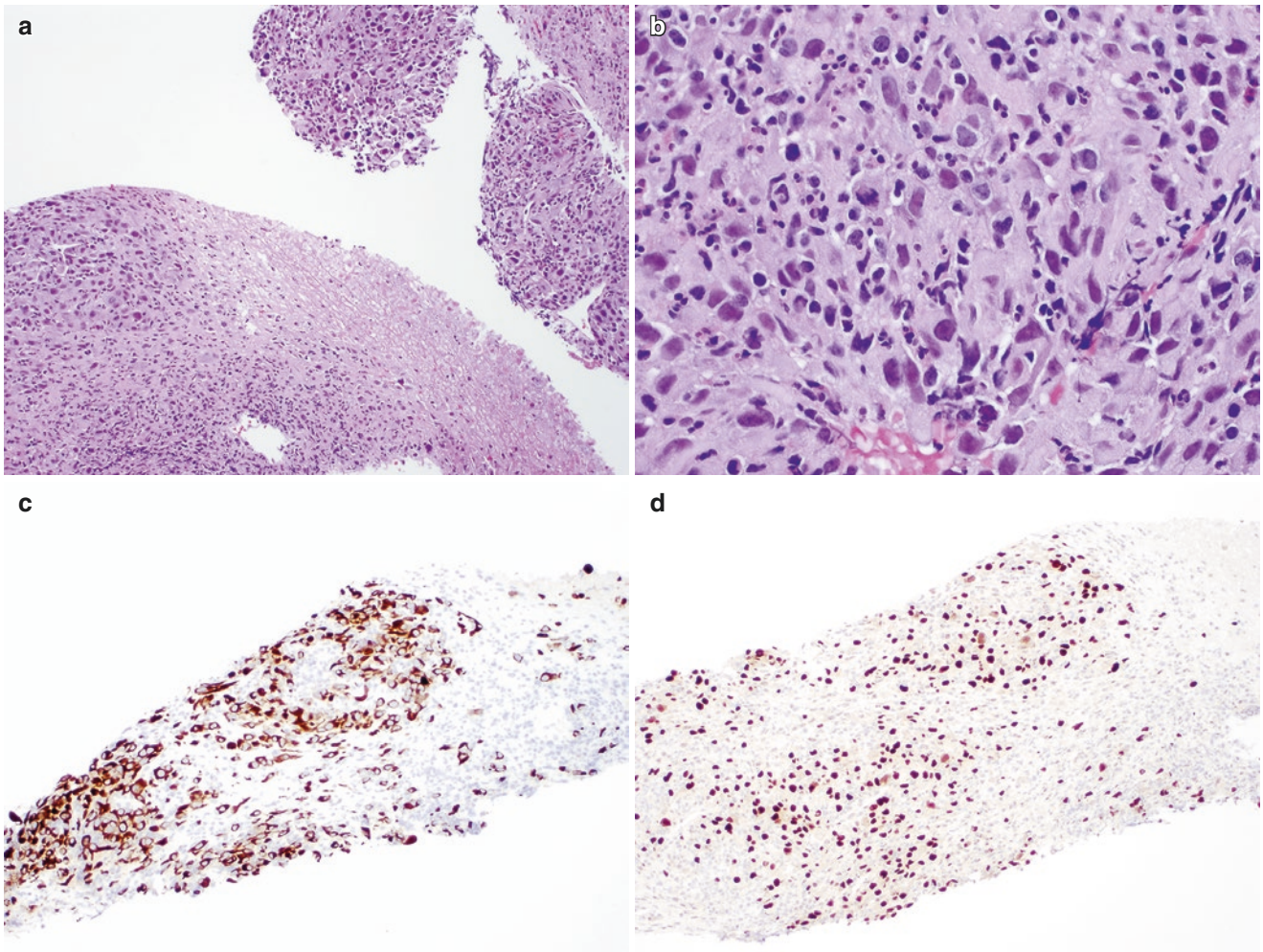


**Fig. 8.49** Case 4. (**a**) Core biopsy shows fragments of a high-grade tumor with necrosis. (**b**) High magnification shows nuclear pleomorphism with scattered neutrophils. Immunohistochemical stains show the tumor cells are positive for (**c**) cytokeratin and (**d**) Pax-8

## Case 4

### Learning Objectives

1. Develop a differential diagnosis for thyroid nodules with high-grade features.
2. Compile a comprehensive immunohistochemical panel for the diagnosis.
3. Become familiar with overlapping immunohistochemical markers in the differential diagnosis.

### Case History

A 65-year-old male presents with a rapidly enlarging neck mass.

### Gross Findings

Fine-needle aspiration was necrotic, and a core biopsy was performed.

### Histologic Findings (Fig. 8.49a, b)

- High-grade cellular areas are admixed with areas of necrosis.
- Sheets of pleomorphic epithelioid cells with mitotic figures are present with an associated inflammatory infiltrate.

### Differential Diagnosis (Table 8.29)

- Lymphoma
- Metastases to thyroid
- Anaplastic (undifferentiated) thyroid carcinoma (Table 8.30)
- Poorly differentiated thyroid carcinoma
- Papillary thyroid carcinoma with high-grade features
- Sarcoma

### Ancillary Studies (Fig. 8.49c, d)

- Positive IHC: cytokeratin, PAX-8
- Negative IHC: TTF-1, thyroglobulin

**Table 8.29** Clinicopathologic features in the differential diagnosis of a high-grade thyroid tumor

| Tumor | Key histologic features | Clinical evaluation |
|---|---|---|
| Anaplastic thyroid carcinoma | Sheetlike growth<br>Varied morphology: epithelioid, spindled, squamoid, pleomorphic, giant cell | Rapid onset of neck mass |
| Lymphoma | Sheetlike growth<br>High-grade epithelioid | Rapid onset of neck mass |
| Metastasis to thyroid | Morphologically overlaps with high-grade, poorly differentiated carcinomas | Prior history of cancer<br>Imaging may highlight disease distribution and possible primary sites |
| Poorly differentiated thyroid carcinomas | Typically not pleomorphic<br>Architecture is insular/trabecular, not sheet like | May present as advanced disease |
| Papillary thyroid carcinoma | Rarely shows necrosis, architecturally papillary, follicular, or solid nests | Can be present in 30–50% of anaplastic thyroid carcinomas |
| Sarcoma | Usually primary soft tissue tumor of the neck with secondary invasion of the thyroid | Typically slower time course |
| Squamous cell carcinoma (SCC) (metastatic or direct extension) | Morphology and immunohistochemistry overlap with primary thyroid SCC and ATC | History of prior upper aerodigestive tract SCC or another site |

**Table 8.30** Immunoprofile of tumors in the differential diagnosis of anaplastic thyroid carcinoma

| ATC type | Tumor | Cytokeratins | TTF1 | Thyroglobulin | PAX8 | Other |
|---|---|---|---|---|---|---|
| | ATC | +70% | <15% | Rare | 50–70% | BRAF V600E (30–50%) |
| Epithelioid | PDTC | + | +variable | Variable | + | |
| | Solid PTC | + | + (98%) | + (>90%) | + (100%) | |
| | Solid FTC | + | + | + | + | |
| | Lymphoma | – | – | – | –[a] | Various |
| | Metastasis to thyroid | | | | | |
| | Renal, GYN, GU | + | – | – | + | Various |
| | Lung | + | + | – | – | |
| | Melanoma | –/rare + | – | – | | melan-A, tyrosinase, HMB-45 |
| | NE carcinoma | + | + in some sites | – | – | Syn, chromo |
| Spindled | MTC | + | + | – | – | Syn, chromo, calcitonin[b] |
| | Sarcoma | – | – | – | – | Various |
| Squamoid | SCC from H/N site | + CK5/6[c] | – | – | /rare + | |
| | Metastatic SCC | + CK5/6[c] | – | – | – | |

*ATC* anaplastic thyroid carcinoma, *PD* poorly differentiated thyroid carcinoma, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *GYN* gynecologic primary, *GU* genitourinary primary, *NE* neuroendocrine, *syn* synaptophysin, *chromo* chromogranin, *MTC* medullary thyroid carcinoma, *SCC* squamous cell carcinoma, *H/N* head and neck

[a]PAX-8 antibodies may cross-react with PAX-5 which is expressed in some lymphoma

[a]Calcitonin is not specific for medullary thyroid carcinoma and occasionally is expressed in neuroendocrine carcinomas from other anatomic sites

[b]Cytokeratin 5/6 may be expressed in ATC with squamoid differentiation; it does not help with differentiating squamoid pattern tumors

**Final Diagnosis** *Consistent with anaplastic thyroid carcinoma*

### Take-Home Messages

1. Anaplastic thyroid carcinomas may show a wide range of morphologic features from epithelioid, giant cell, pleomorphic, squamoid, and spindled.
2. Poorly differentiated thyroid carcinomas are *not* pleomorphic but monomorphic.
3. A well-differentiated papillary thyroid carcinoma may be associated with anaplastic thyroid carcinoma.

References: [211, 212]

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# Parathyroid

9

Shweta Agarwal, Peter M. Sadow, and Xiaoyin "Sara" Jiang

## Frequently Asked Questions

1. What are the characteristics of normal parathyroid glands?
2. How many parathyroid glands do humans have, where are they located, and how does their embryologic development relate to their location?
3. What is the function of parathyroid glands?
4. What is chronic parathyroiditis and which entities are in the differential diagnosis?
5. What are canals of Kürsteiner and how are they related to parathyroid cysts?
6. What are the causes and clinical characteristics of primary, secondary, and tertiary hyperparathyroidism?
7. What genetic syndromes are associated with hyperparathyroidism?
8. What are the features of hyperparathyroidism-jaw tumor syndrome (HPT-JT)?
9. What are the morphological features of parathyroid adenomas and how do they differ from parathyroid hyperplasia?
10. Is a rim of normal parathyroid tissue diagnostic of a parathyroid adenoma?
11. What are the molecular findings associated with parathyroid adenomas?
12. What are double adenomas and do they really exist?
13. What benign entities are in the differential diagnosis of a parathyroid adenoma?
14. Which entities of the parathyroid gland have fibrosis and what is the biological significance?
15. What are the clinical and histologic features of parathyroid carcinoma?
16. What are the molecular characteristics of parathyroid carcinomas?
17. How are parathyroid adenomas distinguished from carcinomas?
18. What is the utility of parafibromin immunohistochemistry, and can it help differentiate parathyroid adenomas from carcinomas?
19. What is the role of cyclin D1 in the pathogenesis of parathyroid neoplasms and what immunohistochemical panel can help distinguish carcinomas from adenomas?
20. What is an atypical parathyroid adenoma and what are the criteria for its diagnosis?
21. What non-parathyroidal entities are in the differential diagnosis of parathyroid carcinoma?
22. What is parathyromatosis and what is its clinicopathologic significance?
23. How do intraoperative parathyroid hormone levels assist in parathyroid surgery for primary hyperparathyroidism?
24. What is the role for intraoperative consultation in parathyroid surgery and how does an Oil red O stain assist in the consultation?
25. Which tumors can secondarily involve parathyroid gland?

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1. *What are the characteristics of normal parathyroid glands?*
   - Normal parathyroid (PT) glands (Fig. 9.1a) weigh 30–40 mg each and range in size from 0.2 to 0.7 cm in greatest dimension. Combined weights vary with age, gender, and race but are generally heavier in females (145 mg) than males (120 mg).
     – A gland weighing greater than 80 mg is considered abnormal.

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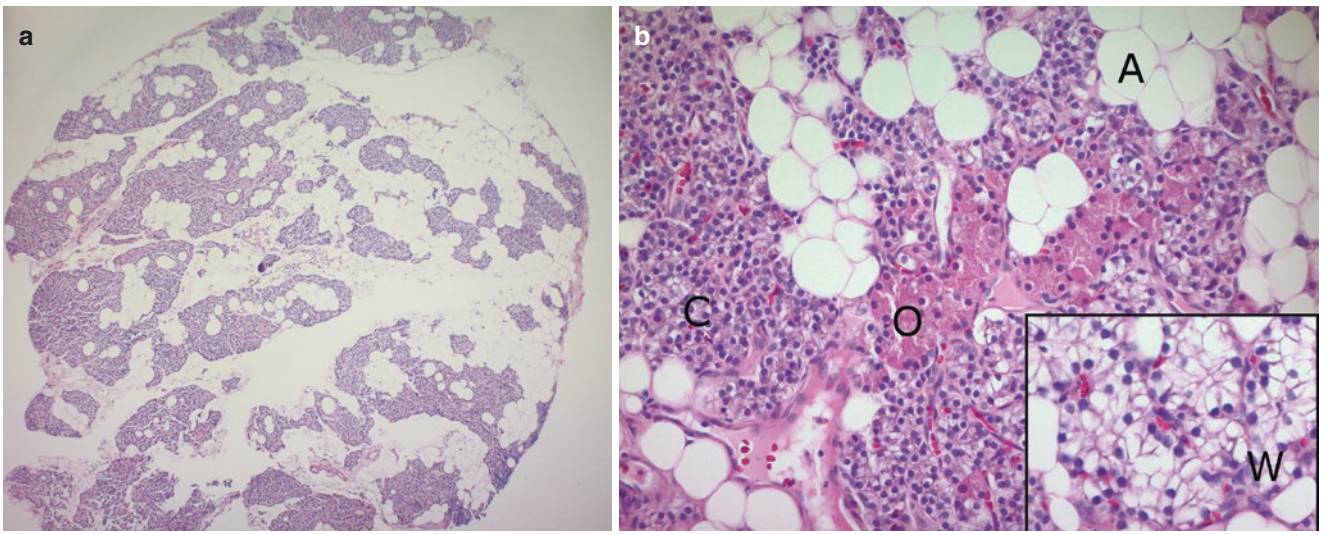


**Fig. 9.1** Normal parathyroid. (**a**) Low magnification shows a relatively equal distribution of parenchyma and fat. (**b**) The normal cell types of parathyroid include adipocytes (A), chief cells (C), oxyphil/oncocytic cells (O), and water-clear cells (W) (inset)

- The cell types (Fig. 9.1b) found in parathyroid include:
  - Chief cells are small cells with a basophilic nucleus and scant cytoplasm with cytoplasmic granules.
  - Water-clear cells are believed to be derived from chief cells and show abundant clear cytoplasm with a small, round nucleus.
  - Oxyphil cells, also known as oncocytic cells, have abundant, granular eosinophilic cytoplasm. These cells are often found in nodules, and their presence increases with age.
  - Adipocytes are present within parathyroid glands, generally increasing in proportion until middle age and comprising approximately 50% of the total gland parenchyma.

References: [1–4]

2. *How many parathyroid glands do humans have, where are they located, and how does the embryologic development relate to their location?*
   - The number of parathyroid glands in the population can vary. Most individuals have four parathyroid glands paired in superior and inferior locations, positioned close to the posterior aspect of the thyroid lobes.
   - About 5% of normal individuals have more than four glands (supernumerary glands). These can be present within the thyroid, thymus, esophagus, hypopharynx, or mediastinum. The most common ectopic locations are intrathymic and intrathyroidal.
     - Intrathyroidal glands (Fig. 9.2) tend to have decreased stromal fat when compared to normally situated glands, but function normally.
   - 1–3% of individuals have only three identifiable glands.

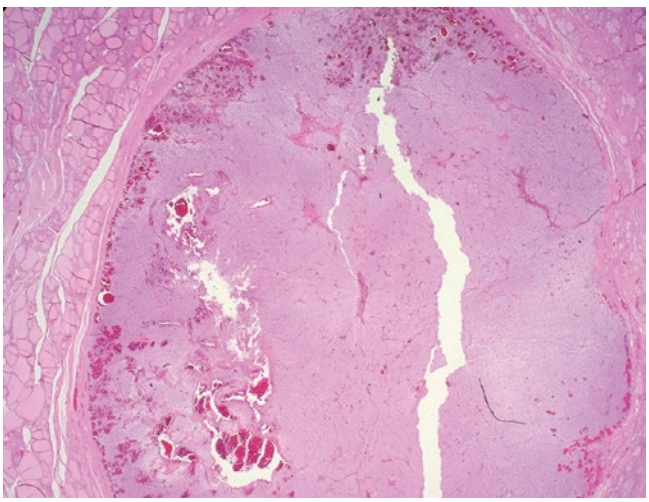

**Fig. 9.2** Intrathyroidal parathyroid gland. The amount of stromal fat is reduced compared to normally situated glands

   - Embryologically, the superior parathyroid glands are derived from the fourth branchial pouch. The inferior pair, along with thymus, is derived from the third branchial pouch.
     - The final position of the superior parathyroid glands is more reliable.
       - 77% of the superior glands lie posterior to the mid-superior thyroid pole, close to the cross point of the recurrent laryngeal nerve and inferior parathyroid artery.
     - The inferior parathyroids have a complex pattern of migration and a longer descent, predisposing them to more frequent ectopic locations.

- They can be found anywhere along the course of migration of the third branchial pouch from the angle of the jaw to the pericardium.
- Approximately 50% are found posterior and lateral to the inferior thyroid poles.

References: [1, 5–7]

3. *What is the function of parathyroid glands?*

The primary role of the parathyroid glands is to ensure calcium homeostasis by maintaining calcium levels within a narrow range of 8–10.5 mg/dl. The chief cells secrete the polypeptide hormone known as parathyroid hormone (PTH) which, along with 1, 25-dihydroxy vitamin D and calcitonin, regulates serum calcium levels.

- PTH is cleaved in the liver resulting in a circulating, biologically active form and inactive, carboxy-terminal fragments.
- Calcium is present in the blood in three forms: protein bound, ionized, and complexed to various anions.
  - Ionized calcium is the principal regulator of PTH levels and functions in a negative feedback loop.
- A calcium-sensing receptor (CaSR) that is present in the parathyroid glands, thyroid, kidney, and brain detects extracellular ionized calcium levels and regulates PTH secretion via intracellular signaling mechanisms.
  - A hypocalcemic state stimulates PTH secretion which in turn increases serum calcium concentrations by activating mechanisms in a variety of tissues such as the bone, kidney, and intestine. The net effect is an increase in serum calcium and a decrease in serum phosphate. This mechanism acts on the following systems to achieve a state of calcium homeostasis:
    - Activates osteoclastic bone resorption to release calcium and phosphate
    - Stimulates reabsorption of calcium and inhibits phosphate reabsorption from the renal tubules
    - Stimulates the renal production of 1,25-dihydroxy vitamin D which increases intestinal absorption of calcium
  - Conversely, hypercalcemia inhibits the release of PTH via a negative feedback mechanism.

References: [5, 8, 9]

4. *What is chronic parathyroiditis and which entities are in the differential diagnosis?*

Parathyroiditis is a rare condition with a poorly understood etiology. The pathogenesis may have an autoimmune origin, but the evidence is limited, as only a few cases have anti-parathyroid antibodies.

- Parathyroiditis primarily affects older females and can occur in association with either hypo- or hyperparathyroidism. Most patients are asymptomatic with only slightly enlarged glands. The condition can affect more than one gland.
- Histology shows aggregates of mature lymphocytes within the interstitium of the parenchyma.
  - Lymphoid follicles with germinal centers and admixed plasma cells are present.
  - The inflammatory process is believed to be an ongoing destructive process with fibrosis and glandular destruction.
- The differential diagnosis of parathyroiditis includes:
  - Viral infections, showing a predominantly lymphocytic infiltrate, which may be sparse with a perivascular distribution.
  - Secondary inflammation of the parathyroid glands in the setting of systemic illnesses such as septicemia, pneumonia, and endocarditis.
    - The inflammatory infiltrate is generally restricted to the perivascular regions, and tissue destruction (e.g., fibrosis, atrophy) is not a feature.
  - Lymphoma may secondarily involve the parathyroid gland.
    - Microscopic features include an atypical lymphoid population, mitoses, and immunohistochemical or other evidence of monoclonality.
  - Parathyroid carcinoma demonstrates acellular fibrosis. Features of malignancy such as invasion, necrosis, and mitoses may be present.

References: [10–14]

5. *What are canals of Kürsteiner and how are they related to parathyroid cysts?*

- Canals of Kürsteiner are rudimentary glandular structures derived from the third and fourth branchial pouches. They may be seen adjacent to some parathyroid glands and have been postulated to give rise to parathyroid cysts.
- Most parathyroid cysts occur in the neck and are asymptomatic. Occasionally patients can present with compressive symptoms like hoarseness, dysphagia, or respiratory distress.
  - Microscopically, the canals and cysts are lined by low cuboidal epithelium, and the lumina are filled with eosinophilic secretions.

References: [15–17]

6. *What are the causes and clinical characteristics of primary, secondary, and tertiary hyperparathyroidism?*

Hyperparathyroidism has multiple causes and is traditionally divided into primary, secondary, and tertiary forms (Table 9.1).

- Primary hyperparathyroidism (HPT) has an incidence of 0.1–0.5% and is characterized by hypercalcemia due to excessive production of PTH by hyperfunc-

**Table 9.1** Clinical and laboratory findings in hyperparathyroidism

| | Primary | Secondary | Tertiary |
|---|---|---|---|
| Symptoms | Early: abdominal pain, constipation, fatigue, bone pain, muscle aches, weakness, neurocognitive symptoms<br>Advanced: pancreatitis, osteoporosis and fragility fractures, peptic ulcer disease, and nephrolithiasis | Usually asymptomatic with laboratory abnormalities<br>Arthritis, bone pain, myopathy, tendon rupture, extraskeletal calcifications | Bone pain, decreased bone mineral density, fractures, pruritus, nephrolithiasis, pancreatitis, soft tissue or vascular calcifications, muscle weakness, mental status changes |
| Serum PTH level | High | High | Very high |
| Serum calcium | High | Low/Normal | High |
| Serum phosphate | Low | High | High |
| Pathogenesis | Hypersecretion of PTH | Low vit D, calcium, phosphorous levels result in oversecretion of PTH | Autonomous gland with unchecked secretion of PTH |
| Common causes | PT neoplasia or hyperplasia | CKD is the most common cause<br>Primary vit D deficiency | Prolonged 2° HPT usually due to CKD resulting in autonomous PTH production |
| Pathology | Single adenoma (85%)<br>Multiple adenomas (5%)<br>4 gland hyperplasia (10%)<br>Carcinoma (<1%) | 4 gland hyperplasia | 4 gland hyperplasia |
| Inherited syndromes | MEN1, MEN2A, FIHP, HPT-JT | None | X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets |
| Management | Parathyroidectomy | Treat underlying cause<br>Parathyroidectomy | Calcimimetic drugs<br>Total or subtotal parathyroidectomy |

*PTH* parathyroid hormone, *CKD* chronic kidney disease, *vit* vitamin, *HPT* hyperparathyroidism, *PT* parathyroid

tioning parathyroid tissue. There is a 2–3:1 female-to-male ratio, and the average age is 60 years old.

- The most common cause or primary HPT is a parathyroid adenoma.
- The most common symptoms of primary HPT are neurocognitive symptoms related to memory, attention, mood, and sleep.
  - Such patients are commonly identified as a result of routine testing of serum calcium levels.
- Other symptoms are largely related to chronic hypercalcemia including abdominal pain, constipation, fatigue, bone pain, muscle aches, and weakness.
  - Advanced symptoms are pancreatitis, osteoporosis and fragility fractures, peptic ulcer disease, and nephrolithiasis.

- Secondary hyperparathyroidism is most commonly a result of chronic kidney disease (CKD) and occurs in the setting of hypocalcemia. PTH levels increase in response to the following physiologic changes caused by CKD:
  1. Decreased 1,25-dihydroxy vitamin D production by the kidney is the earliest stimulus to PTH levels.
  2. Increased serum phosphate levels due to the decline in kidney filtration function.
  3. Hypocalcemia due to decreased gut absorption as a result of low vitamin D production by the kidneys.
- Tertiary hyperparathyroidism is most commonly caused by prolonged stimulation of the parathyroid glands in secondary hyperparathyroidism. This results in a state of autonomous secretion of large amounts of PTH without a physiologic stimulus (i.e., hypocalcemia).
  - These patients are often diagnosed after renal transplantation and have high levels of serum calcium, phosphate, and PTH.
  - Symptoms are similar to primary HPT and correlate with levels of PTH and serum calcium.
    - Skeletal and cardiovascular abnormalities are more commonly seen than in primary HPT.
  - PTH levels are generally around 1000 pg/ml.

References: [5, 18–25]

7. *What genetic syndromes are associated with hyperparathyroidism?*

Five to ten percent of primary hyperparathyroidism cases are associated with familial tumor syndromes

**Table 9.2** Familial hyperparathyroidism syndromes

| | MEN1 | MEN2A | HPT-JT | FIHP | FHH | NSHPT |
|---|---|---|---|---|---|---|
| Inheritance | Autosomal dominant | Autosomal dominant | Autosomal dominant | Variable | Autosomal dominant | Autosomal recessive or compound heterozygous |
| Gene | MEN1 | RET | CDC73 | Variable: MEN1, CaSR, CDC73, GCM | CaSR | CaSR |
| Protein | Menin | c-Ret a | Parafibromin | Variable | CaSR | CaSR |
| Single or multi-gland disease | Multiple (>99% benign) | Both (>99% benign) | Single: adenoma (cystic) or carcinoma (15% of pts) | Multi-gland or single gland disease, chief cell hyperplasia | Mildly enlarged and near normal surgical pathology | Multiple |
| Extra-parathyroidal lesions | GI and pancreatic endocrine tumors, pituitary adenomas, facial angiofibromas, adrenocortical tumors | Medullary thyroid carcinoma, pheochromocytoma | Fibro-osseous jaw lesions, renal cysts, Wilms' tumor, uterine leiomyomas | None | None | None |

*GI* gastrointestinal, *CaSR* calcium-sensing receptor, *pts* patients

(Table 9.2). MEN syndromes are the most common among these.

- 90% of patients with MEN type 1 have hyperparathyroidism and present with multiglandular disease. The mutated gene (MEN1) is a tumor suppressor gene that encodes a nuclear protein, menin, which interacts with SMAD3 to suppress transforming growth factor-beta (TGF-ß). This alteration is extremely rare in parathyroid carcinomas.
- Hyperparathyroidism is present in 20–30% of MEN2A patients and results in a milder form of the disease than that seen with MEN1.
- Patients with hyperparathyroidism-jaw tumor syndrome (HPT-JT) typically present with hyperparathyroidism due to single gland disease (adenoma or carcinoma). Up to 15% of patients with this syndrome present with parathyroid carcinoma.
  - The cell division cycle 73 (CDC73) gene is a putative tumor suppressor gene mapped to chromosome 1q21–32 and is implicated in the pathogenesis of this rare syndrome.
  - CDC73 is inactivated in 70% of parathyroid carcinomas (via both germline and somatic mutations).
- Familial isolated hyperparathyroidism (FIH) is a heterogeneous group of disorders and accounts for 1% of primary hyperparathyroidism cases.
  - Mutations in MEN1, CDC73, GCM, and calcium-sensing receptor (CaSR) have been described in some cases.
  - The most important distinguishing feature from other syndromes is the absence of extra-parathyroidal disease.
- Familial hypocalciuric hypercalcemia (FHH) and neonatal severe primary hyperparathyroidism (NSHPT) are associated with defects in the calcium-sensing receptor (CaSR) gene.

References: [5, 21–23, 26]

8. *What are the features of hyperparathyroidism-jaw tumor syndrome (HPT-JT)?*
   - Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is an exceedingly rare autosomal dominant tumor syndrome constituting 0.1% of the familial forms of hyperparathyroidism.
     - The syndrome is characterized by parathyroid disease (adenoma or carcinoma), benign fibro-osseous lesions of the mandible and maxilla, uterine tumors, and renal tumors and cysts.
     - 80% of patients with HPT-JT present with hyperparathyroidism of which 15% have parathyroid carcinoma.
     - The morphology shows single- or two-gland disease with prominent cystic change.
       - The cystic change varies from multiple follicle-like or crypt-like glandular dilatations to large cysts.
   - 50–75% of HPT-JT patients have a germline, inactivating mutation in the putative tumor suppressor gene CDC73 (also known as HRPT2).
   - Almost 70% of parathyroid carcinomas show inactivating mutations of CDC73.
     - Familial cases have germline mutations of CDC73.
       - The familial parathyroid carcinomas carry a poor prognosis, and parathyroid adenomas

which arise in these patients show a high recurrence rate.
    - These prognostic implications should prompt consideration of genetic testing in certain patients (Table 9.3).
  - Non-syndromic, sporadic cases of parathyroid carcinoma have somatic mutations in CDC73.
    - However, 20% of patients with presumed sporadic parathyroid carcinoma have germline mutations and may represent underrecognized familial cases.

References: [27–34]

9. *What are the morphological features of parathyroid adenomas and how do they differ from parathyroid hyperplasia?*

Parathyroid adenomas typically involve one gland and occur more commonly in the lower glands. On average, they range in size from 1 to 3 cm and 150 to 2000 mg.

- A parathyroid adenoma is a well-circumscribed, hypercellular nodule with a thin, sometimes imperceptible capsule which can be thickened. Overall, extracellular (stromal) fat is absent.
  - The tumor cells are monotonous and arranged in nests, cords, or follicles.
  - Chief cells are the predominant cell type with varying, minor components of oxyphil or transitional cells.
  - The tumor cells are round to polygonal and slightly enlarged with a scant to moderate amount of pale, pink to eosinophilic cytoplasm.
  - Nuclei are round and centrally located with dense, coarsely stippled chromatin and inconspicuous nucleoli.
  - Random nuclear atypia (endocrine-type atypia) with enlargement and/or hyperchromasia and rare mitoses can be seen, usually less than 1 per 10 high-power field (hpf).

The pathologic distinction between parathyroid adenoma and hyperplasia (Fig. 9.3) is difficult because of the significant overlap in morphologic features. Appropriate clinical information along with the histologic examination of more than one gland is required to make the distinction. Table 9.4 highlights the features that favor one diagnosis over the other. However, exceptions exist and are discussed below and in subsequent questions:

- Rare cases of adenoma can also show multinodular growth.
- The presence of double adenomas may confound the picture in the setting of two glands suspected of being hyperplasia.

References: [5, 19, 35–38]

**Table 9.3** Indications for CDC73 (HRPT2) mutational analysis

| |
|---|
| Clinical diagnosis of HPT-JT syndrome |
| Sporadic parathyroid carcinoma |
| Parathyroid adenoma in patients less than 35 years old |
| Sporadic ossifying fibroma of jaw |
| Parathyroid adenoma associated with any of the following:<br>Renal cysts or tumors<br>Pancreatic tumors<br>Thyroid tumors<br>Early-onset uterine lesions |
| Familial isolated hyperparathyroidism patients, negative for MEN1 and CaSR mutations |

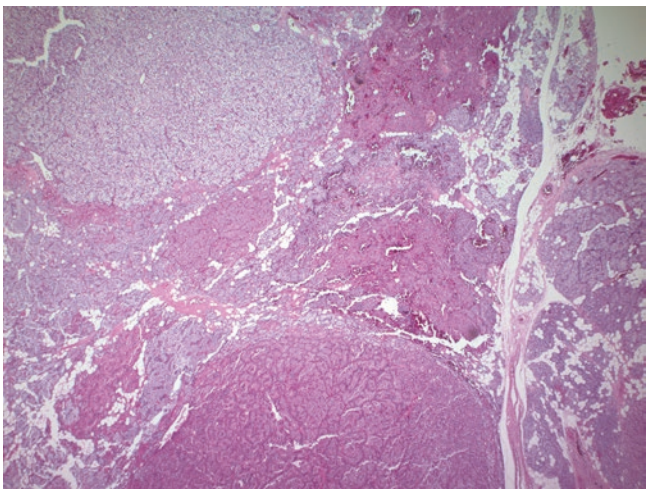

**Fig. 9.3** Hyperplastic parathyroid gland shows a nodular proliferation of chief and oncocytic cells

**Table 9.4** Histopathologic features of parathyroid adenoma and hyperplasia

| | Hyperplasia | Adenoma |
|---|---|---|
| Glands involved | Multiple glands | One gland |
| Architecture | Multiple nodules | Single, encapsulated nodule |
| Cells types | Multiple cell types, chief, and oncocytic | One cell type, monotonous, usually chief cells |
| Uninvolved parenchyma | Absent or admixed with nodular tissue | Present at periphery of nodule |
| Compressed rim of normal tissue | Absent | Present |
| Stromal fat | Minimal to absent | Absent |
| Other findings | Increase in the parenchyma to fat ratio | At least one other PT gland is normocellular<br>Intraoperative PTH level drops to near normal after excision of the single gland |

*PT* parathyroid, *PTH* parathyroid hormone

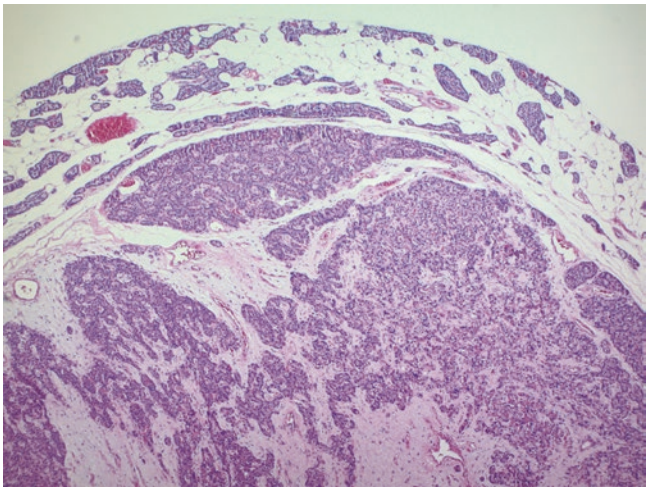

**Fig. 9.4** Parathyroid adenoma demonstrating a rim of compressed normal tissue (top)

**Table 9.5** Genetic alterations associated with parathyroid adenomas

| | Frequency in sporadic adenomas | Genetics |
|---|---|---|
| Cyclin-D1 (aka PRAD1) | 20–40% activation or overexpression<br>8% rearranged | Peri-centromeric rearrangement places Cyclin D1 oncogene near the regulatory regions of PTH gene |
| MEN1 | 20–40% | MEN1 encodes the protein menin which acts as an oncosuppressor protein |
| RET | Rare in sporadic adenomas | Mutated in MEN2A adenomas |
| CDC73 gene (aka HRPT2) | 0–4% | CDC73 is a putative tumor suppressor gene which encodes the protein parafibromin |
| Cyclin-dependent kinase inhibitor (CDKN1B aka p27) | 5% | Somatic mutations in CDKN1B gene play a role in sporadic adenomas, but the mechanism is unclear |

*aka* also known as, *PRAD1* parathyroid adenomatosis-1

10. *Is a rim of normal parathyroid tissue diagnostic of a parathyroid adenoma?*

    Ultimately, the diagnosis of a PT adenoma requires correlation with intraoperative PTH levels, clinical findings, and pathologic evaluation of weight, size, and additional parathyroid glands to rule out multiglandular disease.

    - A compressed rim of normocellular parathyroid gland separated from the adenoma by a thin fibrous capsule (Fig. 9.4) is considered a criterion for the diagnosis of parathyroid adenoma. While this finding supports the diagnosis of adenoma, it does not confirm it. Similarly, its absence does not exclude the diagnosis.
      - A rim of normal is seen in approximately 30 to 50% of adenomas.
      - The rim is often atrophic and may be difficult to visualize as a result of an attenuated or disrupted capsule or a multinodular, irregular tumor.

    References: [39, 40]

11. *What are the molecular findings associated with parathyroid adenomas?*

    Parathyroid adenomas are monoclonal tumors, and various genetic mutations (Table 9.5) are associated with them.

    References: [5, 26, 41–44]

12. *What are double adenomas, and do they really exist?*

    - The term "double adenoma" refers to a form of multiglandular parathyroid disease characterized by the presence of two enlarged, hypercellular parathyroid glands.
      - The existence of this entity has been questioned by some investigators who believe that it might represent asymmetric hyperplasia.
      - The distinction between asymmetric hyperplasia and "double adenoma" is only reliably made after long-term follow-up and demonstration of biochemical cure.
    - The reported incidence of double adenomas in patients with primary hyperparathyroidism is 2–15%. It is a bilateral disease with predilection for the superior parathyroid glands.
      - Clinically, double adenomas are frequently not identified with preoperative imaging. Instead, the absence of a normal intraoperative PTH level after removal of one gland prompts the surgeon to search for another offending gland.
      - Long-term follow-up shows continued eucalcemia in these patients, supporting the theory of double adenomas.
      - Some studies have reported older age at presentation, higher tumor weight, and higher PTH levels for double adenomas when compared to single adenomas. Others fail to demonstrate any statistically significant differences between the two groups.
    - Suggested criteria for the diagnosis of double adenoma are:
      - More than one hypercellular, enlarged gland, with histologic features otherwise consistent with an adenoma
      - Other histologically confirmed, normal, unaffected glands (to exclude hyperplasia)
      - Durable cure of hyperparathyroidism following removal of the enlarged glands

References: [35, 45–50]

13. *What benign entities are in the differential diagnosis of a parathyroid adenoma?*

The differential diagnosis of PT adenomas is largely between PT hyperplasia and PT carcinoma. The former was previously discussed (see question 9). The distinction with PT carcinoma will be discussed in greater detail below. Here we consider other benign entities in the differential diagnosis of PT adenoma.

- Thyroid lesions with clear or oncocytic features can mimic parathyroid nodules. This distinction may be challenging on small biopsies such as those sent for frozen section evaluation. Conversely, parathyroid adenomas might show a follicular pattern with eosinophilic, colloid-like material (Fig. 9.5).
  - Birefringent calcium oxalate crystals within colloid are seen in thyroid and are rarely present in parathyroid tissue (Fig. 9.6).
  - Parathyroid cells typically have a more nested growth and contain cells with smaller, darker nuclei and a delicate vasculature. These morphologic features can be subtle and difficult to appreciate without a side by side comparison.
  - Rarely, challenging cases will require immunohistochemical studies for confirmation (Table 9.6).

References: [20, 40, 51–57]

14. *Which entities of the parathyroid gland have fibrosis and what is the biological significance?*

Fibrous connective tissue can be present in the parathyroid gland in multiple conditions. The most clinically significant of these is parathyroid carcinoma.

- Parathyroid carcinoma generally has thick, acellular bands of fibrosis traversing in between tumor cells, giving the gland a nodular appearance.
  - Intratumoral fibrosis in carcinomas has a predilection for perivascular locations.
  - In addition, the tumor has a thick fibrous capsule that extends into the surrounding tissues along with the tumor cells.
- Atypical adenomas (see question 20) show a similar type of fibrosis but lack invasion into the surrounding tissues.
- Some typical parathyroid adenomas as well as hyperplasia (Fig. 9.7) can show fibrosis as a result of degenerative changes, particularly when large.
  - Other features of degeneration including hemosiderin deposition and chronic inflammation are usually present in association with the fibrosis.
- An entity known as hyalinizing parathyroid adenoma has been reported in the literature.
  - The stroma in these lesions is markedly sclerotic, and the hyalinized fibrous tissue is distributed within and around individual cells and groups of cells.

References: [40, 51, 58–60]

15. *What are the clinical and histologic features of parathyroid carcinoma?*

The clinical presentation of patients with parathyroid carcinoma can differ significantly, but not consistently,

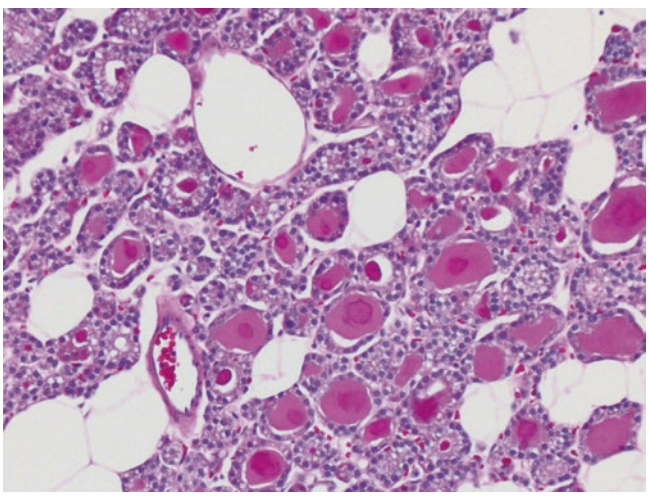

**Fig. 9.5** Parathyroid gland with pseudofollicular change. On small biopsies, this pattern can mimic thyroid tissue, particularly on frozen section

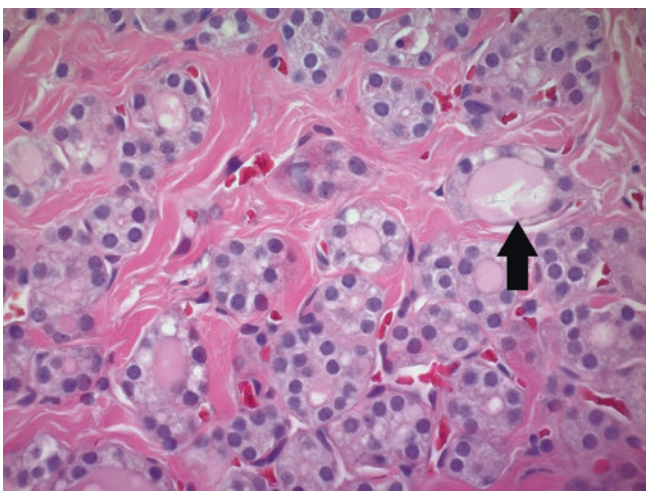

**Fig. 9.6** Microfollicular thyroid tissue mimicking parathyroid. A calcium oxalate crystal (arrow) in one of the follicles is a helpful feature which is absent in parathyroid tissue

**Table 9.6** Immunohistochemistry to differentiate parathyroid from thyroid tissue

| IHC stain | Parathyroid tissue | Thyroid nodule |
|---|---|---|
| PTH | Positive | Negative |
| TTF-1 | Negative | Positive |
| Thyroglobulin | Negative | Positive |
| Chromogranin | Positive | Negative |

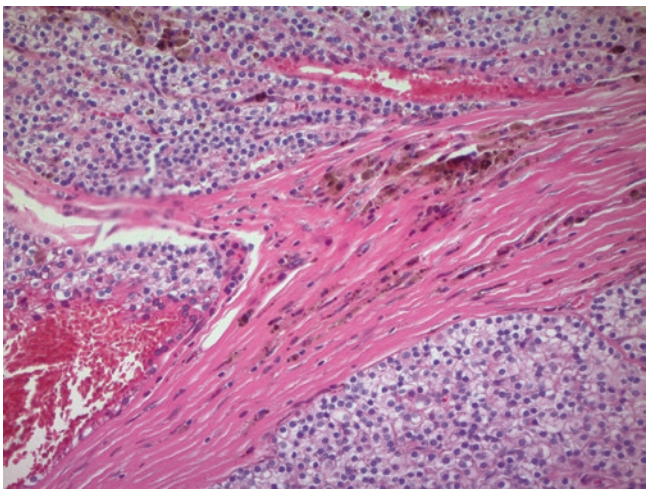

**Fig. 9.7** Hyperplastic parathyroid gland with fibrous bands containing lymphocytes and hemosiderin

from PT adenoma patients. Severe parathyrotoxicosis, markedly elevated calcium levels, and a palpable neck mass at the time of presentation should prompt a presumptive diagnosis of parathyroid carcinoma.

- Parathyroid carcinoma accounts for less than 1% of hyperparathyroidism cases. There is an equal gender distribution with a mean age of 55 years old. Up to 75% of patients will have a palpable, solitary neck mass.
  - The majority of parathyroid carcinomas are functioning tumors with most patients presenting with severe hypercalcemia (≥14 mg/dl) and elevated PTH levels (twice the upper limit of normal).
    - Symptoms include nephrolithiasis, diffuse osteoporosis, osteitis fibrosa cystica, fractures, fatigue, weakness, polyuria, polydipsia, nausea, mood disturbances, vomiting, and weight loss.
  - About 10–20% of parathyroid carcinomas are nonfunctioning with normal levels of PTH and serum calcium.
- Parathyroid carcinomas are indolent tumors with a tendency for local recurrence in the neck with concomitant, profound, recalcitrant hypercalcemia.
  - Common sites of metastases include the cervical lymph nodes, lung, and liver.
    - Distant metastases occur in less than 5% of patients and regional nodal disease in up to 10% of patients
  - Adverse prognostic indicators include advanced age, male gender, and tumor size.
  - Overall 5-year survival rates range from 78% to 82%. Disease-specific survival approaches 90%.

**Table 9.7** Histologic features of parathyroid carcinoma

| Diagnostic histopathologic features | Worrisome morphologic features |
|---|---|
| Unequivocal vascular invasion | Solid growth pattern |
| Capsular invasion | Broad fibrous bands |
| Macroscopic invasion into adjacent structures | Necrosis |
| Metastatic disease | Increased mitotic figures (>5/50 hpf) |
| Perineural invasion | Atypical mitotic figures |

The histopathologic diagnosis of parathyroid carcinoma and its distinction from adenoma relies on the gold standard of finding either tumor invasion or metastasis. This is primarily because there is significant histologic overlap between carcinoma, adenomas, and hyperplasia. Invasion and metastases may not be present upon initial presentation. Due to the lack of definitive histologic criteria and a variable clinical presentation, a definitive diagnosis of parathyroid carcinoma often can only be made after the tumor recurs or metastasizes.

- The histologic diagnosis of PT carcinoma relies on the presence of invasive growth into adjacent structures (Table 9.7).
  - Tumors are typically encapsulated with broad, fibrous, acellular bands that extend from the capsule.
  - Evidence of capsular or vascular invasion is present.
    - Capsular invasion requires infiltration of the capsule and adjacent structures.
    - Vascular invasion requires the presence of tumor in a capsular or extra-tumoral vessel. The tumor should be adherent to the vessel wall with associated fibrin. An endothelial covering is not required.
  - PT carcinomas are hypercellular and composed of polygonal cells arranged in a trabecular architecture with round nuclei and dense chromatin (Figs. 9.8 and 9.9).
  - Nucleoli are typically inconspicuous but may be prominent.
  - Nuclear pleomorphism is usually mild, though more marked atypia with nuclear enlargement, coarse chromatin, and prominent nucleoli can be seen.
  - Necrosis may be present and mitoses are common.
    - Mitotic rates in excess of 5 per 50 hpf are suggestive of carcinoma but not diagnostic. Lower mitotic rates occur and show overlap with adenomas.

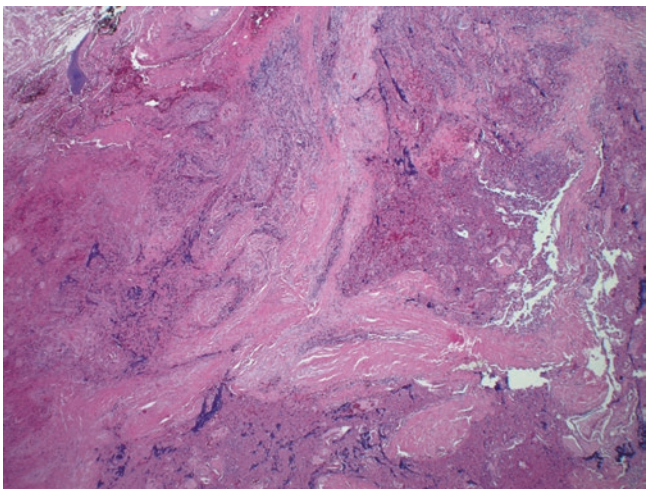

**Fig. 9.8** Parathyroid carcinoma. Broad, fibrous bands separate irregular tumor nodules. Necrosis is present (lower left)

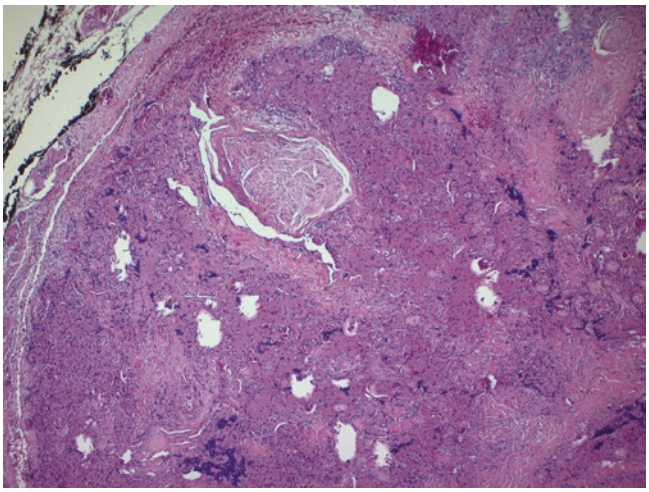

**Fig. 9.9** Parathyroid carcinoma surrounding a nerve

- Some of the above worrisome features can be seen a variety of benign parathyroid lesions and are, therefore, not solely diagnostic of carcinoma.
  - Broad bands of fibrosis can be seen in a variety of benign PT lesions with degenerative changes (see question 14).
  - Necrosis can occur secondary to post-procedure changes (e.g., biopsy or injections).
  - Increased mitotic figures can also be seen in adenomas and multiglandular disease.
- Not all cases of parathyroid carcinoma show the above-listed findings, and their presence is not necessarily diagnostic of malignancy.

References: [20, 52, 61–65]

16. *What are the molecular characteristics of parathyroid carcinomas?*

Parathyroid carcinoma occurs in both sporadic and familial forms. Several genetic aberrations are found in parathyroid carcinoma which includes abnormal expression of cell cycle regulators like retinoblastoma (Rb), breast carcinoma susceptibility (BRCA2), and CCND1 genes.

- Germline and somatic mutations of the CDC73 gene have been found in approximately 70% of parathyroid carcinomas.
  - CDC73 mutations are primarily frameshift or truncating mutations leading to inactivation of the gene.
  - The gene encodes the protein parafibromin, a nuclear transcriptional regulator involved in histone regulation via its association with RNA polymerase/Paf-1 complex.
  - Loss of parafibromin nuclear staining by immunohistochemistry correlates with the mutated (inactive) gene and is seen in carcinomas.
- A gain in copy number of the CCND1 gene that encodes cyclin D1 protein has been implicated in the pathogenesis of sporadic parathyroid carcinoma. Potential inhibition of cyclin D1 expression by parafibromin may initiate neoplastic transformation and has been suggested as a possible mechanism.
- Whole-exome sequencing of PT carcinomas reveals recurrent germline and somatic mutations in prune homolog 2 (PRUNE2), a tumor suppressor gene.
- Sequencing has also demonstrated apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) mutational signature.
  - PT carcinomas with APOBEC had an early age of onset and showed a high mutational burden.

References: [26, 51, 52, 54, 66–69]

17. *How are parathyroid adenomas distinguished from carcinomas?*

- Parathyroid carcinoma presents with markedly elevated calcium and PTH levels as well as other clinical findings that differ, but may overlap with adenomas (Table 9.8).
  - Kidney and bone disease tends to be more severe in carcinoma.
  - While carcinomas often present as a neck mass, adenomas infrequently present in this manner.
  - 15% of carcinomas are nonfunctioning, in contrast to adenomas, which are all functioning.
  - The malignant gland has a thick fibrous capsule and is adherent to adjacent tissues, which may make it difficult to resect.
- Histologically, adenomas do not show invasion or metastases.

**Table 9.8** Clinicopathologic comparison of parathyroid adenomas and carcinomas

| | Adenomas | Carcinoma |
|---|---|---|
| Age | 6th decade | 5th decade |
| Avg gland size and weight | 0.2 – >2 g | 2–20 g |
| Serum calcium | 10–12 mg/dl | ≥14 mg/dl |
| High PTH levels | | 85% |
| Clinical findings | Neurocognitive symptoms, fatigue, constipation, weakness | Pronounced kidney and bone disease |
| Palpable neck mass | Rare | Present |
| Operative findings | Easily removed and well encapsulated | Adherent gland difficult to remove |
| Vascular invasion | Absent | Present |
| Perineural invasion | Absent | Present |
| Necrosis | Absent | Rare |
| Mitoses | <5/50 hpf | >5/50hpf |

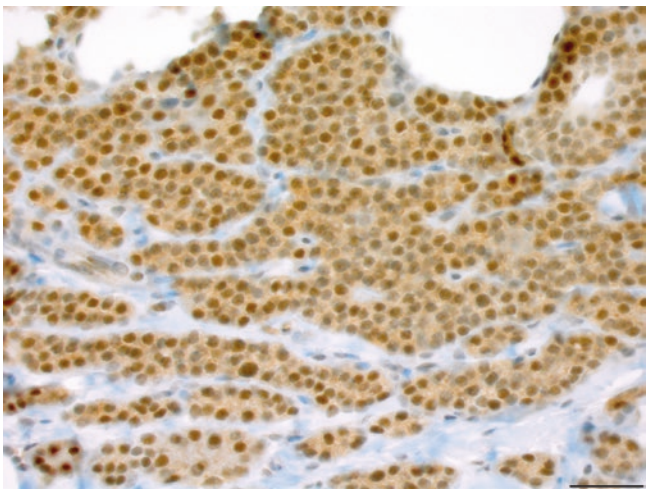

**Fig. 9.10** Parathyroid adenoma. A stain for parafibromin is diffusely positive in the tumor nuclei

- In cases where there is a previous biopsy or surgery, fibrotic adhesions may develop in benign lesions; however, appropriate clinical history will help in arriving at a correct diagnosis.
- Mitotic rate and the amount of atypia may overlap between adenomas and carcinomas.
  - Atypical mitoses and necrosis are not features of adenomas.
- Several immunohistochemical markers differentiate parathyroid adenomas and carcinomas and are discussed in question 18 and 19. However, most of them also show some degree of overlap. Parafibromin and APC are the most helpful in differentiating the two entities.

18. *What is the utility of parafibromin immunohistochemistry, and can it help differentiate parathyroid adenomas from carcinomas?*
    - Parafibromin is the protein product of the CDC73 gene which is inactivated in 70% of PT carcinomas. Parafibromin immunohistochemistry (IHC) can be used as a surrogate marker for the gene mutation.
      - Loss of parafibromin expression is present in 70% of carcinomas and is also associated with:
        - More aggressive tumor behavior in carcinomas
        - A higher risk of recurrence and potential malignancy in cases of atypical adenomas
        - May be present in less than 2% of benign adenomas
    - The majority of sporadic parathyroid adenomas retain nuclear parafibromin (Fig. 9.10).
      - Adenomas arising in patients with HPT-JT syndrome lack parafibromin expression as a result of CDC73 gene inactivation.
      - Gill et al. emphasized the complete absence of nuclear parafibromin staining in conjunction with the presence of a good internal control (lymphocytes and/or stromal cells provide good internal positive control) as criteria that should be used to confirm a diagnosis of parathyroid carcinoma.
        - Using this approach, the authors reported a sensitivity of 73% and a specificity of 100% in the diagnosis of malignancy.
    - Opinions regarding the usefulness of parafibromin immunohistochemistry in the diagnosis of parathyroid carcinoma are mixed. However, proponents have found it useful in the following scenarios:
      - Confirming a morphologic diagnosis of parathyroid carcinoma
      - Triaging patients for germline mutation testing for HPT-JT syndrome
      - As a biomarker of poor prognosis in established cases of parathyroid carcinomas
      - As a predictive marker for possible recurrence in atypical adenomas or tumors of uncertain malignant potential
      - First-line evaluation of parathyroid tumors in cases of suspected familial non-MEN-related hyperparathyroidism

References: [42, 47, 53, 55–57, 70–73]

19. *What is the role of cyclin D1 in the pathogenesis of parathyroid neoplasms, and what immunohistochemical panel can help distinguish carcinomas from adenomas?*
    - CCND1 (or PRAD1) proto-oncogene rearrangement with the PTH gene has been reported in a subset of parathyroid adenomas.
      - Studies have shown amplification of the CCND1 gene locus in parathyroid neoplasms, more frequently in parathyroid carcinomas than in adenomas.
      - Its protein product, cyclin D1, can be detected using immunohistochemistry (IHC) localized to the nucleus.
      - Overexpression of cyclin D1 in parathyroid carcinomas ranges from 71% to 90% versus 21% to 40% in parathyroid adenomas.
        - Due to this overlap, cyclin D1 is not a useful stand-alone marker to differentiate carcinoma from adenoma.
    - Ki-67 can be used along with other markers as part of a comprehensive IHC panel (Table 9.9) to diagnose PT carcinoma.
      - A Ki-67 proliferation index of >5% should raise suspicion for carcinoma. However, it is of limited utility when used alone, given the overlapping proliferation rates with adenomas.

    References: [20, 40, 43, 44, 51–57, 74–76]
20. *What is an atypical parathyroid adenoma and what are the criteria for its diagnosis?*

    Atypical adenoma refers to a subset of parathyroid adenomas with features that are worrisome, but not diagnostic, of malignancy. They usually present as solitary tumors in patients with marked hypercalcemia.
    - Atypical parathyroid adenomas tend to be grossly larger than their typical counterparts and often show a firm cut surface secondary to fibrosis.
      1. Along with parathyroid carcinoma and parathyromatosis, these account for ~2% of all patients with primary hyperparathyroidism.
    - The histologic criteria for the diagnosis of an atypical adenoma require:
      1. Two or more of the features listed in Table 9.10
      2. The absence of invasion into surrounding soft tissues, perineural invasion, angiolymphatic invasion, and metastases
    - Most atypical adenomas (80–90%) have a benign clinical course.
    - Parafibromin (PF) can be helpful in predicting recurrence in atypical adenomas along with other IHC stains.
      - Tumors that are negative for PF have a 10–20% possibility of recurrence. Tumors that are positive for PF behave in a benign fashion.
      - Atypical adenomas demonstrate a low Ki-67 index (<5%) and are positive for Rb with variable expression of galectin-3.

    References: [5, 51, 53, 57, 70]
21. *What non-parathyroidal entities are in the differential diagnosis of parathyroid carcinoma?*

    The malignant mimics of PT carcinoma typically show a solid or trabecular growth of clear or pale cells (Table 9.11). Immunohistochemical stains along with morphology can establish the correct diagnosis.

    References: [20, 61, 77]
22. *What is parathyromatosis, and what is its clinicopathologic significance?*

    Parathyromatosis is multiple nodules of benign, hyperfunctioning parathyroid tissue outside of the gland capsule, usually in the surrounding soft tissues of the neck or mediastinum. Parathyromatosis is a rare but important cause of recurrent and persistent parathyroid disease and can pose a diagnostic challenge. Parathyromatosis is divided into two types.
    - Type 1 is developmental parathyromatosis, embryologic in origin, in which there are multiple rests of parathyroid tissue in the neck and mediastinum. These scattered nests can become hyperplastic in the setting of primary or secondary hyperplasia and result in persistent or recurrent hyperparathyroidism following parathyroidectomy.
    - Type 2 is secondary or postsurgical parathyromatosis. It occurs in patients following parathyroid surgery, and is believed to occur due to tissue spillage

**Table 9.9** Immunophenotypic distinction between adenoma and carcinoma

| IHC stain | Parathyroid adenoma | Parathyroid carcinoma |
|---|---|---|
| Parafibromin | Positive | Negative (~70%) |
| APC | Positive | Negative |
| Ki-67 | <5% | >5% |
| Rb | + | – |
| Bcl-2 | + | – |
| p53 | – | + |
| p27 | + | – |
| Cyclin D1 | + | +++ |
| PGP9.5 | – | + |
| Galectin-3 | – | + |

**Table 9.10** Histologic criteria for atypical parathyroid adenoma

| |
|---|
| Adherent to but not invasive into the surrounding soft tissue |
| Incomplete capsular invasion |
| Fibrous bands |
| Trabecular growth |
| Mitotic figures <5/high-power fields, absent atypical mitosis |
| Tumor necrosis (non-infarct type) |

**Table 9.11** Immunoprofile and morphologic features of parathyroid carcinoma and its mimics

| | PT carcinoma | Medullary thyroid carcinoma | Thyroid carcinoma | Renal cell carcinoma |
|---|---|---|---|---|
| Morphology | Clear cells in nested and trabecular architecture with broad, fibrous bands, invasive growth, and bland cytology | Rare clear cell variants of MTC may mimic parathyroid carcinoma | Oncocytic follicular carcinomas and PD thyroid carcinomas have a solid or trabecular growth and cells with clear or pale cytoplasm | Clear cells with bland nuclei and a prominent vascular pattern. Variable nucleolar prominence and papillary architecture |
| Positive IHC | PTH, GCM2, Gal-3, PGP9.5, GATA-3, synaptophysin, chromogranin | Calcitonin, TTF-1, synaptophysin, chromogranin | PAX-8, TTF-1, thyroglobulin | CD10, RCC, vimentin, CAIX |
| Negative IHC | TTF-1, thyroglobulin | PTH | PTH, synaptophysin, chromogranin | PTH, synaptophysin, chromogranin |

*GCM2* regulatory gene transcription factor, *CAIX* carbonic anhydrase 9, *RCC* renal cell carcinoma antigen

**Table 9.12** Clinicopathologic parameters of parathyroid carcinoma and parathyromatosis

| Features | Parathyroid carcinoma | Parathyromatosis |
|---|---|---|
| Gender predilection | M ≈ F | F >> M |
| Number of nodules | Single, may be multiple foci | Multiple |
| Calcium levels | Marked increase (≥14 mg/dl) | Mild increase (1–2 mg/dl above normal range) |
| Previous history of surgery | Rarely present | Almost always |
| Marked pleomorphism | ++ | + |
| Vascular invasion | + | – |
| Distant/LN metastasis | + | – |
| Mitosis | ++ | + |
| Cause of death | Complications of hypercalcemia | Neuropsychiatric and metabolic complications of HPT |
| Genetics | CDC73 mutation | Unknown |
| Parafibromin IHC | Negative | Positive |
| Ki-67 proliferation index | High | Low |
| Retinoblastoma IHC | Negative | Positive |

during surgery, most commonly in the setting of renal failure. Type 2 is more common than Type 1.

- The main differential diagnosis is with parathyroid carcinoma. The key differentiating features are listed in Table 9.12.
  - While invasion and mitoses are features emphasized in carcinoma, a series reported by Fernandez et al. described invasion of soft tissues of the neck and mitoses in approximately 15% of parathyromatosis cases.

References: [53, 54, 78]

23. *How do intraoperative parathyroid hormone levels assist in parathyroid surgery for primary hyperparathyroidism?*

Intraoperative parathyroid hormone assay (IOPTH) became commercially available in 1996 and has since become commonly used in the operative management of hyperparathyroidism.

- Primary hyperparathyroidism was traditionally managed with bilateral neck exploration (BNE) and excision of abnormal parathyroid glands with a success rate of 95%. Operative success has been defined as eucalcemia for 6 or more months following parathyroid surgery.
- Improved localization studies (e.g., technetium 99m sestamibi scintigraphy (MIBI) and neck ultrasonography) along with IOPTH allow for a more focused, minimally invasive parathyroidectomy (MIP) procedure.
- The advantages of MIP over BNE include:
  - Less invasive procedure
  - Smaller incision
  - Shorter operating time and recovery
  - Excision of only the abnormal gland without disturbing the remaining glands
- With the use of appropriate protocols and interpretation criteria for intraoperative PTH, the assay has been shown to accurately predict postoperative calcium levels and therefore the outcome of surgery.
  - The most popular and widely used criteria for appropriate IOPTH drop are the "Miami" criteria.
    - It requires IOPTH to drop by 50% or more from the highest of either preoperative baseline (collected in the operating room before skin incision) or pre-excision level (collected after dissection of parathyroid gland but before ligation of its vessels) at 10 min after excision of the offending gland.

- IOPTH has the greatest value in cases in which there is discordance between MIBI and neck ultrasound localization studies.
  - The incidence of multi-gland disease in cases with discordant localization studies is 17% (versus 1–3% in concordant cases).
  - The use of IOPTH is highly recommended in this setting to supplement the minimally invasive surgery and avoid operative failure.
- Other applications of IOPTH include:
  - Lateralization of the hyperfunctioning parathyroid tissue by measuring the differential jugular venous gradient. This allows for unilateral neck exploration in patients with equivocal imaging studies.
  - To differentiate parathyroid tissue from non-parathyroid tissue using washings from fine-needle aspiration of the presumed gland.

References: [29, 50, 79–86]

24. *What is the role of intraoperative consultation in parathyroid surgery, and how does an Oil Red O stain assist in the consultation?*
    - Assessment of intracytoplasmic lipids in resected parathyroid glands uses the rationale that parenchymal fat content is inversely related to the functional activity of the gland. Parathyroid glands have both stromal and intracellular fat. Stromal fat varies with age as well as body composition; hence, it cannot be used as reliable evidence of hyperplasia.
      - In a normal parathyroid gland, approximately 80% of the cells are in a nonsecretory phase and contain intracytoplasmic fat (Fig. 9.11).

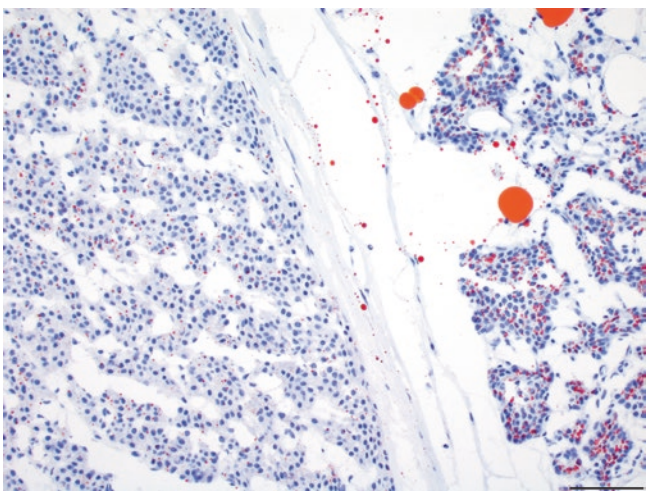

**Fig. 9.11** Normal parathyroid (right) and parathyroid adenoma (left). An Oil Red O stain highlights intracellular fat (orange) within normal parathyroid cells that is largely depleted in the adjacent parathyroid adenoma

      - An abnormal gland (hyperplasia or adenoma) will have depleted intracytoplasmic fat.
    - There are two principal objectives of intraoperative pathology consultation (i.e., frozen section):
      - Confirmation of tissue type
      - Determination of normal versus abnormal parathyroid tissue
    - Intraoperative consultations are frequently performed on parathyroid glands for identification and confirmation of parathyroid tissue typically in the setting of neck surgery for other reasons. Since a variety of tissues (e.g., lymph nodes, thyroid nodules, etc.) can grossly resemble parathyroid glands in surgery, tissue confirmation can help guide surgical approach.
      - An accuracy rate of 99% has been reported for identification of parathyroid tissue.
      - A predominant follicular growth can be misinterpreted as thyroid tissue (see Fig. 9.5). Conversely, thyroid tissue may have a solid or trabecular architecture, suggesting parathyroid tissue.
        - Polarized light microscopy can detect birefringent calcium oxalate crystals in colloid which, if present, can reliably differentiate thyroid tissue from parathyroid tissue (see Fig. 9.6).
        - Demonstration of intracellular fat by Oil Red O staining can also confirm parathyroid tissue.
        - If there is diagnostic uncertainty, the results should be deferred until permanent tissue sections are available. Immunohistochemical stains can be used at that time to confirm the tissue type.
    - The utility of frozen section in determining whether parathyroid tissue is normal or abnormal is controversial, with both false positive and false negative rates up to 30%.
      - The most common intraoperative interpretation on parathyroid tissue is normocellular or hypercellular parathyroid tissue with a mention about whether the gland is enlarged by size and weight.
      - Some centers perform a fat stain (e.g., Oil Red O) as an adjunctive test to assess the hyperfunctioning of a gland.
        - Decreased intracellular and extracellular fat are seen in hyperfunctioning proliferations.
        - Use of a fat stain is also helpful when the specimen is a small biopsy, lacking stromal fat, and having the appearance of a hypercellular gland. An Oil Red O stain will demonstrate a normal amount of intracellular fat in normal glands.
    - Occasionally, surgeons may want to know whether the gland is an adenoma or hyperplasia. Diagnosis of an adenoma can be favored in the proper clinicopathologic context. But multi-gland disease cannot be

definitively excluded without histologic examination of multiple glands.
  - Fat staining cannot reliably distinguish adenoma from hyperplasia since both can show an almost complete loss of intracytoplasmic fat.
- Areas of difficulty in the intraoperative evaluation of parathyroid tissue include:
  - Small fatty biopsies which do not cut well on frozen section may result in small, hard to interpret, portions of cellular tissue.
    - Imprint cytology can be used to complement frozen section in this scenario.
  - Oncocytic parathyroid and thyroid tissue can be difficult to distinguish, and frozen section diagnosis may need to be deferred until special stains can be applied to confirm the tissue type.

References: [39, 87–93]

25. *Which tumors can secondarily involve parathyroid gland?*
    - Secondary tumors involve parathyroid gland(s) by either direct extension from adjoining structures or by metastatic spread (hematogenous/lymphatic). The incidence is <0.1% of surgically excised parathyroid glands.
    - The most common sites of origin are thyroid, larynx, and esophagus that directly invade into the parathyroid gland.
      - Approximately 8% of papillary thyroid carcinomas involve the parathyroid gland as a result of direct extension or angiolymphatic invasion (Fig. 9.12).
    - Primary sites of distant metastasis include the breast, skin (melanoma), lung, kidney, and soft tissue. These metastases almost always occur in the setting of known widely metastatic disease.
    - Patients are mostly asymptomatic with a few presenting with pressure-related symptoms such as hoarseness, dysphagia, and neck pain.
      - Hypoparathyroidism as a presenting sign is reported in the literature, but it is extremely rare.
    - The prognosis of these patients is generally poor and dictated by the behavior of the primary tumor.
    - Secondary tumors generally retain the histologic features of the primary tumor, but occasionally it might be difficult to differentiate metastatic tumor from primary parathyroid carcinoma.
      - Immunohistochemical stains for PTH and sites of suspected origin may be helpful.
      - Benign hyperplastic lesions can sometimes have predominant clear cell morphology (clear cell adenoma) and can be confused with metastatic renal cell carcinoma (Fig. 9.13). The morphologic feature that can help make the correct diagnosis is the presence of an encapsulated tumor with a distinct population of cells that compress the surrounding parathyroid parenchyma. In addition, these tumors would show positive immunohistochemical staining with PTH and parafibromin.

References: [94–97]

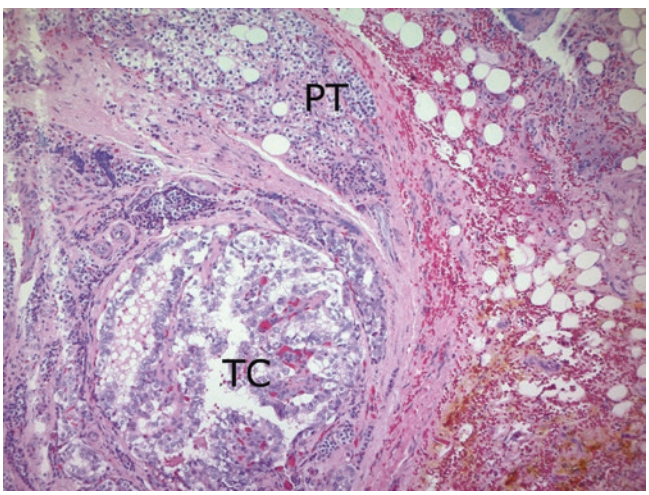


**Fig. 9.12** Papillary thyroid carcinoma (TC) invading parathyroid gland (PT) by direct extension

## Case Presentations

### Case 1

#### Learning Objectives

1. To become familiar with the histologic features of this disease process
2. To generate a differential diagnosis
3. To understand distinct clinical presentations of this disease

#### Case History

A 55-year-old female presents with symptoms of abdominal pain and is found to have kidney stones. Subsequent evaluation reveals an elevated parathyroid hormone level of 142 pg/ml and high serum calcium. Imaging demonstrates a possible enlarged parathyroid gland.

#### Intraoperative Findings

At the time of surgery, an enlarged right superior parathyroid gland is found. The remaining parathyroid glands are visualized and appear normal. Parathyroid hormone assay moni-

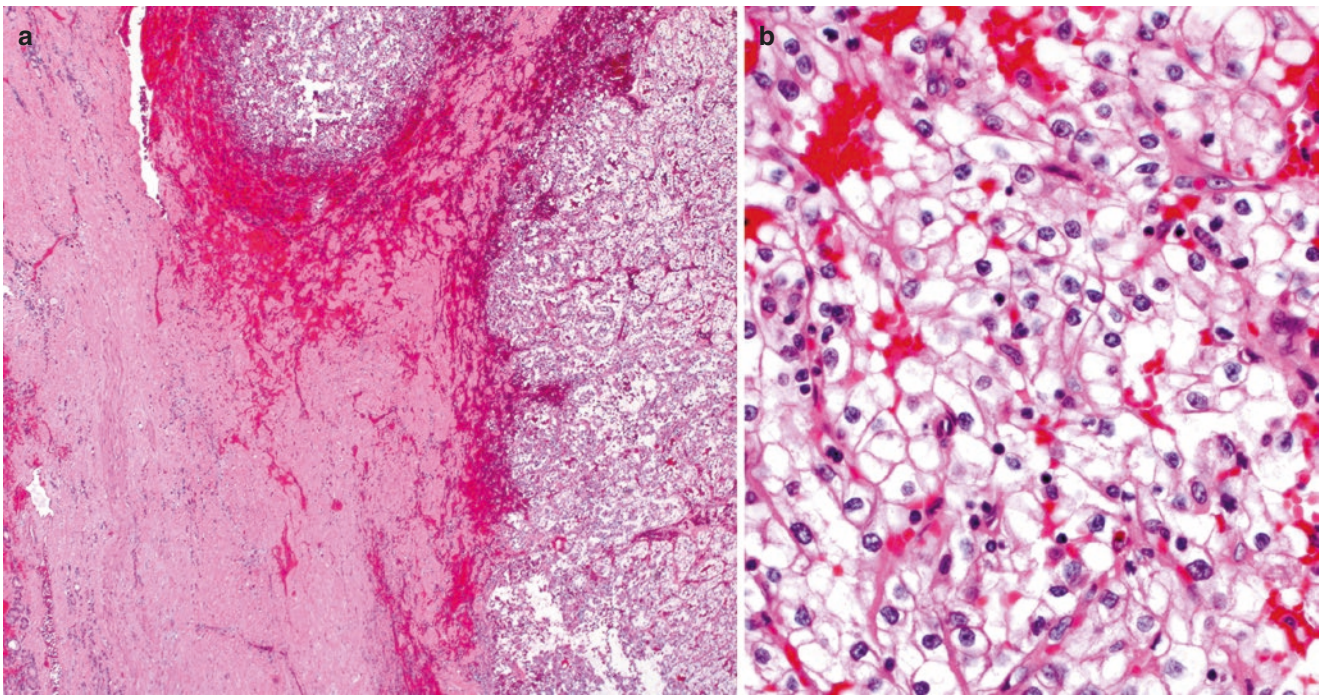


**Fig. 9.13** Metastatic renal cell carcinoma (**a**) to a parathyroid gland. (**b**) The bland clear cells may mimic a clear cell parathyroid adenoma

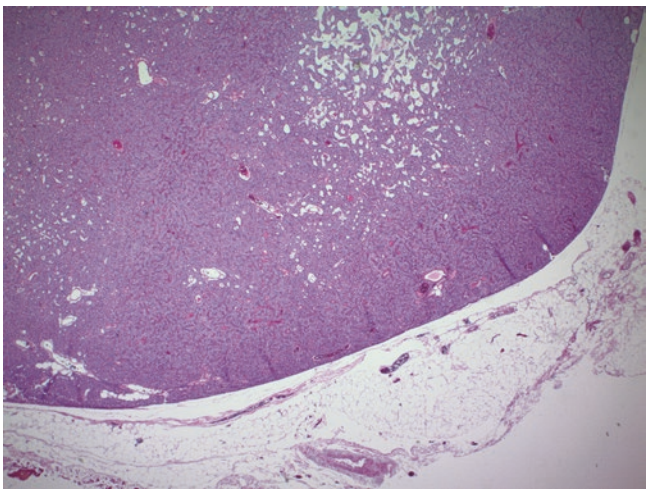

**Fig. 9.14** Case 1. Well-circumscribed, hypercellular nodule largely devoid of stromal fat

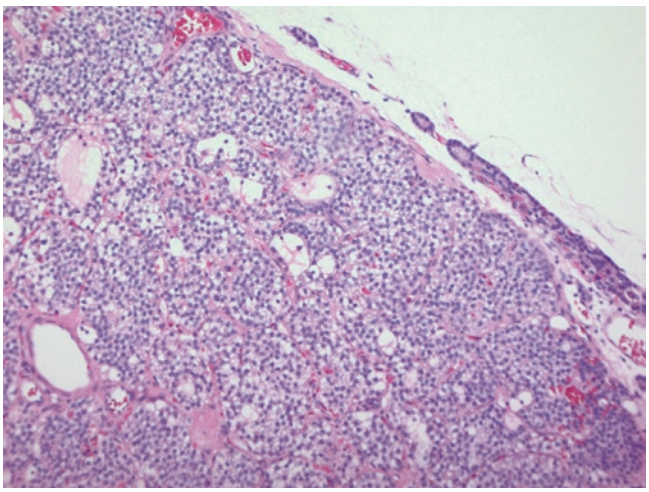

**Fig. 9.15** Case 1. Fibrous bands and invasion are absent. The cells are bland, without increased mitotic activity. A compressed rim of normal parathyroid tissue is present (top right)

toring was performed intraoperatively after resection and revealed a significant decrease compared to the baseline.

### Histologic Findings

- Well-circumscribed, hypercellular nodule composed of monotonous cells (Fig. 9.14).
- Compressed rim of normal tissue (Fig. 9.15).
- No evidence of fibrous bands or invasion. The cells are bland and show no evidence of increased mitotic activity (see Fig. 9.15).

### Differential Diagnosis

- Parathyroid adenoma
- Parathyroid hyperplasia
- Parathyroid carcinoma
- Ectopic thyroid tissue

**Final Diagnosis** *Parathyroid adenoma*

### Take-Home Messages

1. Both adenomas and parathyroid hyperplasia may show similar histologic findings.

2. Clinical evidence of only one enlarged gland and a decrease in intraoperative PTH to a normal level support the diagnosis of parathyroid adenoma.
3. When a compressed rim of normal tissue is present, it may be consistent with adenoma.
4. Parathyroid adenomas usually lack features of carcinoma, such as fibrous bands, invasion, and increased mitotic activity (> 5/50 hpf).
   References: [5, 20, 79]

## Case 2

### Learning Objectives

1. To become familiar with the histologic features of this disease process
2. To generate a differential diagnosis
3. To understand distinct clinical presentations of this disease

### Case History

A 64-year-old male presents for evaluation of hypercalcemia and hyperparathyroidism. He is found to have calcium levels between 13 and 15 mg/dL with a PTH level of over 1000 pg/ml. On examination the patient has an ill-defined area of fullness in his left neck. Imaging demonstrates an enhancing neck mass and no evidence of disease elsewhere.

### Intraoperative Findings

A severely fibrotic mass is found in the neck at the time of surgery. The mass is adherent to the adjacent thyroid and recurrent laryngeal nerve making the dissection difficult and lengthy. Intraoperative parathyroid hormone assay was performed after resection and revealed a significant decrease compared to the baseline.

### Histologic Findings

- Infiltrative mass composed of epithelial cells surrounded by fibrous bands, with areas of necrosis (Fig. 9.16).
- The cells are bland, and nuclear pleomorphism is absent (Fig. 9.17).
- The mass invades surrounding tissues (Fig. 9.18).
- Perineural invasion is focally identified.
- A PTH immunoperoxidase stain is positive in the tumor cells. They are negative for TTF-1.

### Differential Diagnosis

- Parathyroid adenoma
- Parathyroid hyperplasia
- Parathyroid carcinoma
- Follicular thyroid carcinoma

**Final Diagnosis** *Parathyroid carcinoma*

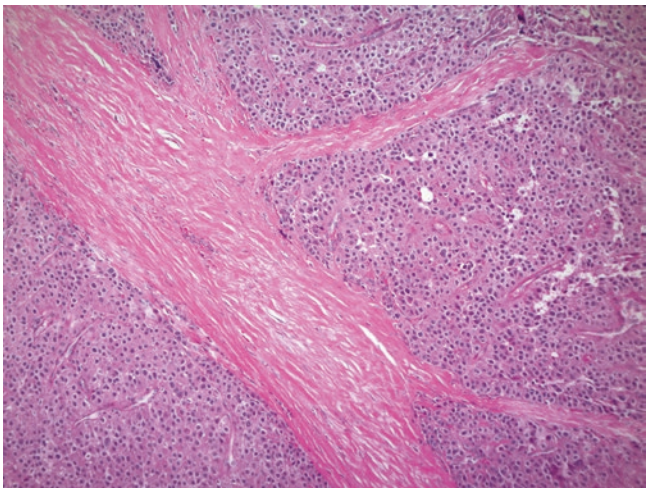

**Fig. 9.17** Case 2. Bland tumor cells with intratumoral, notably *acellular* fibrous bands

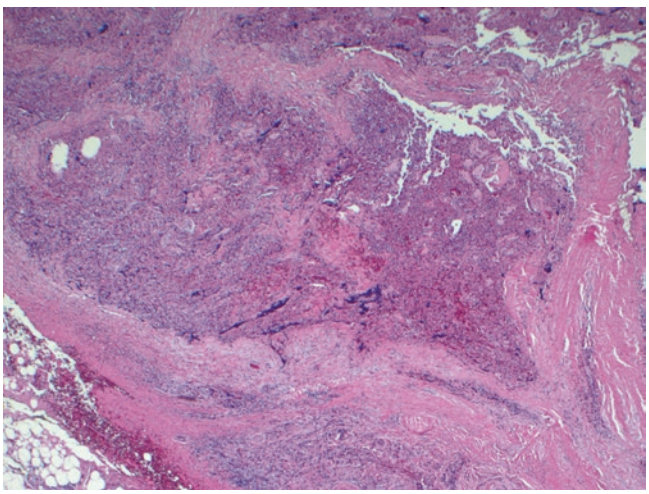

**Fig. 9.16** Case 2. Infiltrative mass composed of epithelial cells surrounded by fibrous bands, with areas of necrosis

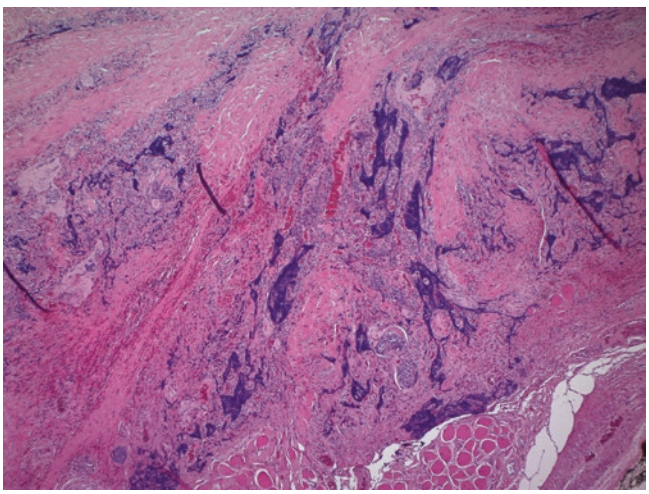

**Fig. 9.18** Case 2. The mass infiltrates the surrounding tissues, including skeletal muscle (bottom right)

**Take-Home Messages**

1. Patients with parathyroid carcinoma tend to present with high levels of PTH, often in the thousands, as well as a solitary neck mass.
2. The presence of severe parathyrotoxicosis, elevated calcium levels ≥14 mg/dl, and a palpable neck mass at the time of presentation should prompt a presumptive diagnosis of parathyroid carcinoma which in turn should trigger further workup to exclude metastasis.
3. Operative findings include dense fibrosis which renders dissection difficult.
4. Features of carcinoma include acellular fibrous bands, necrosis, invasion (into adjacent tissues, lymphovascular, perineural), and increased mitotic activity. However, it should be noted that not all cases of parathyroid cancer show these features; likewise, such worrisome morphologic features are not necessarily diagnostic of malignancy.
   References: [51, 53, 61–64]

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# Soft Tissue and Lymph Nodes of the Head and Neck

# 10

Chad M. McCall, Adam L. Booth, and Nicole D. Riddle

## List of Frequently Asked Questions

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28. What are the common benign cystic masses of the neck and how are they characterized?
29. What is the pattern of metastasis of primary head and neck malignancies and which can present as a cystic neck mass?
30. Which sarcomas have a predilection for the head and neck?

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31. Which are the most common peripheral nerve sheath tumors of the head and neck?
32. How are the common muscle tumors of the head and neck categorized?
33. What are the common sarcomas of the head and neck and which tumors are in the differential diagnosis?
34. What are the clinicopathologic features of the common benign fibroblastic lesions of the head and neck?
35. Which fatty tumors are found in the head and neck and how are they diagnosed?
36. What are the common benign vascular tumors of the head and neck and how are they characterized?
37. Which are the common malignant vascular tumors of the head and neck?
38. Which chondroid tumors are common to the head and neck?
39. Which non-mesenchymal and unclassified soft tissue tumors can be found in the head and neck?

1. *What is the differential diagnosis of a neck mass?*

The differential diagnosis of a neck mass includes a wide variety of benign and malignant, neoplastic and nonneoplastic lesions with a varied histogenesis. Figure 10.1 provides an overview of the different categories of neck masses which loosely correspond to the tables and questions in this chapter. The location of the mass can help narrow the differential diagnosis; therefore a basic understanding of neck anatomy is essential.

Neck masses can be broadly divided into three main categories, and this will provide the framework for the subsequent questions in this chapter:

- Lymph node lesions.
  - Reactive and inflammatory processes
  - Primary hematolymphoid tumors
  - Metastases
- Epithelial lesions include those entities that are generally extrinsic to the soft tissues of the neck.
  - Developmental and congenital anomalies
  - Cystic lesions of the larynx, salivary gland, thymus, and skin
  - Thyroid and parathyroid masses
- Soft tissue lesions.
  - Benign and malignant mesenchymal tumors
  - Paragangliomas

2. *What are the key histologic features of reactive lymphoid hyperplasia?*

One of the most common lymph node specimens in head and neck pathology is reactive lymphoid hyperplasia, and distinguishing it from a lymphoproliferative disorder is essential (Table 10.1). There are two major types of reactive hyperplasia:

- Reactive follicular hyperplasia (Fig. 10.2a, b) shows expansion of the lymph node cortex by reactive germinal centers (secondary follicles). The germinal centers have several features that allow one to distinguish them from neoplastic follicles: the presence of tingible body macrophages with phagocytosed

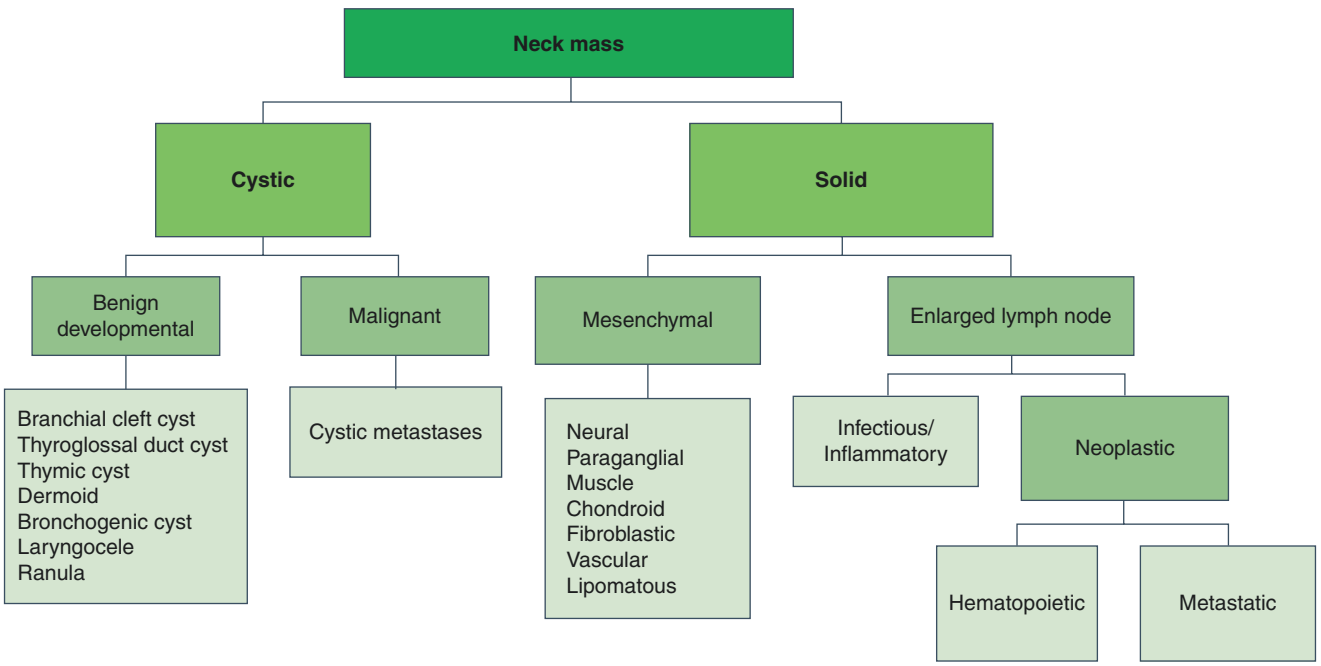


**Fig. 10.1** Clinicopathologic classification of neck masses

**Table 10.1** Pathologic comparison between reactive and neoplastic lymphoid tissue

| Feature | Reactive hyperplasia | Lymphoma |
|---|---|---|
| Follicular architecture | Varying shapes and sizes, some separation | Relatively uniform in shape and size, back-to-back |
| Lymph node sinuses | Patent | Compressed or absent |
| GC polarity | Present | Absent |
| Mantle zones | Present | May be attenuated or absent |
| Cell types | Mixture of cell types, sizes, and shapes | Often monotonous |
| Tingible body macrophages | Present | Usually absent in low-grade lesions, often present in high-grade |
| CD20 | Positive in B cells, mostly cortical, with scattered cells in paracortex | Positive in monotonous B-cell proliferations |
| CD3 | Positive in T cells, mostly paracortical but also scattered within follicles | Variable |
| CD5 | Very faint positive in mantle zone B cells, strongly positive in paracortical T cells | Positive in neoplastic B cells in CLL/SLL and mantle cell lymphoma |
| CD10 | Positive in germinal center B cells | Positive in germinal center-derived B cells (follicular lymphoma, Burkitt lymphoma, some diffuse large B-cell lymphomas) |
| CD23 | Positive in follicular dendritic cells | Positive in small lymphocytes of CLL/SLL |
| BCL2 | Negative in germinal center B cells | Positive in 85–90% of follicular lymphoma B cells |
| Ki-67 | High proliferative rate (>50%) in reactive germinal centers | Variable, often low, proliferative rate in follicular lymphoma follicles |
| Cyclin D1 | Positive in endothelial cells and in rare scattered cycling lymphocytes | Positive in most cases of mantle cell lymphoma |

*GC* germinal center, *CLL/SLL* chronic lymphocytic leukemia/small lymphocytic lymphoma

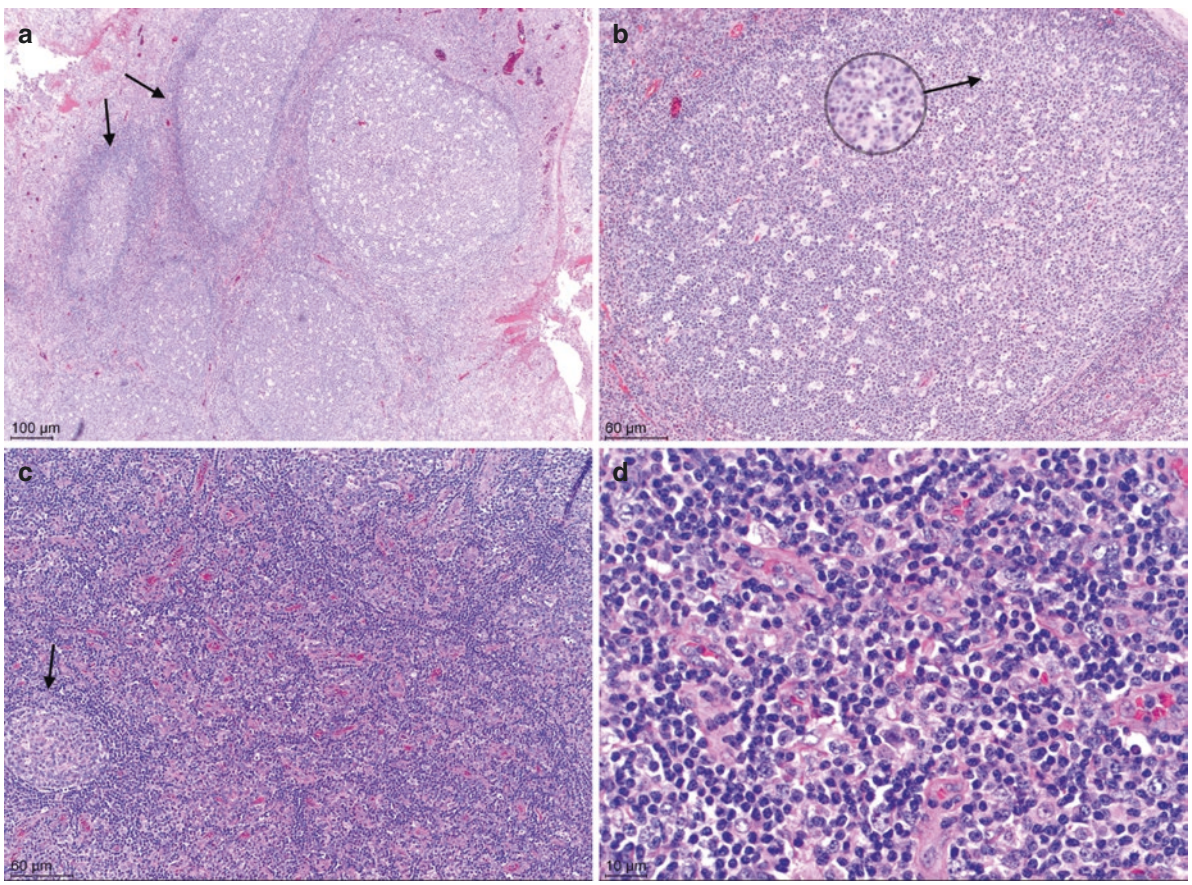


**Fig. 10.2** Reactive lymphoid hyperplasia. (**a**) Enlarged lymphoid follicles with attenuated, darker mantle zones (arrows). (**b**) The reactive germinal centers have scattered, pale staining tingle body macrophages (inset) and vague polarization with a darker area toward the bottom left corner and a lighter area toward the upper right corner characteristic of follicular hyperplasia. (**c**) Paracortical hyperplasia shows expansion of the interfollicular zone between follicles (arrow). (**d**) The paracortex is expanded by predominantly small lymphocytes

cellular debris and polarization of the germinal center lymphocytes into "light" and "dark" zones.

- Reactive paracortical hyperplasia is characterized by expansion of the nodal paracortex by a mixture of small lymphocytes, larger immunoblasts with prominent nucleoli, histiocytes, and plasma cells. The expanded paracortex pushes apart germinal centers (Fig. 10.2c, d).
- Immunohistochemical stains (IHC) are an important part of the workup for reactive lymphoid hyperplasia.

References: [1–3]

**Table 10.2** Histologic features to distinguish EBV lymphadenitis from B-cell lymphoma

| Feature | EBV lymphadenitis | Lymphoma |
|---|---|---|
| Nodal architecture | At least focally preserved, with indistinct border between effaced and preserved areas | Often completely effaced or focal involvement with sharp demarcation |
| Reactive changes | Follicular and paracortical hyperplasia, with the latter more often prominent | Variable in areas not effaced |
| Morphology of atypical cells | Immunoblastic, including Reed-Sternberg-like cells, which vary in size and shape. Present in a typical polymorphous paracortex | Typically more monotonous in appearance |
| Background cellularity in areas with atypical cells | Polymorphous, with typical paracortical components (small lymphocytes, plasma cells, histiocytes) | Variable, from minimal to polymorphous with prominent eosinophils |
| Necrosis | Not helpful, may be present | Not helpful, may be absent |
| Lymph node sinuses | Typically patent or distended | Often compressed or absent |

3. *How is Epstein-Barr virus lymphadenitis distinguished from lymphoma?*

Epstein-Barr virus (EBV) lymphadenitis can be very difficult to distinguish from a large B-cell lymphoma or classic Hodgkin lymphoma.

- Infectious mononucleosis is the typical lymphoproliferative manifestation of EBV infection. Patients are usually teenagers or young adults who present with a sore throat, fever, and malaise. Clinical examination reveals an acute pharyngotonsillitis with exudate and tender, posterior cervical lymphadenopathy. Monospot test or EBV serologies indicate an acute EBV infection.
- There are several histologic features that suggest EBV lymphadenitis over lymphoma (Table 10.2). The most important is at least partial retention of a normal lymph node architecture with follicular and paracortical hyperplasia (Fig. 10.3).
  - The morphologic features may overlap with cytomegalovirus (CMV) lymphadenitis which can be confirmed by molecular testing or immunohistochemical stains.
  - Positive stains: EBV latent membrane protein (LMP) and EBV-encoded RNA (EBER).
  - Negative B-cell clonality results.

References: [3–7]

4. *What are the diagnostic features of cat-scratch lymphadenitis?*

Cat-scratch disease (CSD) is a bacterial infection caused by *Bartonella henselae*. It is an important cause of lymphadenitis, with over 20,000 cases diagnosed yearly in the United States. CSD is self-limited, and patients present with tender, cervical lymphadenopathy, myalgias, and malaise.

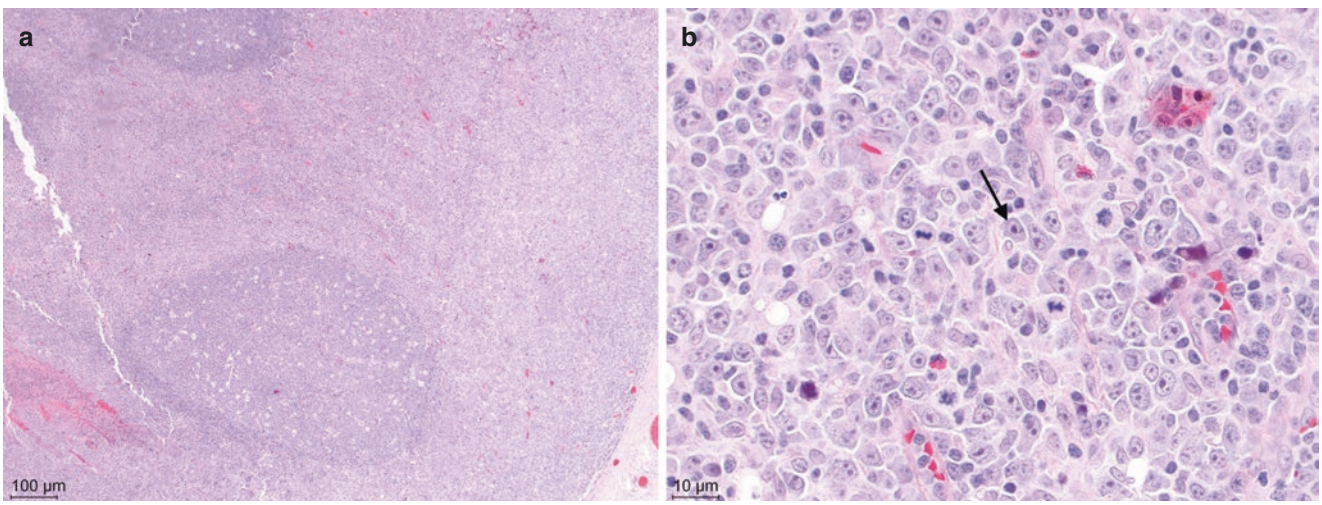


**Fig. 10.3** Epstein-Barr virus lymphadenitis (infectious mononucleosis) of tonsil. (**a**) The paracortex is markedly expanded by (**b**) atypical, mitotically active immunoblasts (arrow)

- The morphologic features vary with disease progression (Table 10.3). But the classic histologic finding in CSD is the stellate granuloma with central necrosis surrounded by neutrophils and palisading histiocytes (Fig. 10.4).
  - Organisms are found in more than half of cases in areas of necrosis.
  - The most specific test available to identify *B. henselae* is polymerase chain reaction (PCR), which can be performed on paraffin-embedded tissue. An immunohistochemical stain is also available.

References: [8–13]

5. *What are the histologic features of toxoplasma lymphadenitis?*

*Toxoplasma gondii* is a protozoal organism which has been reported to cause up to 15% of lymphadenopathy in immunocompetent adults, for which other specific etiologies cannot be identified. An isolated enlarged cervical lymph node is the most typical presentation.

- A classic triad of findings includes reactive follicular hyperplasia, clusters of epithelioid histiocytes, and sinuses with collections of monocytoid B cells. These features have limited sensitivity and specificity and can be seen in other entities (Table 10.4). Because of this, the morphologic features alone are not sufficient to make a diagnosis.
  - The epithelioid histiocytes often impinge on reactive follicles.
  - An immunohistochemical stain for the organism is specific but not sensitive.
- PCR-based detection of *T. gondii* DNA and serologic testing are essential to confirm the diagnosis (Table 10.5).
- The differential diagnosis of toxoplasma lymphadenitis is broad. If there has been travel to an endemic region, leishmaniasis causes a very similar lymphadenitis. Other forms of lymphadenitis with florid follicular hyperplasia, such as early cat-scratch disease and infectious mononucleosis, should be considered.

References: [3, 10, 14–16]

**Table 10.3** Histopathologic features of cat-scratch lymphadenitis

| Feature | Description |
|---|---|
| Nodal architecture | Typically preserved |
| Reactive changes | Prominent reactive follicular hyperplasia, particularly in early lesions |
| Early lesions | Small necrotic abscesses with neutrophils around the subcapsular sinuses |
| Late, classic lesions | Stellate-shaped, necrotizing granulomas with neutrophils and palisading histiocytes |
| Morphology of bacteria with Warthin-Starry stain | Curved or L-shaped, small bacilli |
| Other diagnostic modalities | Gram-negative organism, PCR, IHC, culture (less sensitive due to fastidious nature of organisms) |

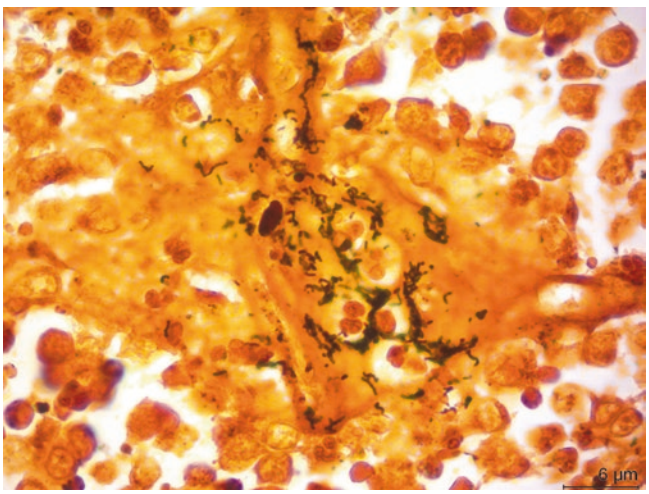


**Fig. 10.4** Cat-scratch lymphadenitis. Warthin-Starry stain shows an aggregate of curved bacilli usually found in the microabscesses

**Table 10.4** Morphologic features commonly associated with toxoplasma lymphadenitis and the differential diagnosis

| Feature | Differential diagnosis |
|---|---|
| Reactive follicular hyperplasia | Numerous reactive conditions |
| Clusters of epithelioid histiocytes, often in association with germinal centers | Leishmaniasis<br>Sarcoidosis – usually more well-formed granulomas<br>Lennert variant of peripheral T-cell lymphoma – usually does not have an intact architecture |
| Collections of monocytoid B cells | Acute HIV infection<br>Infectious mononucleosis |

**Table 10.5** Laboratory testing for toxoplasmosis and potential pitfalls

| Test | Pitfalls |
|---|---|
| PCR for Toxoplasma gondii DNA | May have false-positive results in recently resolved infections due to residual organismal DNA |
| Immunohistochemical stain for *Toxoplasma gondii* | Limited sensitivity in tissue sections, although quite specific |
| Serologic testing for IgM and IgG antibodies to *Toxoplasma gondii* | May be negative in the first few days of infection<br>IgM antibodies rise first and then decrease over weeks to months; IgG antibodies take up to 8 weeks to rise to high levels but usually persist<br>Positive IgG antibodies alone do not indicate active infection |

6. *What is the differential diagnosis of granulomatous lymphadenitis?*

   A frequent finding in biopsies of head and neck lymph nodes is granulomatous lymphadenitis (Table 10.6). Granulomas can be found in a variety of infectious, inflammatory, and neoplastic conditions. Lymphogranuloma venereum lymphadenitis (Fig. 10.5), syphilitic lymphadenitis and sarcoidosis are among the many entities in this differential diagnosis.

   References: [3, 6, 10, 13, 17–19]

7. *Which systemic diseases are commonly associated with lymphadenopathy?*

   Lymphadenopathy is a common sequela of a variety of systemic diseases and does not always imply a lymphoproliferative disorder. Reactive systemic conditions must be included in the differential diagnosis of a biopsied lymph node, particularly if the patient's lymphadenopathy is diffuse. The most common of these conditions are described below:

   - Systemic lupus erythematosus (SLE) may present with enlarged lymph nodes, particularly in patients who are newly diagnosed and have not been treated with immunosuppressive medications.
     - The most common findings in a lymph node of a patient with SLE are areas of necrosis, often without an acute inflammatory response, and with abundant apoptotic debris.
     - This is often morphologically indistinguishable from Kikuchi lymphadenopathy, but two features, both of which are specific but not sensitive, can help to suggest SLE: hematoxylin bodies (extracellular deposition of necrotic material) and blood vessels with fibrinoid necrosis and the Azzopardi phenomenon (hematoxylin-positive material in blood vessel walls).
     - Plasma cells are also usually prominent in SLE lymphadenopathy but are typically few in Kikuchi.
   - Patients with rheumatoid arthritis (RA) may present with enlarged lymph nodes in many sites throughout the body, most commonly in the axillary, cervical, and supraclavicular regions.
     - Lymphadenopathy is often associated with constitutional symptoms, such as fever and weight loss, in RA patients.

**Table 10.6** Clinicopathologic findings in the differential diagnosis of granulomatous lymphadenitis

| | Clinical | Etiologic agent | Morphology | Stains, lab tests |
|---|---|---|---|---|
| Bacterial lymphadenitis | Generally children<br>Acute, unilateral<br>Submandibular, upper cervical LNs | *Staphylococcus aureus*, *Streptococcus pyogenes*, anaerobes (poor dentition) | Typically associated with abscess formation rather than granulomas but may have suppurative granulomas like cat-scratch disease | Gram, Warthin-Starry |
| Actinomycosis | Cervicofacial is the most common presentation.<br>Usually due to poor dentition<br>Lymphadenopathy at the angle of the mandible or submandibular region, ±cellulitis | *Actinomyces israelii* | Granulomatous inflammation with central foci of neutrophils<br>Aggregates of deeply basophilic, filamentous, slender branching bacteria (sulfur granules) on routine histology | Gram, modified AFB (Fite) |
| Syphilitic lymphadenitis | Sexually transmitted<br>Congenital<br>Initial inguinal LAD, asymptomatic patients may present with cervical LAD | *Treponema pallidum* | Follicular hyperplasia and germinal centers with scattered histiocytes showing a starry pattern. Occlusion vasculitis, perivascular inflammation with plasma cells, thickened capsule, groups of epithelioid histiocytes with necrosis, and giant cells | Warthin-Starry in mucosal lesions, but LNs are usually negative |
| Lymphogranuloma venereum lymphadenitis | Cervical lymph nodes are common presenting site in women, men typically present with inguinal lymphadenopathy | *Chlamydia trachomatis* | LGV is very similar morphologically to cat-scratch disease. Organisms can occasionally be seen in vacuoles at the periphery of palisading granulomas (Fig. 10.5) | Warthin-Starry stain<br>PCR testing |
| Sarcoidosis | Most common head and neck presentation is cervical LAD, may be seen in mucosal sites (oropharynx, sinonasal tract) | Idiopathic | Granulomas are classically well-formed, non-necrotizing, and small. Multiple granulomas are seen, often adjacent to one another. Histiocytes with inclusions, such as asteroid bodies, are pathognomonic | AFB, GMS, Warthin-Starry, Gram stain to exclude infectious etiology |
| Tuberculosis lymphadenitis | Cervical LAD is the most common presentation.<br>Mucosal sites may be affected (pharynx, oral cavity, larynx) | *Mycobacterium tuberculosis* | Early granulomas may not be necrotic or caseating, but the classic feature is caseating granulomas with acellular debris. It is necessary to identify the microorganisms, which are often few in number, slender slightly curved rods | AFB (Ziehl-Neelsen or Kinyoun) |

**Table 10.6** (continued)

| | Clinical | Etiologic agent | Morphology | Stains, lab tests |
|---|---|---|---|---|
| Nontuberculous (atypical) mycobacterial lymphadenitis | Scrofula-cervical lymphadenitis in children<br>Immunosuppressed patients<br>High cervical LNs<br>May be isolated or disseminated | *Mycobacterium avium* complex, *M. kansasii*, *M. chelonae*, *M. scrofulaceum*, *M. fortuitum*, *M. leprae* | Suppurative granulomatous inflammation is usually present in immunocompetent.<br>Immunosuppressed – sheets of large, foamy histiocytes with abundant intracellular bacteria, non-caseating | AFB |
| Histoplasma lymphadenitis | Usually mediastinal but may present as cervical LAD<br>Endemic areas: Ohio and Mississippi river valleys | *Histoplasma capsulatum* | Histologically, it is very similar to tuberculous lymphadenitis; immunosuppressed may not show granulomas, just collections of histiocytes filled with organisms | GMS numerous small, thin-walled, 2–4 μm, narrow-based, budding yeast |
| Coccidiomycosis lymphadenitis | In endemic areas of the southwest USA and San Joaquin Valley and particularly in immunosuppressed patients, this should be a consideration<br>Head and neck disease typically involves the skin, but disseminated disease may involve LNs | *Coccidioides immitis* | Analogous to *Histoplasma*, this is typically mediastinal rather than cervical, although rare cases of cervical lymphadenitis have been reported. The morphology is similar to *Histoplasma* and tuberculous lymphadenitis on H&E section<br>There may be neutrophils around granulomas | GMS, large spherules, often with endospores, thick-walled, non-budding yeast<br>Complement fixation for IgG antibodies |

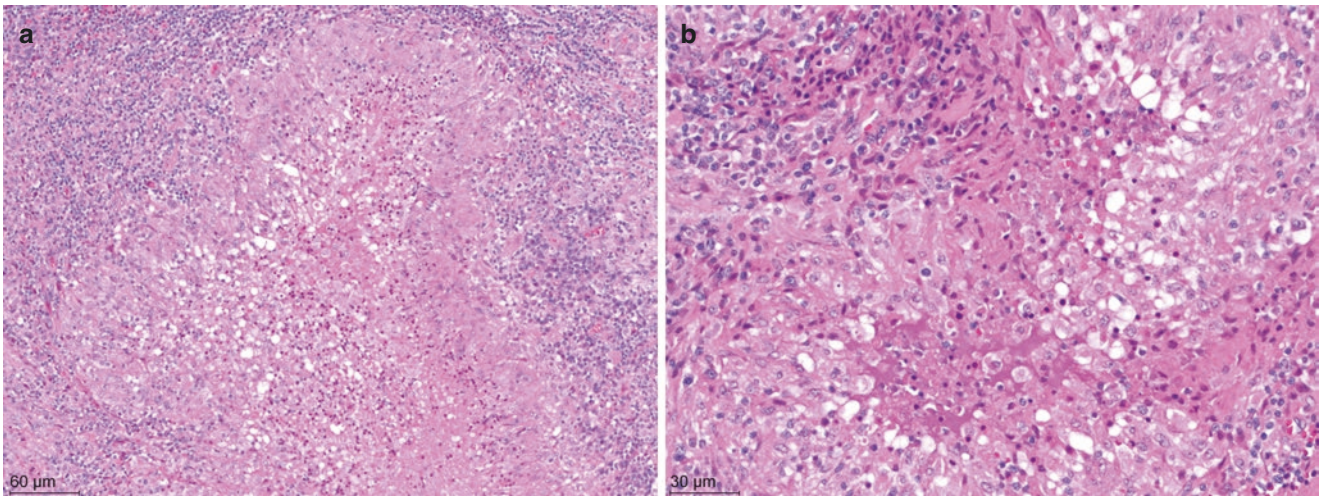


**Fig. 10.5** Lymphogranuloma venereum (LGV). (**a**) Suppurative granulomatous lymphadenitis, caused by *Chlamydia trachomatis* with palisading granulomatous inflammation characterized by (**b**) vacuolated histiocytes typical of LGV

  - These patients are at an increased risk of lymphoma, which also presents commonly with constitutional symptoms and lymphadenopathy, so a lymph node biopsy may be performed to aid in the differential diagnosis.
  - Histologically, lymph nodes in RA usually show florid follicular hyperplasia with interfollicular plasmacytosis and occasional vascular proliferation.
  - The differential diagnosis includes numerous other etiologies of reactive follicular hyperplasia, most importantly syphilis and Castleman disease. RA patients usually do not show the vasculitis associated with syphilis or the hyalinization of germinal centers and blood vessels associated with Castleman disease.
- Dermatopathic lymphadenopathy (DL) is a very common cause of enlarged lymph nodes and lymph node biopsies in patients with dermatologic disorders.
  - DL is associated with many chronic skin diseases, such as psoriasis and eczema, and is also common in patients with cutaneous T-cell lymphomas (mycosis fungoides/Sezary syndrome – MF/SS).

  - Histologically, lymph nodes with dermatopathic lymphadenopathy have prominent paracortical hyperplasia with nodular areas of increased interdigitating dendritic cells and Langerhans cells.
  - Pigment is typically present in histiocytes, which is usually melanin, although hemosiderin may also be seen.
  - DL is particularly challenging in patients with MF/SS; patients with minimal lymph node involvement by MF/SS are indistinguishable morphologically from DL unless there is evidence of an aberrant T-cell phenotype or evidence of T-cell molecular clonality.

References: [3, 15, 20–26]

8. *What are the common drugs that cause drug-induced lymphadenopathy?*

A patient's medications must be reviewed to completely assess lymphadenopathy, particularly if another etiology is not obvious. Several common medications have been associated with lymphadenopathy (Table 10.7).

- Patients on methotrexate or other immunosuppressive medications have an increased risk of iatrogenic lymphoproliferative disorders, which have a spectrum similar to posttransplant lymphoproliferative disorders (see question 26).
- A distinct lymphadenopathy associated with the anticonvulsants phenytoin (Dilantin) and carbamazepine (Tegretol) shows prominent paracortical hyperplasia with immunoblastic and vascular proliferation. This can be confused with angioimmunoblastic T-cell lymphoma, and evaluation of cellular atypia, flow cytometry, and molecular clonality studies may be necessary for a definitive diagnosis.

References: [23, 27–30]

9. *How is Kikuchi lymphadenopathy distinguished from systemic lupus erythematosus lymphadenopathy?*

Kikuchi lymphadenopathy (LAD), or Kikuchi-Fujimoto lymphadenopathy, is a benign, typically self-limited disorder. Patients are typically young females who present with tender, bulky, unilateral, posterior cervical LAD, fever, and upper respiratory symptoms.

- In Kikuchi LAD, the lymph node architecture is partially effaced by a necrotizing, histiocytic process. The areas of necrosis are remarkable for their lack of neutrophils and the presence of apoptotic cells and paucicellular debris.
  - Histiocytes surrounding the areas of necrosis contain phagocytosed fibrinoid material, imparting a crescent shape to the nucleus.
  - The histiocytes classically show dim expression of cytoplasmic myeloperoxidase by immunohistochemistry.
  - Clusters of plasmacytoid dendritic cells are also present and express CD123.
  - Occasional immunoblasts and numerous, small, CD8-predominant T cells are usually seen.
  - The remaining lymph node often has reactive follicular hyperplasia.
- The morphology of systemic lupus erythematosus (SLE) lymphadenopathy is similar to Kikuchi LAD and should be clinically excluded.

References: [13, 22, 31–36]

10. *What are the histologic features of Kimura lymphadenopathy?*

Kimura lymphadenopathy (Kimura disease) is a chronic inflammatory disorder, which is common in Asia but unusual elsewhere. Lesions are found in subcutaneous tissues and draining lymph nodes and are invariably associated with peripheral eosinophilia and elevated serum IgE levels.

- The head and neck are the most commonly involved regions of the body, most frequently around the ear. Single lesions are found in 60% of cases.
- Lymph nodes display prominent reactive follicular hyperplasia. An increase in eosinophils, including microabscesses and infiltration of germinal centers, is typically seen (Fig. 10.6).
  - Warthin-Finkeldey-type giant cells are common.
  - There is often hyperplasia of postcapillary venules, and older lesions can show sclerosis.
  - Deposits of IgE in the germinal centers can be detected by immunohistochemical staining for IgE.
- The differential diagnosis includes classic Hodgkin lymphoma, due to the eosinophilia and sclerosis, but Reed-Sternberg cells are absent.

References: [3, 35, 37–40]

11. *How is Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) diagnosed and what entities are in the differential diagnosis?*

Rosai-Dorfman disease is a benign, often self-limited condition, which typically involves a solitary lymph node (often cervical) but can rarely involve almost any organ in the body. As the name "sinus histiocytosis with massive lymphadenopathy" suggests, in this condition, the lymphoid architecture is mostly intact, with sinuses markedly expanded with a proliferation of unusual histiocytes:

- The histiocytes in Rosai-Dorfman disease have a unique morphologic appearance and immunophenotype (Fig. 10.7):

**Table 10.7** Common medications associated with drug-induced lymphadenopathy

| | |
|---|---|
| Phenytoin | Sulfonamides |
| Lamotrigine | Penicillin |
| Abacavir | Allopurinol |
| Carbamazepine | Aspirin |
| Gabapentin | Tetracycline |

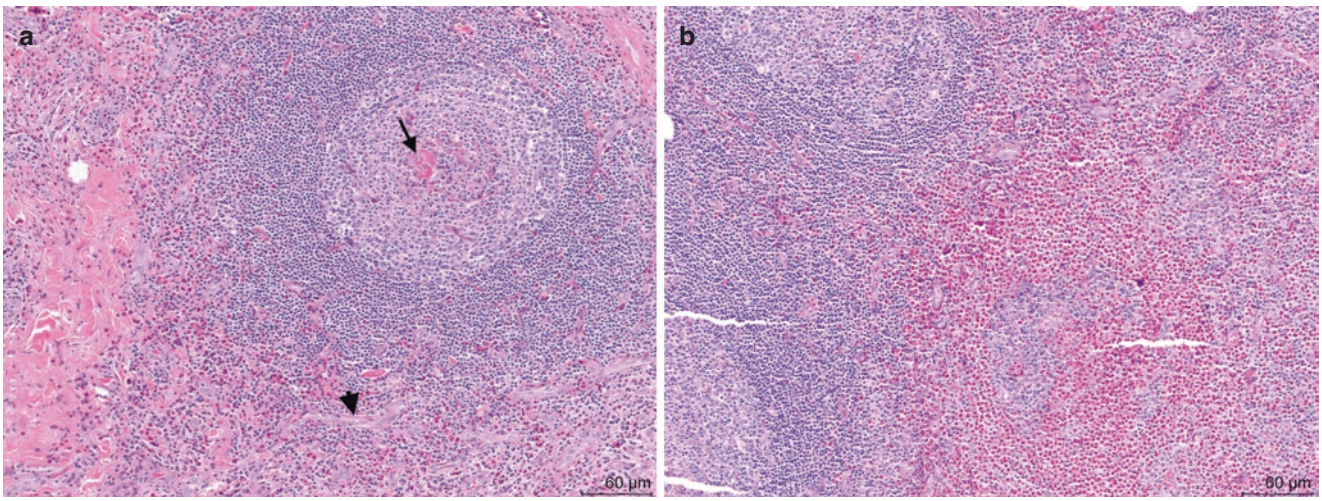


**Fig. 10.6** Kimura disease. (**a**) This lymph node shows reactive follicular hyperplasia with eosinophilic material (arrow) in the germinal center. Focal fibrosis, increased paracortical vasculature (arrowhead), and visible eosinophilia. (**b**) Eosinophilic microabscess formation

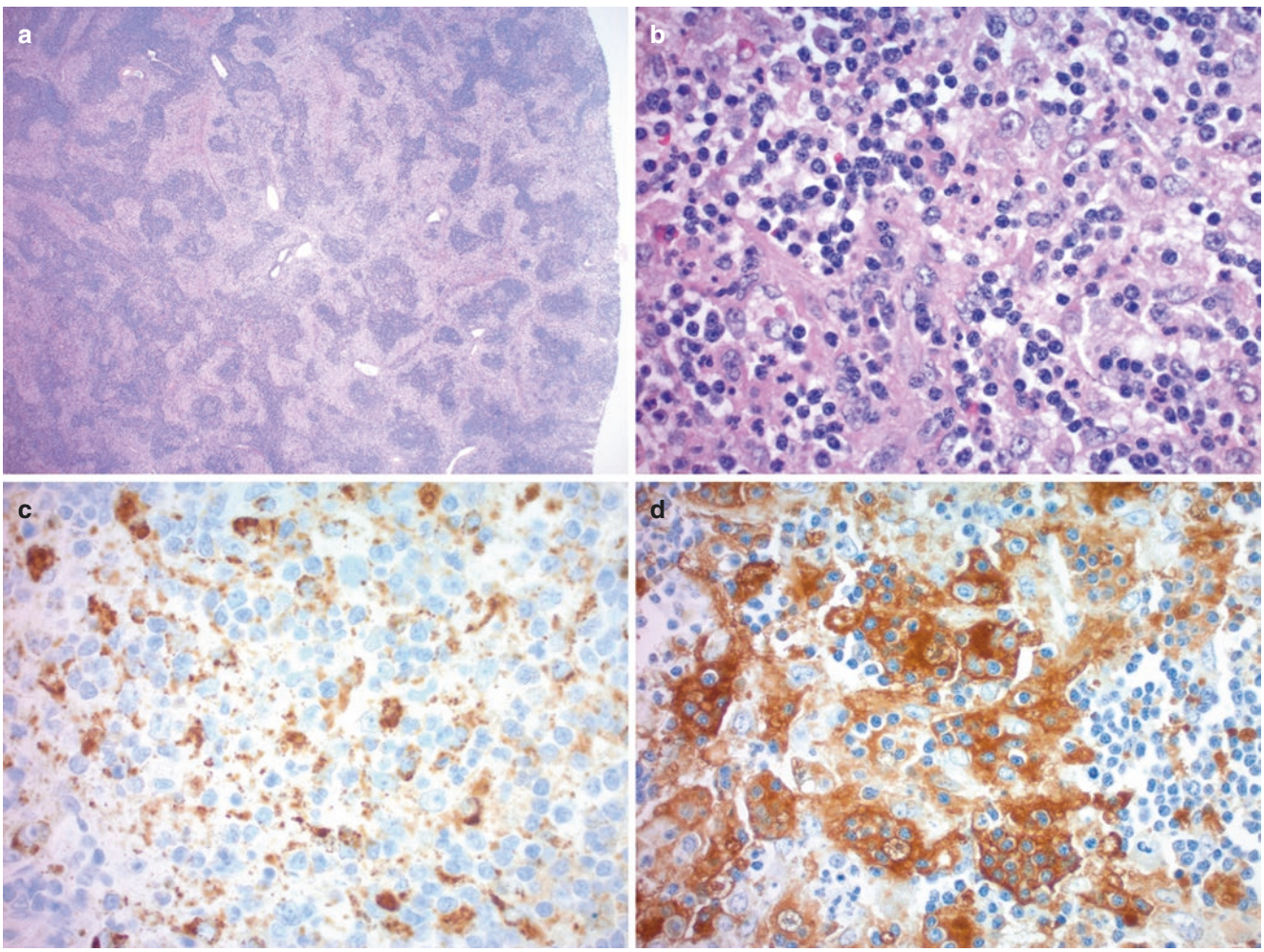


**Fig. 10.7** Rosai-Dorfman disease. (**a**) The lymph node shows pale serpiginous areas corresponding to sinuses filled with histiocytes. (**b**) Histiocytes with engulfed cells (emperipolesis) and vesicular nuclei are positive for (**c**) CD68 immunohistochemical stain. (**d**) S-100 immunohistochemical stain highlights histiocytes with emperipolesis

  - Histiocyte cytoplasm is abundant and pale, with evidence of emperipolesis, engulfed, intact cells. These are most often small lymphocytes, but other cell types can be seen.
  - The nucleus is slightly enlarged, with unusual vesicular chromatin.
  - These cells are present in a mixed inflammatory background that almost always contains increased plasma cells. If plasma cells are absent, the diagnosis can be made but only with caution.
  - Positive IHC: S100 (typical sinus histiocytes are negative), CD68, CD1a.
- The differential diagnosis includes usual sinus histiocytosis, Langerhans cell histiocytosis, and Erdheim-Chester disease. A summary of the most important ways to distinguish these four entities is provided in Table 10.8.

  Langerhans cell histiocytosis (LCH) is a clonal proliferation of Langerhans cells with an associated, mixed inflammatory infiltrate. It is predominantly a disease of childhood with approximately 90% of cases being diagnosed in patients under 10 years old. The head and neck is a common site of disease and is involved in up to 90% of cases.
- Males are twice as likely to be affected as females.
- Common sites of involvement include mandible, maxilla, cervical lymph nodes and temporal bone. Mucosal sites include the palate and gingiva. Patients present with cervical lymphadenopathy, rash, or otitis media.
- Involved sites show sheets of tumor cells and inflammation usually involving bone or submucosa.
  - Langerhans cells have a histiocytoid appearance with eccentric, convoluted, bean-shaped nuclei with longitudinal grooves and irregular indentations. The cytoplasm can be abundant and ranges from pale and vacuolated to eosinophilic. Mitoses are rare. The tumor has a characteristic, mixed inflammatory infiltrate of neutrophils, lymphocytes, and plasma cells, but eosinophils predominate. Eosinophilic microabscesses and intracellular Charcot-Leyden crystals can be seen.
  - Positive IHC: CD1a, S100, CD207, CD68.

References: [3, 35, 41–43]

12. *How is hyaline vascular Castleman disease distinguished from reactive lymphoid hyperplasia?*

    Castleman disease is an uncommon cause of lymphadenopathy, which has two unrelated forms: hyaline vascular and plasma cell variants (see question 13).
    - Hyaline vascular Castleman disease (HVCD)is a benign proliferation that usually involves a solitary lymph node, often cervical, but can involve multiple contiguous lymph nodes throughout the body. It often enters the differential diagnosis with reactive follicular hyperplasia due to overlapping morphologies (Fig. 10.8). Key histologic features comparing HVCD to reactive follicular hyperplasia are summarized in Table 10.9.
    - Plasma cell variant of Castleman disease (PCCD) should always be excluded in HVCD biopsies.
      - Positive IHC in HVCD: polytypic light chain expression (lambda increased or restricted in PCCD).
      - Negative IHC in HVCD: HHV8 (positive in PCCD).

    References: [37, 44–48]
13. *What are the histologic features of plasma cell variant of Castleman disease?*

    Plasma cell variant of Castleman disease (PCCD) is uncommon and usually presents in older patients. It is often multicentric (multicentric Castleman disease), but unicentric cases are seen. Important features distinguishing the types of Castleman disease are described in Table 10.10.
    - Evidence of HHV8 infection can be found in roughly half of plasma cell variant of Castleman disease and in most multicentric cases. HHV8-positive multicentric Castleman disease is often associated with HIV infection and often presents with Kaposi sarcoma. An HHV8 immunohistochemical stain should be performed in all cases where Castleman disease is suspected.
    - Histologic features include reactive follicular hyperplasia, with follicles widely separated by sheets of plasma cells.
      - Lymph node sinuses are usually present and patent.

**Table 10.8** Entities in the differential diagnosis of Rosai-Dorfman disease

| | S100 | CD68 | CD1a | Morphology |
|---|---|---|---|---|
| Rosai-Dorfman disease | + | + | – | Enlarged histiocytes with abundant cytoplasm, large nuclei with vesicular chromatin, and prominent emperipolesis. Present in a background of mixed inflammatory cells, with plasma cells almost invariably present |
| Langerhans cell histiocytosis | + | –/+ | + | Langerhans cells with grooved/folded nuclei in a background of eosinophils, neutrophils, small lymphocytes, and histiocytes. Eosinophils are often prominent, hence the previous term "eosinophilic granuloma" |
| Erdheim-Chester disease | – | + | – | Foamy histiocytes with small nuclei. Occasional Touton-type giant cells. Background with reactive lymphocytes, plasma cells, neutrophils |

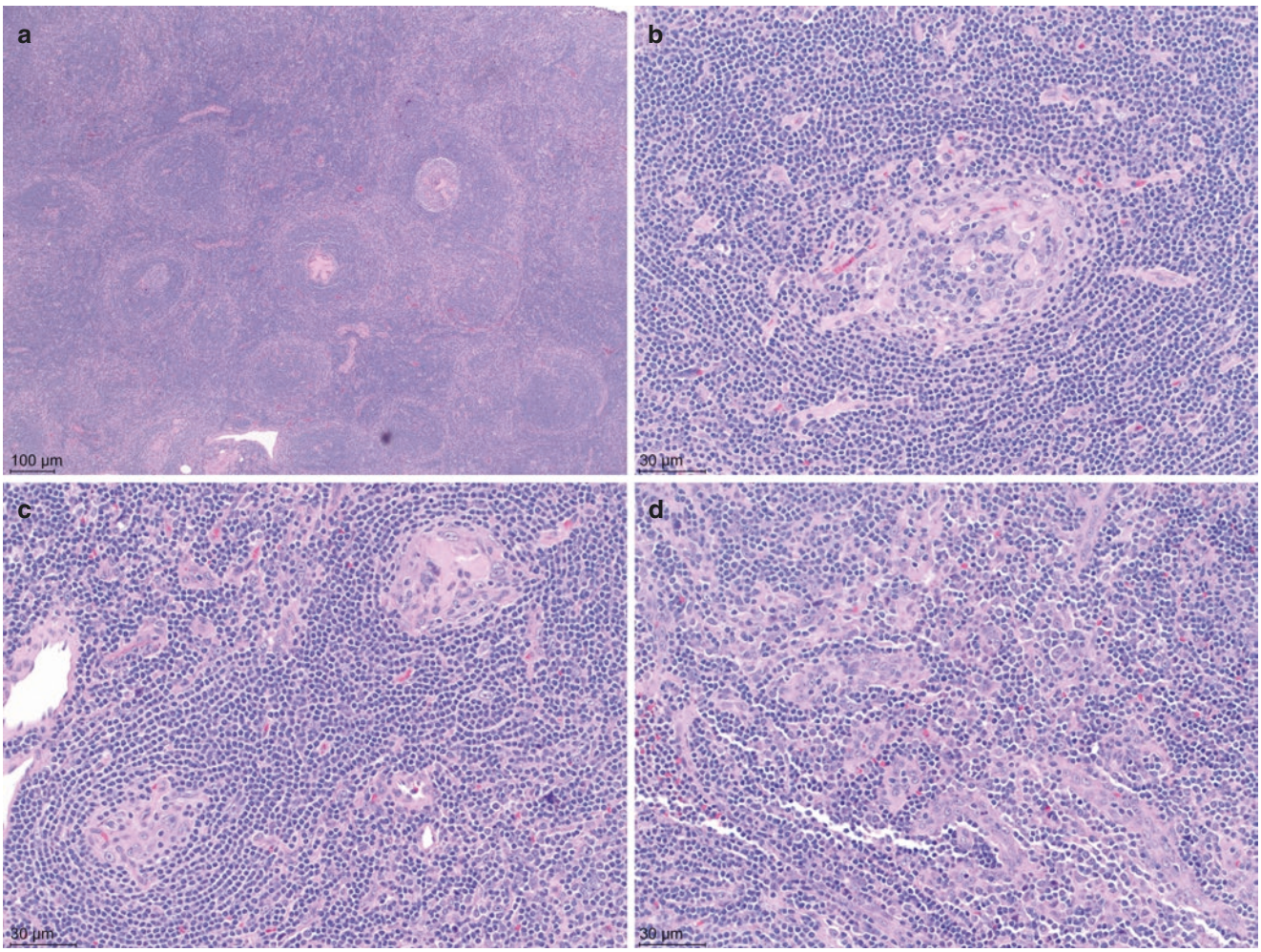


**Fig. 10.8** Hyaline vascular Castleman disease. (**a**) Regressed/atretic follicles with a conspicuous absence of nodal sinuses. (**b**) An atretic follicle with hyalinized blood vessels. (**c**) Twinning of germinal centers. (**d**) Interfollicular areas with increased vasculature

**Table 10.9** Morphologic features of hyaline vascular Castleman disease compared with reactive follicular hyperplasia

| Feature | HVCD | Reactive follicular hyperplasia |
|---|---|---|
| Germinal centers | Variably sized, regressed/atretic germinal centers with decreased lymphocytes and prominent follicular dendritic cells<br>Hyaline material deposition within follicles, hyalinized blood vessels, occasional merging of adjacent centers (twinning)<br>Pathognomonic "lollipop" appearance of some follicles created by a single hyalinized, penetrating vessel extending into the germinal center from the mantle zone | Reactive, with polarization, mitotic figures, and tingible body macrophages |
| Mantle zone | Prominent, with concentric rings of lymphocytes (onion skinning) | Variably prominent with polarization |
| Interfollicular areas | Characteristic vascular proliferation with endothelial cell hypertrophy | Appropriate mix of small lymphocytes, immunoblasts, histiocytes, etc. |
| Sinuses | Absent, except at periphery of the lesion | Visible throughout |

**Table 10.10** Morphologic features distinguishing plasma cell from hyaline vascular Castleman disease

| Feature | PCCD | HVCD |
|---|---|---|
| Germinal centers | Reactive, often florid. A subset shows HVCD changes | Regressed/atretic in many cases, with lymphocyte depletion. Classic vascular hyalinization |
| Mantle zones | Usually polarized and distinct from paracortex | Prominent and often show lymphocyte "onion skinning" |
| Interfollicular areas | Sheets of plasma cells, mature in HHV8-negative; immature plasmablasts in HHV8-positive | Prominent hyperplastic vasculature, plasma cells are scattered and may be prominent |
| Sinuses | Present and patent | Absent except at the periphery |

  - Most cases of PCCD have a subset of germinal centers with features similar to hyaline vascular Castleman disease.
  - HHV8-positive cases are distinguished morphologically by the presence of plasma cells with varying maturity, including immature plasmablasts, and increased interfollicular vascularity.
  - Plasma cells are usually polytypic in HHV8-negative cases, as well as in the majority of HHV8-positive cases.
- Lambda-restricted plasma cells, are classically associated with HHV8-positive, multicentric Castleman disease, but are only seen in a minority of cases.
- Multicentric disease commonly requires systemic therapy.

References: [22, 45, 47–51]

14. *Which are the most common lymphomas of extranodal head and neck sites and where do they occur?*

Lymphomas are the third most common malignancy of the head and neck and account for 10% of all malignant tumors in this region. Approximately two-thirds of head and neck lymphomas arise in lymph nodes; the remaining third occurs at extranodal sites.

- 30% of non-Hodgkin lymphomas and 5% of Hodgkin lymphomas in the head and neck occur at extranodal sites (Table 10.11).
- Diffuse large B-cell lymphoma is by far the most common type of extranodal lymphoma involving the head and neck.
- Waldeyer ring (palatine tonsil) is the most common site of head and neck extranodal lymphomas.
- Among all hematolymphoid tumors, the head and neck is the:
  - Most common site for extraosseous plasmacytomas
  - Second most common extranodal site for mantle cell lymphoma
  - Second most common site for extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) and for all extranodal lymphomas
  - The most common site of follicular dendritic cell sarcoma

References: [6, 52–61]

15. *Which hematolymphoid lesions show a predilection for the head and neck?*

In addition to the common lymphomas of the head and neck highlighted above in question 14, a handful of rare hematopoietic neoplasms have a predilection for head and neck sites. Table 10.12 summarizes some of these tumors. A few notable ones will be discussed here and in later questions.

- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) most commonly involves the orbit and accounts for up to 75% of ocular lymphomas. Other sites include the salivary gland, thyroid, Waldeyer ring, and larynx.
  - Chronic lymphocytic thyroiditis is a risk factor for lymphoma in the thyroid gland. Likewise, Sjogren's disease is a known risk factor for MALT lymphoma in the salivary gland, and lymphoepithelial sialadenitis is believed to be a precursor lesion.
  - Sheets of small, centrocyte-like (cleaved) lymphoid cells efface the normal tissue architecture. Lymphoepithelial lesions and reactive lymphoid follicles are usually present. The tumor cells are irregular lymphocytes with a scant to moderate

**Table 10.12** Hematolymphoid neoplasms with predilection for head and neck sites

| Tumor | Head and neck site (order of frequency) |
|---|---|
| CD30+ T-cell lymphoproliferative disorder | Oral cavity, tongue |
| Plasmablastic lymphoma | Oral cavity, nasopharynx, sinonasal cavity |
| Langerhans cell histiocytosis | Temporal bone, orbit, jaw |
| Extramedullary myeloid sarcoma | Oral cavity (gingiva) |
| Burkitt lymphoma | Oropharynx, jaw |
| Follicular dendritic cell sarcoma | Cervical LN, Waldeyer ring |
| Extranodal marginal zone lymphoma (MALT) | Eye, salivary gland, Waldeyer ring |
| Extranodal NK/T-cell lymphoma, nasal type | Nasal cavity |
| Extraosseous plasmacytoma | Sinonasal cavity, nasopharynx, oropharynx, larynx |

**Table 10.11** Most common primary extranodal head and neck lymphomas by site

| | Oral cavity | Oropharynx | Nasopharynx | Larynx | Nasal cavity/paranasal sinuses | Salivary gland | Thyroid |
|---|---|---|---|---|---|---|---|
| Percent of all head and neck lymphomas | 2% | 35–65% | 15% | 4% | 12–15% | 5% | 3–5% |
| Most common types of lymphoma | DLBCL (50%)<br>– Palate<br>– Gingiva<br>– Tongue | DLBCL (70%)<br>– Tonsil | DLBCL<br>Extranodal NK/T-cell lymphoma<br>Peripheral TCL | MALT<br>DLBCL<br>– Supraglottic | Extranodal NK/T-cell lymphoma, NT<br>DLBCL | MALT<br>DLBCL<br>FCL[a] | DLBCL<br>MALT |

[a]Large percentage of cases involve salivary gland but may be primary to intraglandular lymph node

amount of cytoplasm. Monocytoid cells with more abundant clear cytoplasm and larger lymphocytes may also be present. Initial lesions show infiltration of the epithelium which progresses to nodular infiltrates and sheets of tumor cells.
  - Tumors show monotypic light chain expression with IgM > IgA/IgG and express a number of B-cell antigens.
  - Positive IHC: CD45, CD20, BCL2.
  - Negative IHC: CD10, CD5, BCL6, MUM1, cyclinD1.
  - Genetics: t(14;18), t(11;18), and t(3;14).
- Plasmablastic lymphoma is an aggressive lymphoma with a poor prognosis.
  - It is often associated with immunosuppression (particularly HIV) and most frequently presents in the head and neck region (classically the oral cavity).
  - EBV is associated with most cases, although not required for the diagnosis.
  - Morphologically, PBL comprises medium to large lymphoid cells with amphophilic cytoplasm, round nuclei, and prominent nucleoli reminiscent of immunoblasts and plasmablasts (Fig. 10.9). Associated plasma cells and reactive T cells may be present.
  - Plasmablastic lymphoma should be distinguished from other lymphomas with plasmablastic morphology, such as ALK-positive diffuse large B-cell lymphoma and HHV8-associated lymphoproliferative disorders.
  - Positive IHC: CD138, CD38, IRF4/MUM1. CD30 expression is common, and cytoplasmic light chain restriction can usually be demonstrated. Ki-67 proliferation index is typically high (>90%). MYC translocation is found in roughly half of the cases
  - Negative IHC: CD45, CD20, PAX5, ±CD79a. translocation
- Extranodal NK/T-cell lymphoma, nasal type (ENKTL) is a rare and aggressive lymphoma, which is much more prevalent in Asian and Native American populations than in Caucasian or African communities.
  - ENKTL most commonly affects the upper aerodigestive tract, with the nasal cavity being the classic site. Other extranodal sites, such as the gastrointestinal tract and skin, are also occasionally involved.
  - Morphologically, there is a diffuse infiltrate of medium-sized, atypical cells, which are often angiocentric and angiodestructive (Fig. 10.10). Necrosis is common.
  - Positive IHC: CD2, CD56, cytoplasmic CD3-epsilon, and cytotoxic markers (granzyme B, TIA-1, perforin). EBV is invariably positive. A subset may express CD5 and CD8.
  - Negative IHC: Other T-cell antigens such as surface CD3, CD4, CD5, and CD8.
- Extramedullary plasmacytoma (EMP) is a rare tumor that accounts for only 3% of all plasma cell neoplasms. There is a male predominance with a median

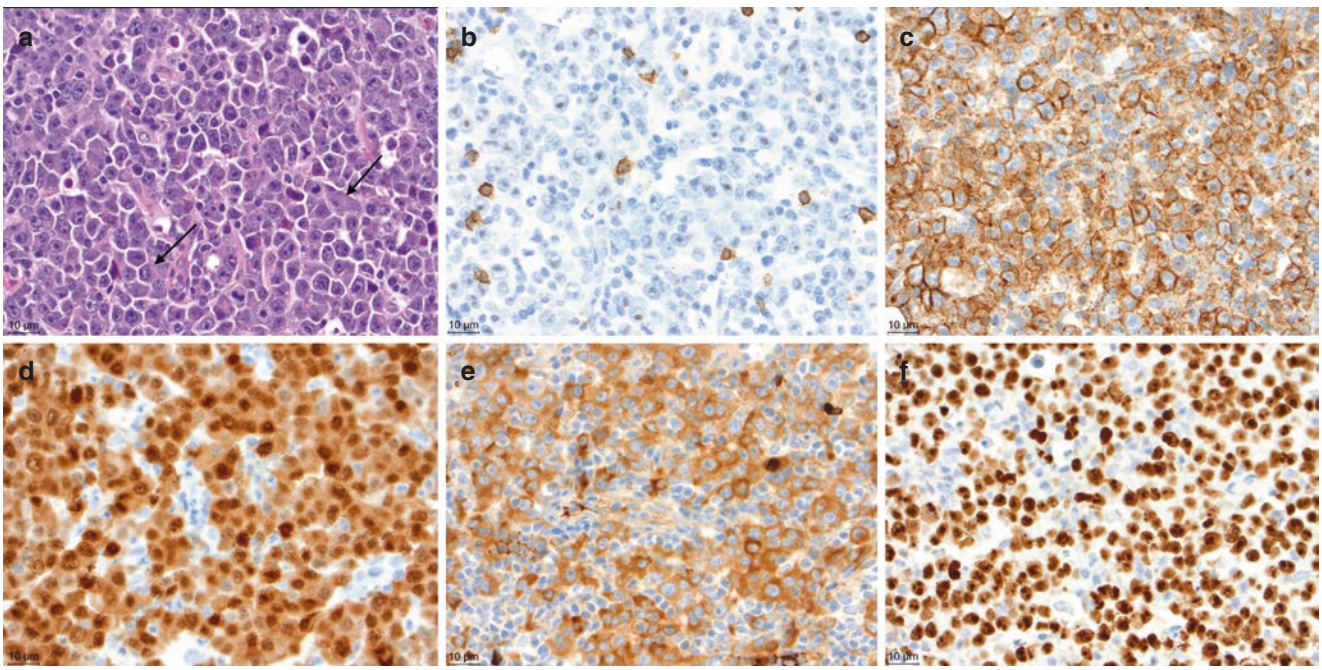


**Fig. 10.9** Plasmablastic lymphoma. (**a**) Diffuse infiltrate of large, atypical cells with prominent nucleoli. Occasional cells show plasmablastic features with eccentric nuclei, abundant cytoplasm, and perinuclear clearing (arrows). The tumor cells are negative for (**b**) CD20 and positive for (**c**) CD138, (**d**) IRF4/MUM1, and (**e**) cytoplasmic lambda immunohistochemistry. (**f**) Ki-67 proliferation index is high (>90%)

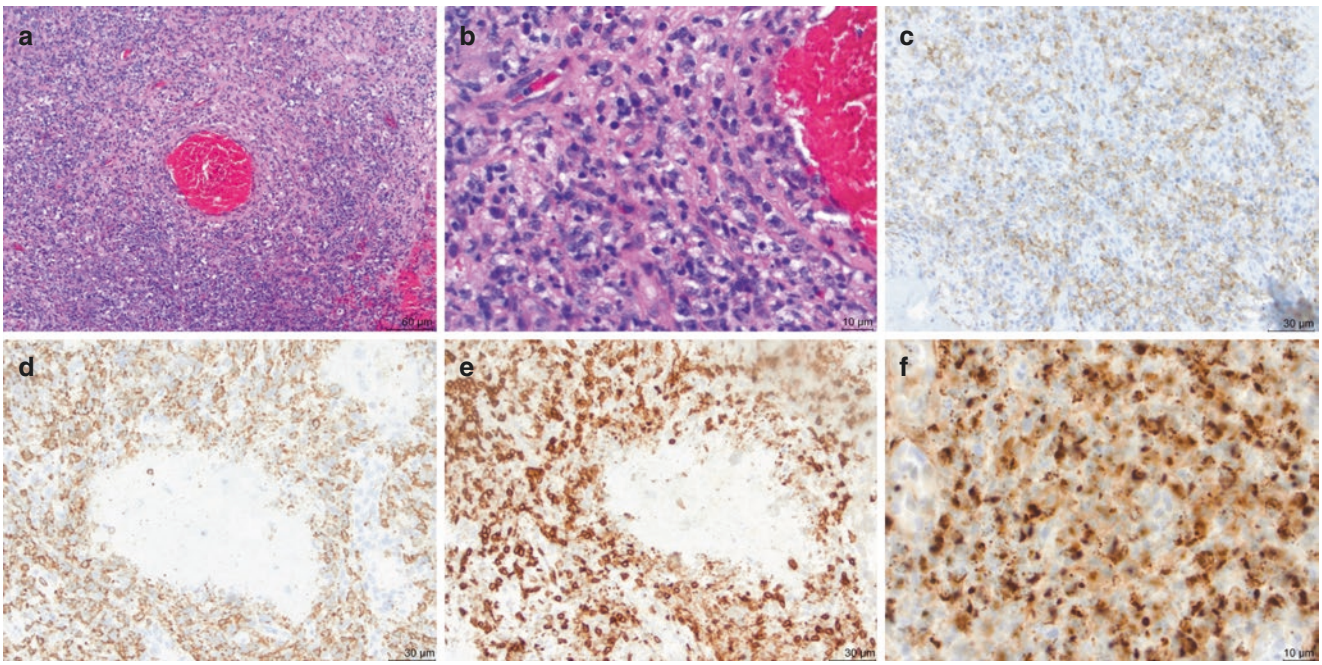


**Fig. 10.10** Extranodal NK/T-cell lymphoma, nasal type. (**a**) A destructive, angiocentric, infiltrate composed of (**b**) small- to intermediate-sized, atypical cells with pale cytoplasm infiltrates a blood vessel wall. The atypical cells are positive for (**c**) CD56, (**d**) CD2, (**e**) CD3, and (**f**) granzyme B by immunohistochemistry

age of 55 years. The head and neck is the most common site of EMP with approximately 80% occurring in this area. Patients present with epistaxis, rhinorrhea, dysphagia, and hemoptysis. EMP tends to be solitary, but up to 15% of patients will develop multiple myeloma.

- Histologic sections show sheets of plasma cells in the submucosa. The tumor cells have a moderate amount of eosinophilic cytoplasm with an eccentric nucleus. There is a perinuclear area of pallor (hof), and the nuclei have dense chromatin with classic peripheral margination. Plasma cells vary from well to poorly differentiated.
- Amyloid deposition may be present and show monotypic light chain expression. EBV may be positive, but plasmablastic lymphoma should be excluded.
- The prognosis for EMP is better than for myeloma; however, patients may develop recurrence, and a small proportion of patients will progress to myeloma.
- Positive IHC: CD138, CD38, MUM1, ±EMA, ±CD56.
- Negative IHC: CD20, PAX5.

- Primary mucosal CD30+ T-cell lymphoproliferative disorder is thought to be closely related to primary cutaneous anaplastic large cell lymphoma. Patients may have isolated mucosal disease, mucocutaneous disease, or systemic disease. The oral cavity is the most common site (lip, gingiva, tongue). The sinonasal tract and orbit may also be affected. There is a male predominance and a mean age of 54 years old. Patients present with a nodule or an ulcerative lesion.
  - The tumor is characterized by a nodular infiltrate of large, atypical mononuclear cells with abundant, amphophilic cytoplasm and irregular nuclei. "Hallmark" cells are usually present and have horseshoe, eccentric, or circular nuclei. Mitoses are frequent, and pagetoid spread of the atypical cells into the overlying epithelium may be present.
  - The accompanying inflammatory infiltrate comprises neutrophils and eosinophils. The tumor cells are, by definition, CD30-positive and ALK (anaplastic lymphoma kinase)-negative.
  - Positive IHC: CD30, CD3, CD4, rare CD8, ±EMA.
  - Negative IHC: CD20, ALK, CD7, CD56, EBER/EBV.
  - A systemic workup should be performed to exclude systemic disease which requires more aggressive therapy.
- Follicular dendritic cell (FDC) sarcoma is a tumor derived from the follicular dendritic cells, a normal stromal cell found in nodal and extranodal lymphoid follicles. Patients are typically in the fourth decade of life and present with cervical lymphadenopathy; common mucosal sites include the pharynx and oral cavity.

**Table 10.13** Recommended initial immunohistochemistry panel for classic Hodgkin lymphoma

| Stain | Expected results Reed-Sternberg cells of classic Hodgkin lymphoma | Differential diagnosis |
|---|---|---|
| CD3 | Usually negative in Hodgkin/Reed-Sternberg cells<br>Positive in numerous small background T cells | Positive in many anaplastic large cell lymphomas |
| CD20 | Positive (usually dim and focal) in atypical cells in a minority (<20%) of CHL cases | Positive in mediastinal gray zone lymphoma and primary mediastinal (thymic) B-cell lymphoma |
| PAX5 | Positive (usually dim) in Hodgkin/Reed-Sternberg cells in most CHL cases | More brightly positive in mediastinal gray zone lymphoma and primary mediastinal (thymic) B-cell lymphoma |
| CD30 | Strongly positive in most cases of CHL | Strongly positive in anaplastic large cell lymphoma, variably positive in gray zone lymphoma and primary mediastinal B-cell lymphoma |
| CD15 | Positive in the majority of CHL cases | Occasionally positive in anaplastic large cell lymphoma and gray zone lymphoma; negative in primary mediastinal B-cell lymphoma |

  - FDC sarcoma is characterized by a spindle cell proliferation arranged in a storiform, fascicular, or sheetlike pattern. The tumor cells have indistinct cell borders with a syncytial appearance. Tumor nuclei are bland, oval, or elongated with a finely granular or vesicular chromatin and inconspicuous nucleoli. Mitoses are usually less than 10 per hpf and necrosis is rare.
  - High-grade tumors will show more pronounced pleomorphism, necrosis, and frequent mitoses.
  - A lymphocytic infiltrate is present within the tumor and is composed of B- or T-cells. A subset of tumors (10–20%) arise in the setting of Castleman disease.
  - Positive IHC: CD21, CD23, CD35, clusterin (highly specific and sensitive).
  - Negative IHC: CD1a, CD34, CD3, CD79a, desmin, HMB-45, high-molecular-weight CK.
- EBV-related mucocutaneous ulcer is a recently described entity that presents as an ulcer, usually of the oral cavity, in immunosuppressed patients.
  - The tumor cells are polymorphous, with atypical, large B-cells, occasionally showing Reed-Sternberg like morphology in a background of T-cells.
  - Positive IHC: CD30, EBER, CD15 (half of cases).

References: [6, 54, 61–73]

16. *What are the histologic and immunophenotypic features of classic Hodgkin lymphoma?*

Classic Hodgkin lymphoma (CHL) is one of the most commonly diagnosed lymphomas (15–25% of cases) and most commonly presents as painless, enlarged cervical lymph nodes. It should be toward the top of the differential diagnosis for any patient with painless neck lymphadenopathy. The subtypes of CHL have distinctive histologic features (see question 17), but there are also some common features.

- Histologic features include scattered large, atypical cells in a mixed inflammatory background.
  - The mixed inflammatory background is composed of numerous small, mature lymphocytes but also variably prominent eosinophils, histiocytes, neutrophils, and plasma cells.
  - The diagnostic cell is the Reed-Sternberg cell, which has two enlarged nuclei, vesicular chromatin, abundant cytoplasm, and very prominent, often cherry-red nucleoli.
  - Also diagnostic is the mononuclear version of the Reed-Sternberg cell and the Hodgkin cell.
    - The diagnostic cell of the nodular sclerosis subtype is the lacunar cell, which has a retracted, pale cytoplasm and irregular hyperchromatic to vesicular nuclei.
  - Fibrosis is variable, depending upon the subtype.
- The immunophenotype is summarized in Table 10.13. The large, atypical cells are positive for CD30 in the vast majority of cases.
- CD15 is expressed in roughly three-fourth of cases: CD15 negativity should prompt a more careful evaluation for mimics of classic Hodgkin lymphoma, such as anaplastic large cell lymphoma and EBV-positive diffuse large B-cell lymphoma.
- CD20 is positive in a minority of cases and is usually weak and focal in expression. Strong CD20 staining should prompt evaluation for a mediastinal gray zone lymphoma (B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma), primary mediastinal (thymic) B-cell lymphoma, and EBV-positive diffuse large B-cell lymphoma.

References: [1, 55, 56, 62, 74–78]

17. *How are the various subtypes of classic Hodgkin lymphoma identified?*

Classic Hodgkin lymphoma has four distinct subtypes (Table 10.14). Nodular sclerosis and mixed cellularity types are the most common and account for over 80% of cases. It is most common in cervical lymph nodes and rare in mucosal sites of the head and neck.

- The most common extranodal head and neck site of Hodgkin lymphoma is Waldeyer ring.

References: [55, 56, 62, 74–79]

**Table 10.14** Distinctive features of the subtypes of classic Hodgkin lymphoma

| | Nodular sclerosis | Mixed cellularity | Lymphocyte-rich | Lymphocyte-depleted |
|---|---|---|---|---|
| % of all HL | 70–85% | 15–25% | 5% | 1% |
| Peak age (years), gender | 15–34, M = F | Children and older patients, M:F = 2:1 | Older patients | 30–40, M:F = 3:1 |
| Clinical | Painless cervical LAD with mediastinal extension<br>Localized disease | Presents with more advanced disease<br>30% splenic disease<br>10% BM disease | Presents with low stage disease<br>Predilection for cervical LN and Waldeyer ring | Historically associated with advanced HIV/AIDS<br>Predilection for abdominal disease |
| Overall morphology | Dense fibrosis with fibrous bands creating nodules and a mixed inflammatory background | Diffusely effaced architecture without fibrosis<br>Interfollicular growth in early stages | Nodular architecture formed by scattered residual germinal centers<br>Rare eosinophils and neutrophils | Completely effaced architecture in a diffusely fibrotic background |
| Hodgkin/ Reed-Sternberg cells | Variable number of classic HRS cells<br>Lacunar cells are more numerous | Numerous classic HRS cells<br>Lacunar cells are not prominent | Classic HRS cells are scant and usually seen in mantle zones and adjacent to GC | Numerous HRS and variant cells |
| Background cellularity | Variable in density; mixture of eosinophils (often prominent), histiocytes, small lymphocytes, neutrophils, plasma cells | Mixture of small lymphocytes, histiocytes, eosinophils, plasma cells | Predominantly small lymphocytes, with few eosinophils and histiocytes | Numerous histiocytes, eosinophils, and occasional small lymphocytes |
| Fibrosis | Thick, fibrotic capsule and paucicellular fibrous bands separating infiltrate into lobules | Minimal<br>Bands of mature collagen should not be present | Minimal | Diffuse fibrosis, but fibrous bands are absent |
| | Syncytial variant contains aggregates of atypical cells, often in the periphery of nodules and associated with necrosis | High association with HIV | Closely mimics nodular lymphocyte-predominant Hodgkin lymphoma | May mimic a spindle cell proliferation |
| EBV positive | 10–25% | 75% | 30–50% | Frequent 50–80% |

*HL* Hodgkin lymphoma, *HRS* Hodgkin/Reed-Sternberg, *BM* bone marrow, *GC* germinal centers

18. *What are the histologic features of nodular lymphocyte-predominant Hodgkin lymphoma and how is it distinguished from reactive progressive transformation of germinal centers?*

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon B-cell lymphoma, which has morphologic features reminiscent of classic Hodgkin lymphoma but is phenotypically distinct.

- Normal lymphoid architecture is effaced by large nodules composed of small lymphocytes and scattered large, atypical cells with convoluted nuclei ("popcorn" cells) and vesicular chromatin (LP cells). Follicular dendritic cells (FDCs) are commonly seen, and there is a dense FDC meshwork (Fig. 10.11). There are several morphologic patterns seen in NLPHL, which have prognostic significance.
  - The LP cells are mature B cells which are often surrounded by rosettes of small T cells with a follicular T-helper phenotype (positive for CD4, CD57, and PD-1)
  - Positive IHC of LP cells: CD20, CD79a, BCL2, Oct-2, BOB1
  - Negative IHC of LP cells: CD30, CD15, EBER
- The differential diagnosis includes:
  - Benign progressive transformation of germinal centers (Table 10.15) is a reactive condition characterized by focally enlarged, distorted germinal centers partially replaced by small lymphocytes.
  - T-cell/histiocyte-rich large B-cell lymphoma (TCRLBCL), which can only be diagnosed if there are no detectable nodular areas. A diffuse (TCRLBCL-like) variant of NLPHL also exists, but, unlike true TCRLBCL, the T cells in the background are CD4-positive.

References: [2, 62, 80–86]

19. *How is follicular lymphoma distinguished from reactive follicular hyperplasia?*

Lymph node biopsies of the head and neck often show expanded lymphoid follicles, and the differential diagnosis is typically reactive follicular hyperplasia (RFH) versus follicular lymphoma (FL):

- The low power architectural appearance of RFH and FL is distinct:
  - RFH germinal centers have distinct polarity, with dark and light zones imparted by cells with less (dark) and more (light) cytoplasm.
  - Mitotic activity is brisk in RFH germinal centers, and there are usually multiple tingible body macrophages.
  - FL follicles do not demonstrate polarity and, usually, do not show abundant mitotic figures or tingible body macrophages.

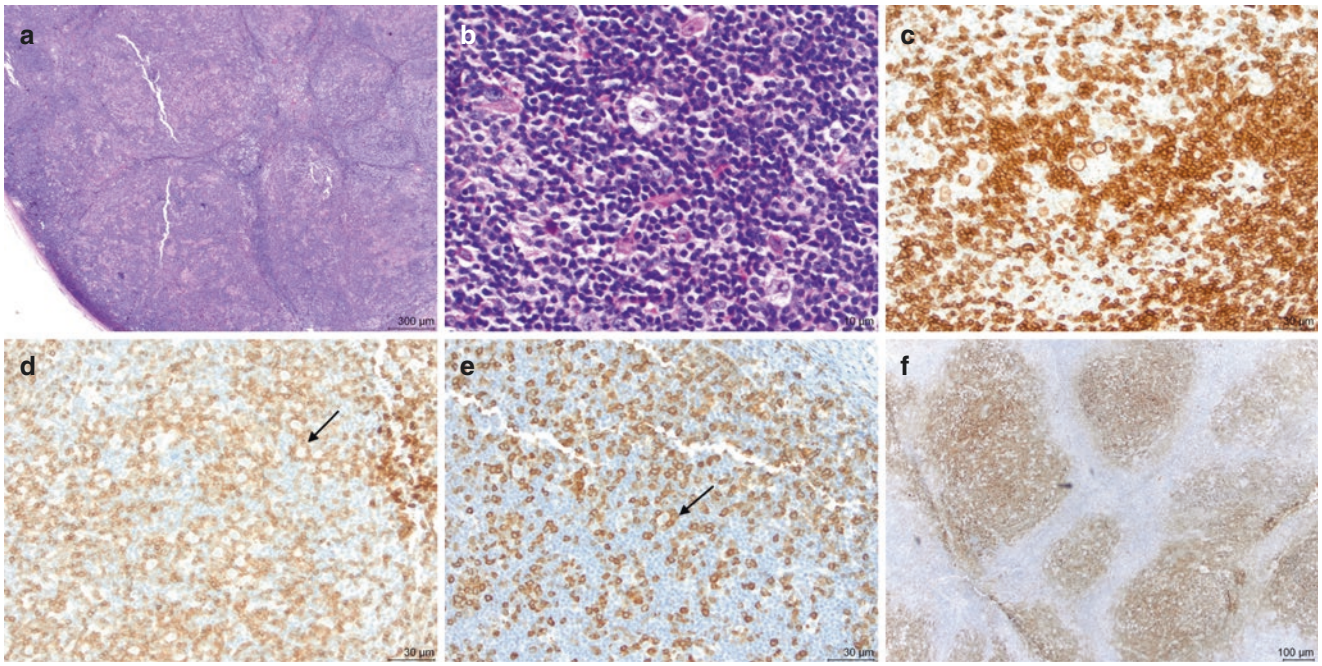


**Fig. 10.11** Nodular lymphocyte-predominant Hodgkin lymphoma. (**a**) An irregular proliferation of large nodules. (**b**) Scattered large, atypical ("popcorn") cells are in a background of small lymphocytes. (**c**) CD20 IHC stain highlighting both large, atypical cells and background small B cells. (**d**, **e**) CD3 and CD57 IHC stains highlight T cells forming rosettes around the large, atypical cells. (**f**) CD21 highlights the expanded follicular dendritic cell meshwork in the nodules

**Table 10.15** Features distinguishing nodular lymphocyte-predominant Hodgkin lymphoma from progressive transformation of germinal centers

| | NLPHL | PTGC |
|---|---|---|
| Extent of nodules | Entire lymph node or at least large areas | Single or scattered in most cases, almost never confluent or occupying the majority of a node |
| Large, atypical cells | Scattered | Absent |
| CD57/ PD1-positive T cells | Typically form rosettes around atypical cells | Scattered throughout |
| Background lymph node | Often not present | Reactive follicular hyperplasia |

- A panel of IHC stains (Table 10.16) can aid in the diagnosis.
- In rare cases, additional testing with flow cytometry or molecular B-cell clonality studies can be performed.
  - Genetics: 80% of FL harbor the t(14;18)(IGH/BCL2) translocation which can be identified by fluorescent in situ hybridization (FISH) analysis.

References: [2, 6, 62, 87, 88]

20. *How is follicular lymphoma graded?*

To best determine the prognosis and treatment of follicular lymphoma, it must be accurately graded (Table 10.17).

**Table 10.16** Immunoprofiles of reactive follicular hyperplasia and follicular lymphoma

| Stain | Reactive follicular hyperplasia | Follicular lymphoma |
|---|---|---|
| BCL2 | Negative in reactive germinal center B cells | Positive in >80% of follicular lymphomas, often brighter than background T cells |
| CD10 | Positive in reactive germinal centers | Positive in most follicular lymphomas, particularly within nodules |
| BCL6 | Positive in reactive germinal centers | Positive in most follicular lymphomas, usually within and outside nodules |
| CD20 | Positive in germinal center and mantle zone B cells, only occasional positive cells in the paracortex | Positive in follicular lymphoma cells, both within and often between nodules |
| Ki-67 | High proliferation index (>50%) with obvious polarization in reactive germinal centers | Variable proliferation index, often very low (<10%) in low-grade follicular lymphomas, and usually lacking typical polarization |

**Table 10.17** Grading criteria for follicular lymphoma

| Grade | Centroblasts per high-power (40× objective) field |
|---|---|
| 1–2 | 0–15 (grade 1 = 0–5, grade 2 = 6–15) |
| 3A | >15, but centrocytes are still present |
| 3B | Follicles composed of centroblasts or immunoblasts |

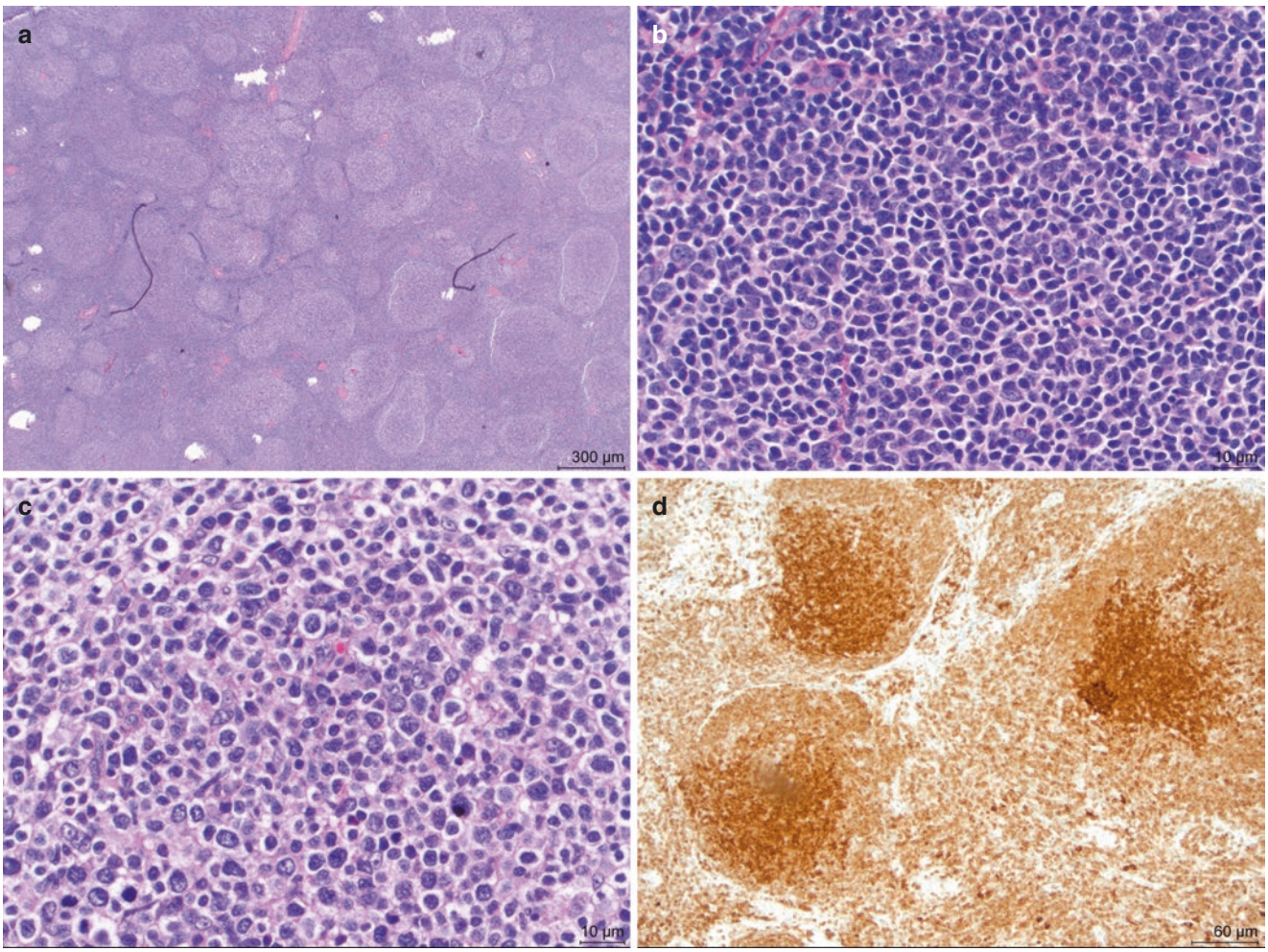


**Fig. 10.12** Follicular lymphoma grading. (**a**) Back-to-back follicles with scant mantle zones and no obvious polarization. (**b**) WHO grade 1–2: less than 15 centroblasts per high-power field. (**c**) WHO grade 3A: greater than 15 centroblasts per high-power field, but centrocytes are also present. (**d**) BCL2 immunohistochemical stain highlights the neoplastic follicles

- Follicular lymphoma is divided into three grades: 1–2, 3A, and 3B (Fig. 10.12). These are determined by the number of centroblasts (larger cells with more rounded nuclear contours and visible nucleoli) per 400× high-power field.
  - At least ten neoplastic follicles should be evaluated, and the predominant grade, not the highest grade, is assigned.
  - Historically, follicular lymphomas were further divided into grades 1 and 2, but given the poor reproducibility and similar prognosis, the current World Health Organization (WHO) classification does not recommend this subdivision. Instead such cases are graded as 1–2.
- In addition to grading by the number of centroblasts, the relative proportion of follicular and diffuse areas in the follicular lymphoma should be determined.
  - Diffuse areas in a follicular lymphoma grade 3A or 3B should be diagnosed as diffuse large B-cell lymphoma.
  - Diffuse areas are defined by the WHO as areas with absent follicular dendritic cell meshworks, which are usually positive for CD21 and CD23.

References: [1, 2, 62, 68, 87, 88]

21. *Which histologic features of mantle cell lymphoma correlate with prognosis?*

    Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma with a median survival of 3–5 years. The head and neck is the second most common extranodal site of MCL. As much as 20% of patients with MCL will have involvement of Waldeyer ring. Some histologic features correlate with prognosis and can help stratify patient outcomes.

    - MCL is composed of small to intermediate, monomorphous lymphoid cells in a vaguely nodular pattern. The tumor cells have irregular nuclear membranes; granular, coarse chromatin; and absent to inconspicuous nucleoli (Fig. 10.13).
      - Scattered epithelioid histiocytes and hyalinized vessels are usually present.

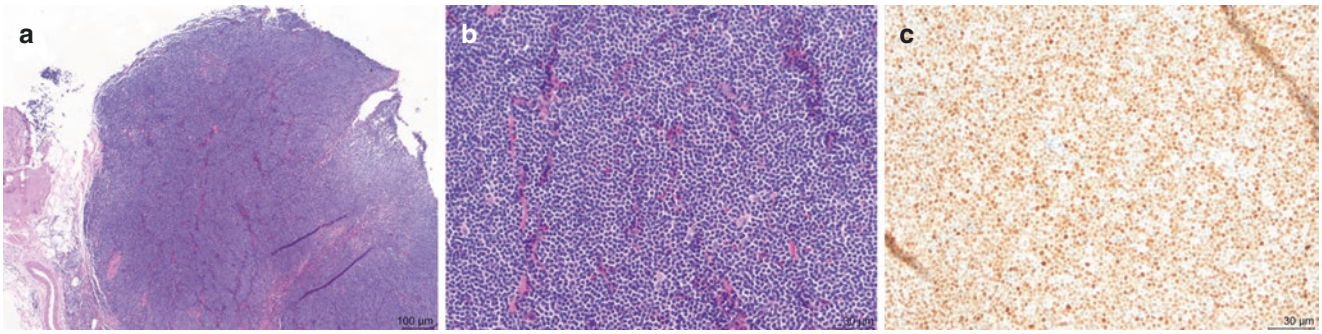


**Fig. 10.13** Mantle cell lymphoma. (**a**) Characterized by a diffuse infiltrate of small lymphocytes which obliterate the normal nodal architecture. (**b**) The monotonous infiltrate comprises small, atypical lymphocytes with slightly irregular nuclear contours which are positive for (**c**) cyclin D1

**Table 10.18** Pathologic features to distinguish diffuse, low-grade B-cell lymphomas

| Feature | Chronic lymphocytic lymphoma | Mantle cell lymphoma | Marginal zone lymphoma |
|---|---|---|---|
| Architecture | Mottled appearance due to proliferation centers with larger cells | Varies from diffuse to nodular | May see expanded areas between residual reactive follicles |
| Cell morphology | Monomorphous, small lymphocytes with minimal nuclear irregularities and coarse chromatin. Scattered larger prolymphocytes and paraimmunoblasts, more prominent in proliferation centers | Classic pattern: small lymphocytes with irregular nuclear contours and coarse chromatin<br>Blastoid type: more open chromatin, increased mitotic activity<br>Pleomorphic type: resembles diffuse large B-cell lymphoma | Small- to medium-sized lymphocytes with increased pale cytoplasm (monocytoid) and coarse chromatin. Scattered large cells may be prominent but do not form sheets. A significant subset shows plasmacytic differentiation |
| CD5 | Positive (less intense than background T cells) | Positive | Negative |
| CD10 | Negative | Negative | Negative |
| BCL6 | Negative | Negative | Negative |
| BCL2 | Positive | Positive | Positive |
| CD23 | Positive | Negative | Variable |
| Cyclin D1 | Negative | Positive | Negative |
| SOX11 | Negative | Positive | Negative |
| Genetics | Deletion of 13q (50%)<br>Trisomy 12 (20%)<br>Deletion of 11q<br>Deletion of 17p (TP53) | t(11;14)(q13;q32) (IGH/CCND1)<br>Rare variants CCND1, CCND2, or CCND3 rearrangements | Non-specific gains of chromosomes 3 and 18<br>Loss of 6q23-24 |

  - The small cell variant is morphologically indistinguishable from small lymphocytic lymphoma (SLL) and is more likely to behave indolently.
- Blastoid and pleomorphic variants of mantle cell lymphoma are aggressive.
  - Blastoid mantle cell lymphoma is characterized by cells that resemble lymphoblasts, with fine chromatin, more conspicuous nucleoli, high mitoses, and a high proliferation rate.
  - Pleomorphic mantle cell lymphoma has pleomorphic cells, which are often large and may resemble cells of diffuse large B-cell lymphoma.
- The immunoprofile is summarized in Table 10.18. A Ki-67 proliferation index of <10% is associated with an indolent clinical course, while an index of >30% indicates aggressive behavior.

References: [61, 62, 89–95]

22. *How can the most common diffuse low-grade lymphomas be distinguished?*

Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), mantle cell lymphoma, and nodal marginal zone lymphoma are the more common tumors in the differential diagnosis of diffuse, low-grade B-cell lymphomas. Morphologic features, characteristic immunoprofiles, and cytogenetic alterations can be used to distinguish these three neoplasms (Table 10.18).

References: [1, 2, 6, 54, 58, 61, 70, 96, 97]

23. *What are the diagnostic features of Burkitt lymphoma?*

Burkitt lymphoma is an aggressive B-cell lymphoma with a good prognosis. The endemic variant, which occurs in tropical regions of Africa and Papua New Guinea, has a predilection for the jaws and facial bones (50–70% of cases) of children and teenagers. Table 10.19

**Table 10.19** Comparison of the three variants of Burkitt lymphoma

| | Sporadic | Endemic | Immunosuppressed |
|---|---|---|---|
| Demographics | Children, young adults | Children, Africa | Adults, HIV+ |
| Involved sites | Extranodal, abdominal | Jaw bones and face | Any nodal site and bone marrow |
| EBV expression | 20–30% | > 95% | 25–40% |

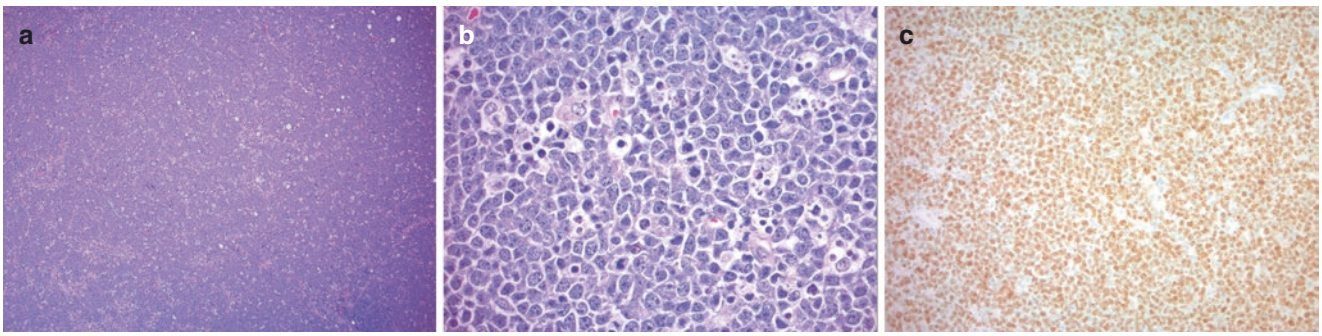


**Fig. 10.14** Sporadic Burkitt lymphoma. (**a**) Diffuse, lymphoid infiltrate effaces the normal nodal architecture and contains scattered tingible body macrophages imparting a starry sky appearance on low magnification. (**b**) The atypical cells are small to intermediate in size with vesicular chromatin and scattered nucleoli. Frequent mitotic activity is seen, and abundant apoptotic debris is present in tingible body macrophages. (**c**) A Ki-67 stain shows the typical proliferation index which approaches 100%

highlights the clinical features of the three variants of Burkitt lymphoma.

- Burkitt lymphoma is composed of relatively monotonous, small- to medium-sized lymphocytes with multiple small nucleoli and deeply basophilic cytoplasm with occasional vacuoles. Apoptotic and mitotic activity is very brisk, and numerous tingible body macrophages are present, imparting a "starry sky" appearance (Fig. 10.14).
- Burkitt lymphoma has a germinal center B-cell phenotype and should have a nearly 100% Ki-67 proliferation index.
- Positive IHC: CD20, CD10, BCL6, MYC, Ki-67.
- Negative IHC: BCL2, CD5, TdT, cyclin D1.
- Genetics: 90% of cases have an identifiable rearrangement of MYC, most commonly t(8;14)(q24;q32) (MYC/IGH), with less than 10% of cases having (2;8)(p12;q23) (IGK/MYC) or (8;22)(q24;q11) (MYC/IGL).

References: [62, 98–102]

24. *How is diffuse large B-cell lymphoma identified, subtyped, and distinguished from other high-grade B-cell lymphomas?*

Diffuse large B-cell lymphoma is the most common extranodal lymphoma of the head and neck and accounts for over a third of non-Hodgkin lymphomas. Waldeyer ring is the most frequently involved site. It is considered an aggressive lymphoma and represents a heterogeneous group of tumors.

- The tumor shows a diffuse proliferation of large lymphoid cells that are typically two to four times the size of a normal lymphocyte. The cells contain scant basophilic cytoplasm, round nuclei with irregular membranes, and vesicular chromatin, and nucleoli range from central and prominent (immunoblast-like) to small, multiple, and peripherally located (centroblast-like) (Fig. 10.15).
- Positive IHC: CD20, PAX5, CD79a.
- Negative IHC: CD3, CD4, CD8.
- An IHC panel should be performed to:
  1. Exclude other high-grade lymphomas (Table 10.20)
  2. Assign a subtype for prognostic information, typically using the Hans method (CD10, BCL6, and MUM1 IHC):
     - Germinal center (GC) origin conveys a better prognosis: either CD10+, CD10−/BCL6+/MUM1−, or CD10−/BCL6−/MUM1−.
     - Non-GC (activated B-cell) origin conveys a worse prognosis: CD10−/BCL6+/MUM1+ or CD10−/BCL6−/MUM1+.
     - This distinction in subtype and prognosis is less established for extranodal sites.

References: [1, 6, 61, 62, 97, 99–101, 103–110]

25. *What are the clinical and histologic features of myeloid sarcoma?*

Myeloid sarcoma (or granulocytic sarcoma) is an extramedullary mass of myeloid blasts or blast equivalents (such as promonocytes). The oral cavity is the most common head and neck site, and patients are usually in the sixth decade of life.

- Extramedullary myeloid sarcoma (EMS) typically occurs in a patient with a known diagnosis of acute

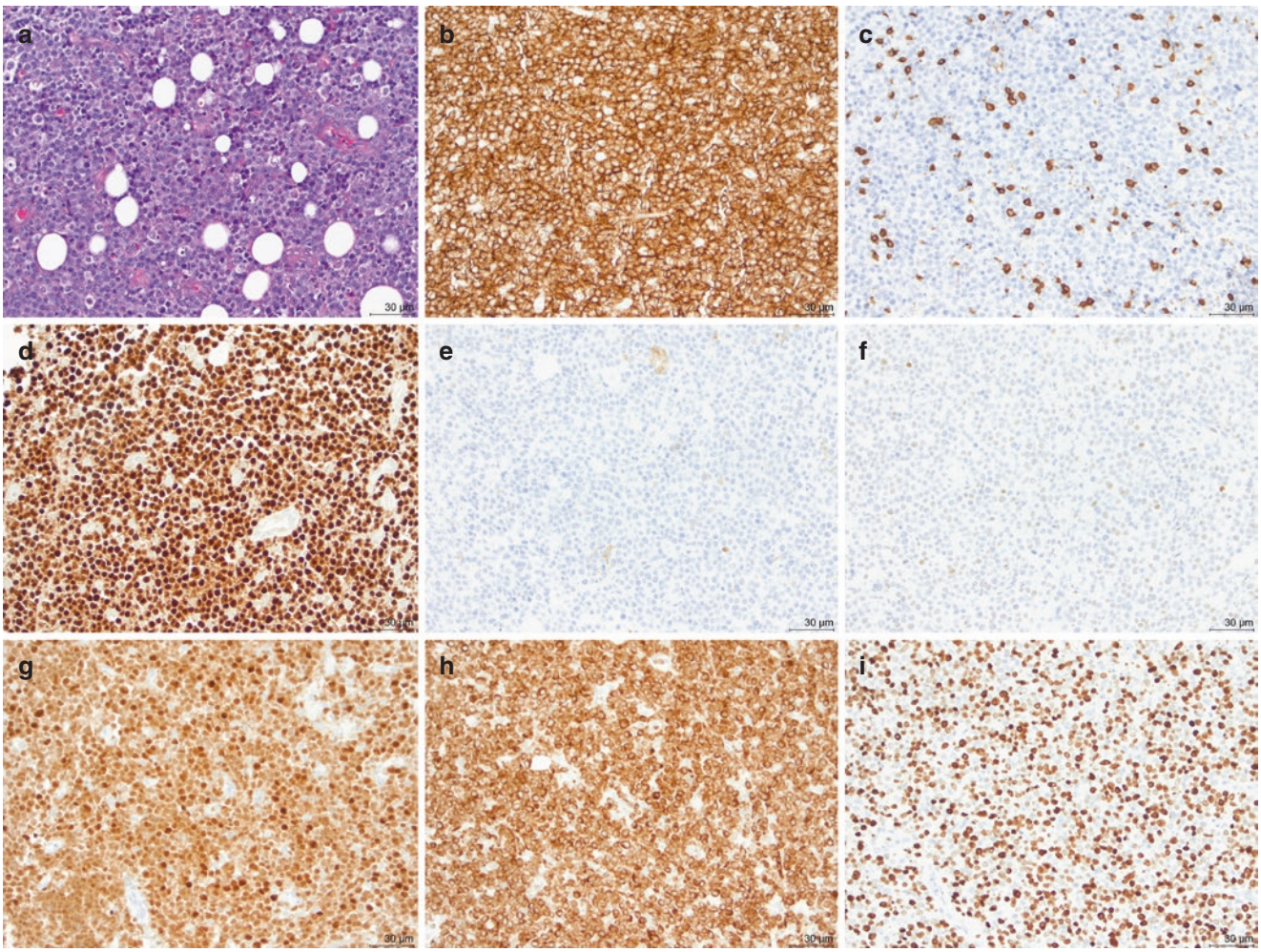


**Fig. 10.15** Diffuse large B-cell lymphoma, non-germinal center subtype. (**a**) Diffuse infiltrate of medium to large, atypical cells is positive for (**b**) CD20 with (**c**) rare CD3-positive small T cells in the background. (**d**) The tumor cells are also positive for PAX5 and (**e**) negative for CD10 and (**f**) BCL6. (**g**) Expression of IRF4/MUM1 and (**h**) BCL2 are also present. (**i**) Ki-67 shows an elevated proliferation index (60–70%)

**Table 10.20** Immunohistochemical and FISH panel for distinguishing DLBCL from high-grade B-cell lymphomas

| | DLBCL, NOS | Burkitt lymphoma | Blastoid mantle cell lymphoma | Lymphoblastic lymphoma | "Double hit" lymphoma[a] | High-grade B-cell lymphoma, NOS |
|---|---|---|---|---|---|---|
| CD20 | + | + | + | –/+ | + | + |
| PAX5 | + | + | + | + | + | + |
| CD10 | +/– | + | – | +/– | Usually + | Usually + |
| CD5 | +/– | – | + | – | – | – |
| MYC | +/–[b] | + | –/+ | –/+ | + | Usually + |
| BCL2 | +/–[b] | –/wk | + | +/– | + | Usually + |
| BCL6 | +/– | + | – | – | Usually + | Usually + |
| Cyclin D1 | – | – | + | – | – | – |
| Ki-67 | Usually high (>50%) | >95% | High (>50%) | High (>50%) | >95% | >95% |
| TdT | – | – | – | + | – | – |
| *MYC* rearrangement | +/–[c] | + | – | – | + | +/–[c] |
| t(14;18) (BCL2/IGH) | +/–[c] | – | – | – | +/–[d] | –/+[c] |
| *BCL6* rearrangement | +/–[c] | – | – | – | +/–[d] | –/+[c] |

[a]Formal name: "High grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6*"
[b]Co-expression of MYC and BCL2 has been associated with a poorer overall prognosis
[c]If *MYC* rearranged, then cannot have either t(14;18) or *BCL6* rearrangement
[d]One of t(14;18) or *BCL6* rearrangement must be present

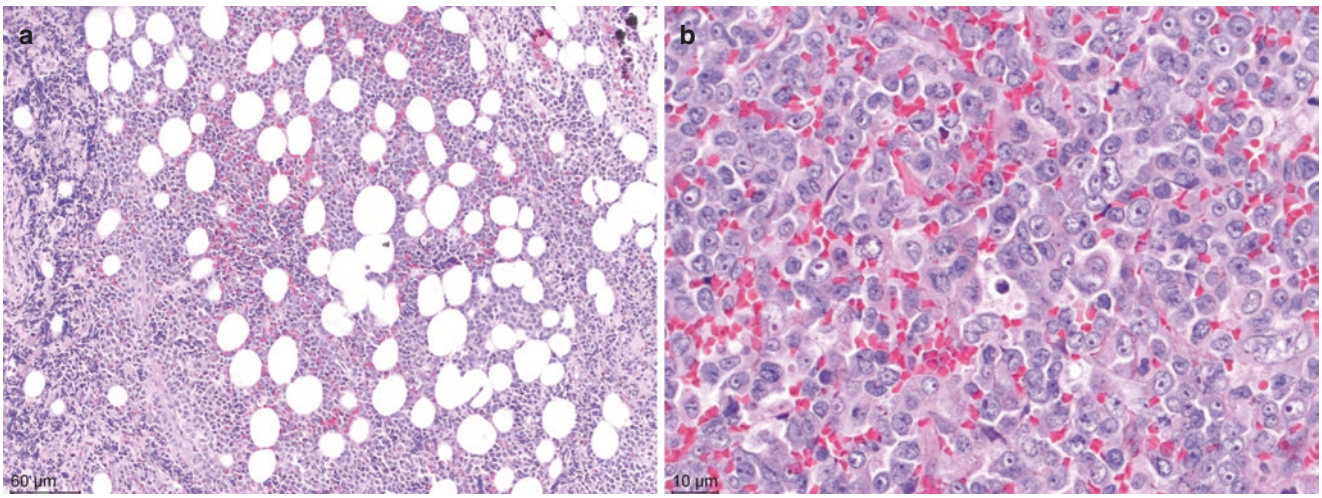


**Fig. 10.16** Extramedullary myeloid sarcoma. (**a**) Diffuse infiltrate of medium to large cells extending from the lymph node into surrounding fibroadipose tissue. (**b**) Higher magnification shows atypical cells with bean-shaped and folded, convoluted nuclei, fine chromatin, and punctate nucleoli consistent with monocytic differentiation

myeloid leukemia (AML). The gingiva is a common site of presentation in the head and neck.
  - In up to 25% of cases, the diagnosis is made in a patient without an established diagnosis of AML. In such cases, the bone marrow may or may not be involved, but the presence of myeloid sarcoma is diagnostic of AML.
  - Patients with EMS who do not currently have marrow disease almost invariably progress to a more typical bone marrow presentation of AML.
- EMS is most commonly seen in AML with myelomonocytic or monocytic differentiation but can be found in any subtype.
  - The cellular morphology recapitulates what is seen in the bone marrow and varies widely (Fig. 10.16).
  - The tumor cells are arranged in sheets and comprise immature myeloid cells with scant to moderate amounts of cytoplasm which may contain granules. The nuclei are round to oval with nuclear folds, fine chromatin, and prominent nucleoli. Other evidence of extramedullary hematopoiesis including maturing granulocytes, erythroid precursors, and megakaryocytes may be present.
- Positive IHC for AML: myeloperoxidase and CD33.
- Positive IHC for myelomonocytic/monocytic subtypes: lysozyme, CD4, CD43, and CD14.
- Negative IHC: CD34 and CD117 are frequently negative in monocytic subtypes.
- Mutations of *NPM1* are found in the majority of myeloid sarcomas and are more prevalent than in AML as a whole.

References: [62, 111–113]

26. *What are the subtypes of posttransplant lymphoproliferative disorders?*

Posttransplant lymphoproliferative disorders (PTLDs) represent a spectrum of lymphoid proliferations found in immunosuppressed patients who have undergone solid organ or bone marrow transplantation. There is a striking 4:1 incidence of PTLD in children compared to adults. The head and neck are involved in 25–40% of PTLD cases. Table 10.21 summarizes the common sites and presentation of head and neck PTLD.
- There are four major classes of PTLD (Table 10.22): nondestructive, polymorphic, monomorphic, and classic Hodgkin lymphoma.
- Nondestructive PTLDs were previously called "early lesions," but new evidence shows that they can occur years after transplantation. The characteristic feature is a lack of architectural effacement.
  - They are morphologically indistinguishable from reactive conditions. A mass lesion and an appropriate clinical history are essential for the diagnosis.
- Polymorphic PTLD shows architectural effacement. EBV is usually positive. There may or may not be evidence of clonality by plasma cell kappa/lambda staining or B-cell clonality.
- Monomorphic PTLD is classified according to the type of lymphoma ordinarily assigned in a non-transplant patient.
  - The most common type is diffuse large B-cell lymphoma (DLBCL).
  - The majority of monomorphic PTLDs are EBV-positive, but a significant number of cases, particularly years after transplant, are EBV-negative.

**Table 10.21** Clinical presentations of PTLD in head and neck sites

| Site | Presentation | Features | Type |
|---|---|---|---|
| Adenoids, tonsils | Snoring, sleep apnea, recurrent infections | Most common site of H/N PTLD<br>Usually children<br>45% of adenotonsillar hyperplasia in posttransplant patients is EBV-related (PTLD) | Usually polyclonal |
| Sinonasal | Epistaxis, nasal polyposis | Clinically mimics invasive fungal disease<br>Polyps usually in children s/p lung transplant for cystic fibrosis | Monoclonal |
| Oral | Ulcers, mass, gingival hyperplasia | May manifest as EBV+ mucocutaneous ulcers | Monoclonal |
| Laryngotracheal | Airway obstruction | Mass | Monoclonal |
| Skin | Red plaques progress to ulcers and nodules | 30% of cutaneous PTLDs occur in the H/N | Monoclonal, T cell > B cell |

**Table 10.22** Subtyping of posttransplant lymphoproliferative disorders

| Class | Subtype | EBV | Clonality | Morphology |
|---|---|---|---|---|
| Nondestructive | Plasmacytic hyperplasia | + | Polyclonal | Interfollicular expansion of plasma cells and small lymphocytes |
| | Infectious mononucleosis (IM) | + | Polyclonal | Interfollicular expansion with mixed infiltrate including numerous immunoblasts, similar to non-PTLD IM |
| | Florid follicular hyperplasia | Usually + | Polyclonal | Similar to typical reactive follicular hyperplasia |
| Destructive | Polymorphic | + | Monoclonal or polyclonal | Effaced architecture<br>Diffuse infiltrate with a range of cells from small lymphocytes to immunoblasts and plasma cells, some with marked atypia (Reed-Sternberg-like). Necrosis is common |
| | Monomorphic | Variable | Monoclonal | Variable, depending upon the class of lymphoma that the PTLD resembles (B- or T-cell lymphomas) |
| | Classic Hodgkin lymphoma | + | n/a | Resembles non-PTLD classic Hodgkin lymphoma |

- EBV-negative cases, mostly DLBCL, are essentially indistinguishable, by morphology and molecular genetics, from non-transplant DLBCL.
- Classic Hodgkin lymphoma may also be diagnosed in the PTLD setting. These cases may be very difficult to distinguish from EBV-positive monomorphic PTLD (diffuse large B-cell lymphoma), which can also show Reed-Sternberg-like cells.
  - The most important distinguishing feature between CHL and monomorphic PTLD is the presence of EBV in the Reed-Sternberg cells.

References: [62, 114–119]

27. *What is the branchial apparatus and why is it important?*

The branchial arches are the embryologic precursors that give rise to the structures of the head, face, neck, and pharynx. Branchial arch anomalies are the second most common congenital lesion after thyroglossal duct remnants. They are responsible for almost 20% of the neck masses seen in children. Branchial anomalies (Table 10.23) may present as cysts, fistulas, or sinuses in the head and neck, and the varied clinical presentations include extensive differential diagnoses.

- 2–3% of branchial anomalies are bilateral and are likely familial.
- The external aspect of each branchial arch is lined by an ectodermal-lined cleft. The internal aspect of the arches is lined by an endodermal layer called a pouch. In normal development, both clefts and pouches are eventually obliterated when the adult structures are formed.
- Knowledge of the branchial apparatus derivatives is helpful in understanding the clinical presentations, complications, and differential diagnoses of branchial arch remnants.
- Most branchial anomalies present as cysts lined by squamous, respiratory or pseudostratified, columnar epithelium.
- Branchial anomalies that result in fistulas and sinuses are more frequently lined by squamous epithelium and typically present with complications of infections and drainage.
- Over 90% of branchial anomalies are from the second branchial cleft which is divided into four types:
  I. Most superficial, along anterior border of the sternocleidomastoid muscle (SCM)
  II. Most common. Anterior to SCM, posterior to submandibular gland, lateral to the carotid
  III. Between the bifurcation of internal and external carotid arteries, lateral to the pharyngeal wall
  IV. Deep to the carotid in the pharyngeal wall

**Table 10.23** Embryologic and clinicopathologic features of branchial anomalies

| | First | Second | Third | Fourth |
|---|---|---|---|---|
| Musculoskeletal structures | Incus, malleus, mandible<br>Muscles of mastication<br>Temporal and palatine bones | Stapes, styloid, superior portion of hyoid bone<br>Facial expression muscles | Stylopharyngeus muscle, inferior portion of hyoid bone | Soft palate muscles, laryngeal cartilages, and thyroid cartilage |
| Derived structures | Middle ear auditory canal, tympanic membrane | Supratonsillar fossa, palatine tonsils | Thymus, inferior parathyroid glands, pyriform sinus | Superior parathyroid glands, C cells of thyroid, ultimobranchial body, apex of pyriform sinus |
| % of all branchial anomalies | 4–10% | 90% | 2–8% | 1–2% |
| Age, gender | Female > Male, cysts in adults, fistulas/sinuses in children | Female > Male | Any age | Any age, usually <10 years old |
| Type of anomaly | Cyst: fistula/sinus = 2:1 | Cyst: fistula/sinus = 3:1 | Cyst, sinus | Cyst, sinus |
| Clinical presentation of anomaly | *C*: preauricular swelling or lower parotid mass<br>EAC mass with a normal TM ±drainage<br>*F/S*: located between EAC and submandibular triangle, usually at the angle of the mandible | *C*: mass at the anterior border of the upper one-third of SCM muscle<br>*F/S:* lateral to the IJ vein at the level of the carotid bifurcation | May present as abscess, usual left side<br>*C/S*: tract starts near pyriform sinus and extends inferiorly.<br>Presents with posterior cervical cyst or abscess | Over 95% occur on left side<br>*C/S*: starts near pyriform sinus, extends inferiorly to anterior neck. Presents with recurrent abscesses in anterior neck, acute thyroiditis, or obstructive airway symptoms usually in children |
| Clinical differential diagnosis | Parotitis<br>Lymphoepithelial cyst | Lymphangioma<br>Cystic LN metastasis<br>Schwannoma | Lymphangioma<br>Cervical thymic cyst<br>TGD cyst<br>Laryngocele<br>Cystic LN metastasis<br>Lymphangioma | |
| Pathology | Work type I: ectodermal only. Squamous-lined cysts without adnexa or cartilage<br>Work type II: ecto- or mesodermal. Squamous lined with adnexa and cartilage | Squamous-lined cyst with lymphoid stroma | Squamous or respiratory-lined cyst or sinus tract with possible thymic or parathyroid tissue | |
| Pathologic differential diagnosis | Dermoid cyst<br>Parotid cyst | Metastatic squamous cell carcinoma | TGD cyst<br>Thymic cyst | TGD cyst<br>Thymic cyst<br>Laryngocele |

*C* cyst, *F* fistula, *S* sinus, *EAC* external ear canal, *IJ* internal jugular, *TM* tympanic membrane, *LN* lymph node, *TGD* thyroglossal duct

- Third and fourth branchial anomalies are very rare and present as cysts or sinuses; fistulas are theoretical but not reported.

References: [120–123]

28. *What are the common benign cystic masses of the neck and how are they characterized?*

Most cystic neck masses (Table 10.24) represent developmental cysts and can present at any time from birth to adulthood. The majority occur before the age of 50. Cystic neck masses beyond middle age should be presumed malignant until proven otherwise.

- The histologic features of the cysts may overlap, making the location an important diagnostic parameter in the pathologic evaluation.
  - These lesions can present as inflamed, infected cysts, and the lining may be attenuated, metaplastic, or ulcerated.
  - Extensive sampling may be required to definitively characterize the cyst.
- Branchial cleft cysts are a single manifestation of a set of anomalies derived from the branchial apparatus.
  - The most common branchial anomaly originates from the second branchial pouch and is included in Table 10.24 as it commonly presents as a cystic neck mass (Fig. 10.17). The remaining branchial anomalies are discussed above in question 27.
  - Nonspecific p16 staining may be seen in up to 50% of branchial cleft cysts, typically in a patchy, focal pattern limited to the superficial layers of the epithelium. This should not prompt a diagnosis of metastatic squamous cell carcinoma (HPV-related).
- Thyroglossal duct (TGD) cysts do not always contain thyroid tissue in the wall. A midline location and characteristic vertical movement on swallowing support the diagnosis.
  - The thyroid tissue present in a TGD cyst (Fig. 10.18) may undergo any of the changes seen

**Table 10.24** Benign cysts of the neck

| | Branchial cleft cyst | Thyroglossal duct cyst | Cervical thymic cyst | Dermoid cyst | Laryngocele | Ranula | Bronchogenic cyst |
|---|---|---|---|---|---|---|---|
| Demographics | Third–fifth decade | Birth to fourth decade | Birth–first decade | <10 years old | Birth to elderly | Third–fourth decade | Birth–sixth decade |
| Neck location | Superior-lateral, anterior border of SCM | Midline, anterior, infrahyoid | Midline > lateral<br>Jaw to sternum | Midline, subcutaneous | Midline, anterior | Submental | Cervical neck |
| Pathogenesis | Most common branchial anomaly, remnant of 2nd branchial arch | TGD fails to involute<br>Occurs anywhere along TGD descent from tongue to thyroid | Implantation of thymic tissue during its embryologic descent | Rare in the neck<br>Arise from pluripotential cells, ecto- or mesoderm derived | Laryngeal ventricle herniates through thyrohyoid membrane | Sublingual duct obstruction with extravasation of duct contents | Diverticulum of foregut during tracheobronchial development |
| Epithelial lining | Stratified squamous, respiratory | Respiratory, squamous | Cuboidal, columnar, squamous | Stratified squamous | Respiratory | None | Respiratory |
| Cyst contents | Watery or mucinous | Clear, mucoid | Clear, serous fluid | Keratinous or sebaceous material | Air | Extravasated mucus | Serous or mucoid |
| Cyst wall morphology | Lymphoid aggregates and germinal centers | Thyroid tissue, malignancy rate of 1–3% | Thymic tissue with Hassall corpuscles and lymphoid tissue<br>±Parathyroid tissue | Adnexal structures, no endodermal tissues | Submucosal tissue of ventricle | Inflamed fibrous and granulation tissue | Seromucinous glands, cartilage, smooth muscle |

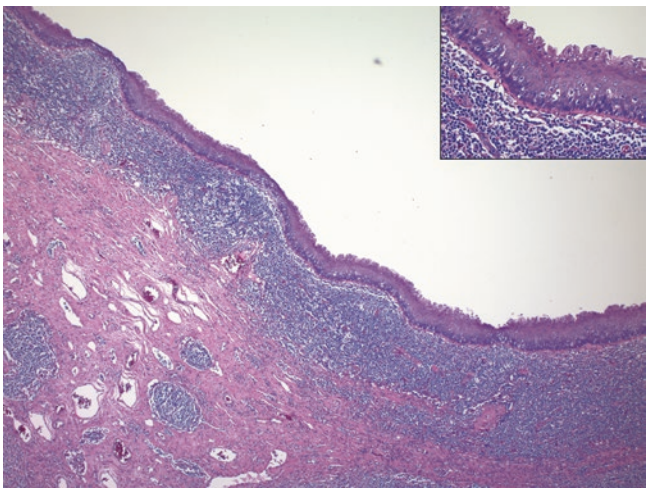

**Fig. 10.17** Branchial cleft cyst. The cyst wall contains lymphoid tissue and is lined by a bland squamous epithelium (inset)

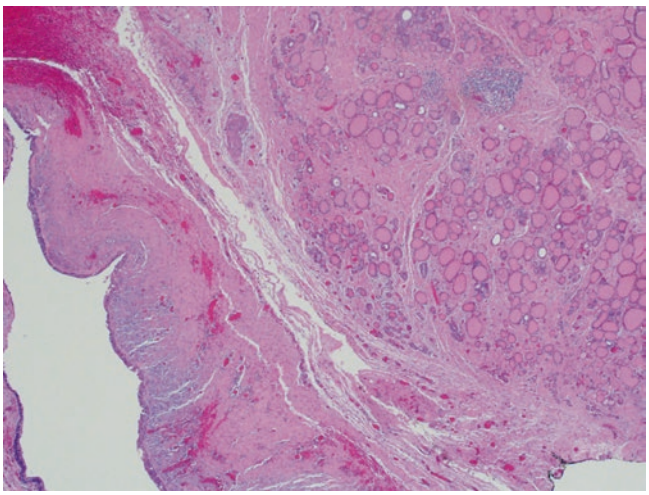

**Fig. 10.18** Thyroglossal duct cyst. The cyst wall is fibrotic and lined by respiratory (lower left) and metaplastic squamous epithelium. Benign thyroid tissue in the wall (upper right) confirms the diagnosis

in the thyroid gland proper, including nodular hyperplasia, thyroiditis, and malignancy.
  - 1–2% of TGD cysts harbor a carcinoma, usually papillary thyroid carcinoma.
- Dermoid cysts are squamous-lined with associated adnexal structures and may be mistaken for an epidermal inclusion cyst (EIC) or a teratoma.
  - EIC is squamous-lined but lacks adnexal structures.
  - A teratoma is a neoplasm, not a developmental abnormality. It often contains tissue from all three embryologic germ layers.

References: [124–135]

29. *What is the pattern of metastasis of primary head and neck malignancies and which can present as a cystic neck mass?*

The most common malignant cysts of the neck represent metastases from two of the most common carcinomas of this region, squamous cell carcinoma and thyroid carcinoma. When a metastasis to a lymph node is suspected, the location of the lymph node offers clues to the possible sites of origin. Table 10.25 summarizes the lymphatic drainage patterns in the head and neck.

**Table 10.25** Lymphatic drainage of head and neck[a]

| Lymph node group | Primary drainage sites | Secondary drainage site |
|---|---|---|
| Parotid/facial | Skin of head and face | |
| I – Submandibular triangle | Floor of mouth<br>Cheek, gingiva<br>Ventral tongue | Oral tongue |
| II – Upper deep cervical (upper jugular incl. jugulodigastric) | Nasopharynx<br>Oral tongue<br>Tongue base<br>Tonsil<br>Larynx<br>Hypopharynx | Floor of mouth<br>Cheek, gingiva |
| III – Middle deep cervical (middle jugular) | Rarely a primary drainage site | Tongue base<br>Tonsil<br>Larynx<br>Hypopharynx |
| IV – Lower deep cervical (lower jugular incl. jugulo-omohyoid) | Involved via overflow from higher levels or skip metastases. Almost always from tongue and tongue base primaries | |
| V – Posterior triangle | Involved via overflow from higher levels | Nasopharynx |
| VI – Central | Thyroid | n/a |
| Supraclavicular | Skin, lung, and distant sites (e.g., GI, prostate, breast) | |

*n/a* not applicable
[a]Primary drainage sites are based on the highest frequency of metastases; secondary sites are the second most frequent level involved

**Table 10.26** Characteristics of malignant cystic neck lesions

| | Cystic papillary thyroid carcinoma | Cystic squamous cell carcinoma metastasis |
|---|---|---|
| Location | Central (if in thyroid), lateral neck (if lymph node metastasis) | Lateral neck |
| Histology | Cyst lined by tumor cells contains oval, pale, grooved nuclei with pseudoinclusions<br>Papillae, colloid, and cyst contents may be present | Cyst lined by atypical squamous epithelium<br>Necrotic debris and keratin debris<br>Unilocular with solid tumor nests in wall |

- Papillary thyroid carcinoma (PTC) and squamous cell carcinoma (SCC) are notorious for producing cystic metastases (Table 10.26). They are a common cause of cystic neck lesions in older adults.
  - Cystic changes are often seen in lymph node metastasis from PTC but are less frequent in the primary tumor.
  - The cyst lining may be atypical or even resemble normal thyroid epithelium.
- Cystic metastasis from an oropharyngeal squamous cell carcinoma may be the initial presentation in some patients.
  - Areas where the lining is attenuated or inflamed can mimic a branchial cleft cyst.

References: [135–146]

**Table 10.27** Soft tissue sarcomas of the head and neck

| Adults | Children |
|---|---|
| Undifferentiated pleomorphic sarcoma<br>Kaposi sarcoma<br>Angiosarcoma<br>Rhabdomyosarcoma, leiomyosarcoma<br>Chondrosarcoma<br>Malignant peripheral nerve sheath tumor | Rhabdomyosarcoma<br>Other unclassified sarcoma<br>Undifferentiated pleomorphic sarcoma<br>Osteosarcoma<br>Ewing sarcoma<br>Malignant peripheral nerve sheath tumor<br>Chondrosarcoma<br>Synovial sarcoma |

**Table 10.28** Peripheral nerve sheath tumors of the head and neck

| | Schwannoma | Neurofibroma |
|---|---|---|
| Head/neck sites by frequency | Skin/scalp, face<br>Neck<br>Oral cavity<br>Parotid<br>Sinonasal tract | Face<br>Gingiva<br>Neck=scalp=tongue<br>Other oral sites |
| Neurofibromatosis association | Type 2 | Type 1 |

30. *Which sarcomas have a predilection for the head and neck?*

Sarcomas are relatively uncommon tumors, accounting for 1% of all malignancies. Approximately 15–20% of sarcomas occur within the head and neck; the paranasal sinuses and neck are the most frequent sites of origin. Approximately 80% of head and neck sarcomas occur in adults, and 10–20% occur in children. Table 10.27 lists the common head and neck sarcomas in adults and children.

- In the head and neck, the most common sarcoma in children is rhabdomyosarcoma.
- In adults, osteosarcoma, angiosarcoma, and undifferentiated pleomorphic sarcoma are most common.

References: [147–150]

31. *Which are the most common peripheral nerve sheath tumors of the head and neck?*

The head and neck is a common site for peripheral nerve sheath tumors. The most common of these are schwannomas and neurofibromas. Both are derived from the neural support cells. Sporadic forms are more common in both tumors, though both may be associated with neurofibromatosis (NF). Mean patient age is in the fourth to fifth decades. Morphologic comparisons of the two tumors is detailed in Chaps. 1 and 5. Table 10.28 compares the clinical features of each as they relate to head and neck sites.

- Schwannomas (Fig. 10.19) are the most common nerve sheath tumor of the head and neck. They are derived from cranial, peripheral, and autonomic nerves. Acoustic schwannomas are derived from the

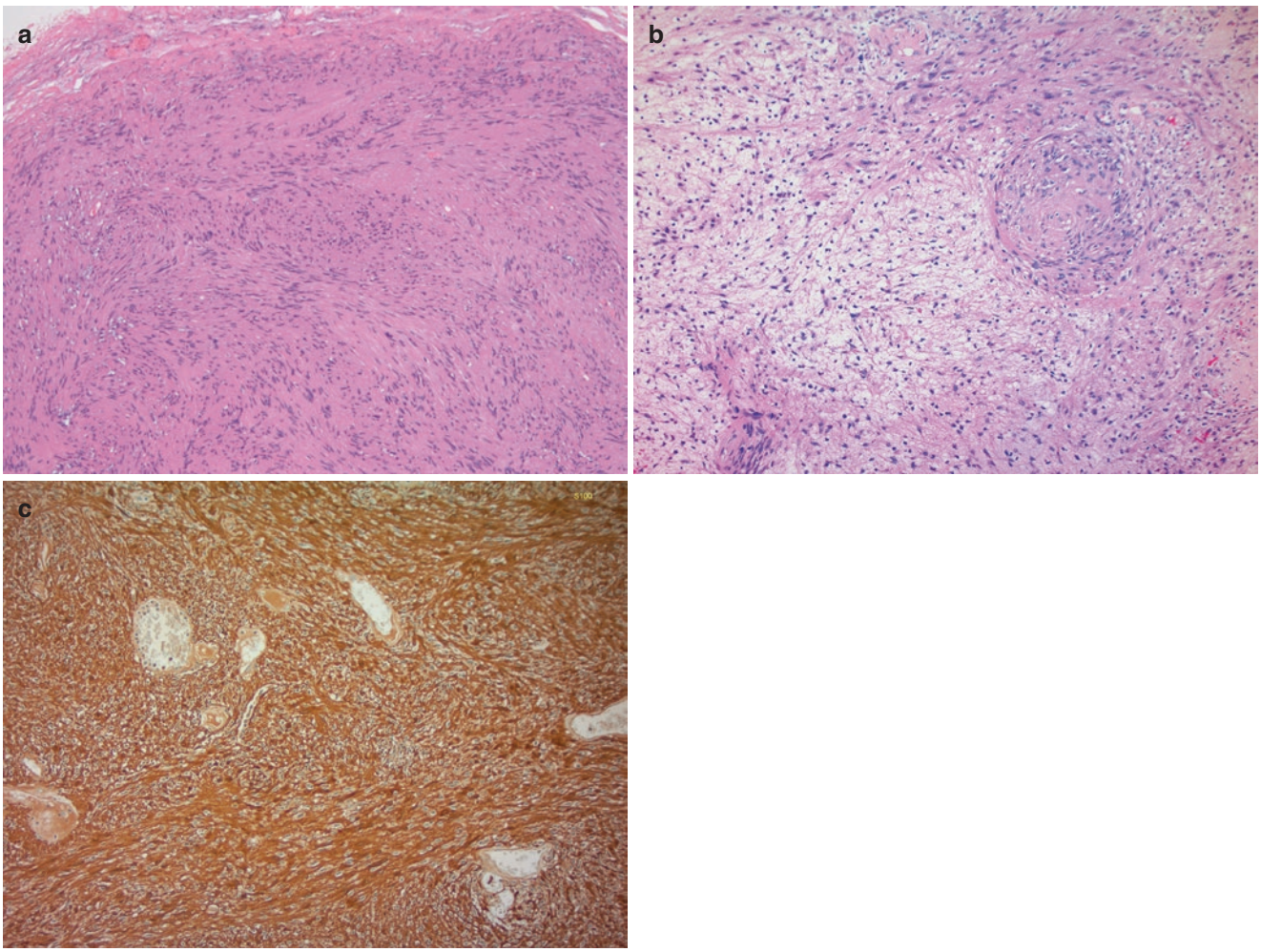


**Fig. 10.19** Schwannoma. (**a**) The well-circumscribed tumor has spindle cells arranged in broad fascicles with areas of vague nuclear palisading. (**b**) Alternating hypercellular and hypocellular foci correspond to Antoni A and B areas, respectively. (**c**) Strong diffuse S100 expression is characteristic

eighth (vestibulocochlear) cranial nerve and have been discussed in detail in Chap. 7.
  - Within the neck, parapharyngeal tumors are common. They usually arise from the vagus nerve and sympathetic nerves of that location.
- The nerve of origin may not be identified in all cases.
  - Schwannomas are more commonly associated with NF type 2 rather than type 1.
  - Patients present with an asymptomatic, enlarging mass related to a nerve.
- Mucosal tumors may be painful, but do not suggest malignancy.
  - Schwannomas are usually encapsulated except in mucosal sites.
- 25% of all neurofibromas occur in the head neck.
  - Neurofibromas are most commonly associated with neurofibromatosis type 1 (NF-1).
  - 2–6% of neurofibromas in NF-1 patients undergo malignant transformation.
  - Submucosal or dermal, circumscribed, nonencapsulated tumors composed of fusiform, spindle, "comma-shaped" nuclei with fine chromatin and tapered ends. Loose, variably myxomatous stroma and wavy collagen bundles are also present (Fig. 10.20).
  - The plexiform variant has tangled bundles of tumor cells with myxoid change, each representing a nerve that is distended by tumor cells (Fig. 10.21).

Malignant peripheral nerve sheath tumors (MPNSTs) are high-grade sarcomas with a recurrence rate of up to 50% and a distant metastatic rate of over 30%. There is a strong association with NF-1.
- MPNST accounts for 5–10% of all soft tissue sarcomas, and head and neck tumors comprise approximately 10% of all MPNST cases.
- 25–40% of MPNSTs arise in the setting of NF-1.

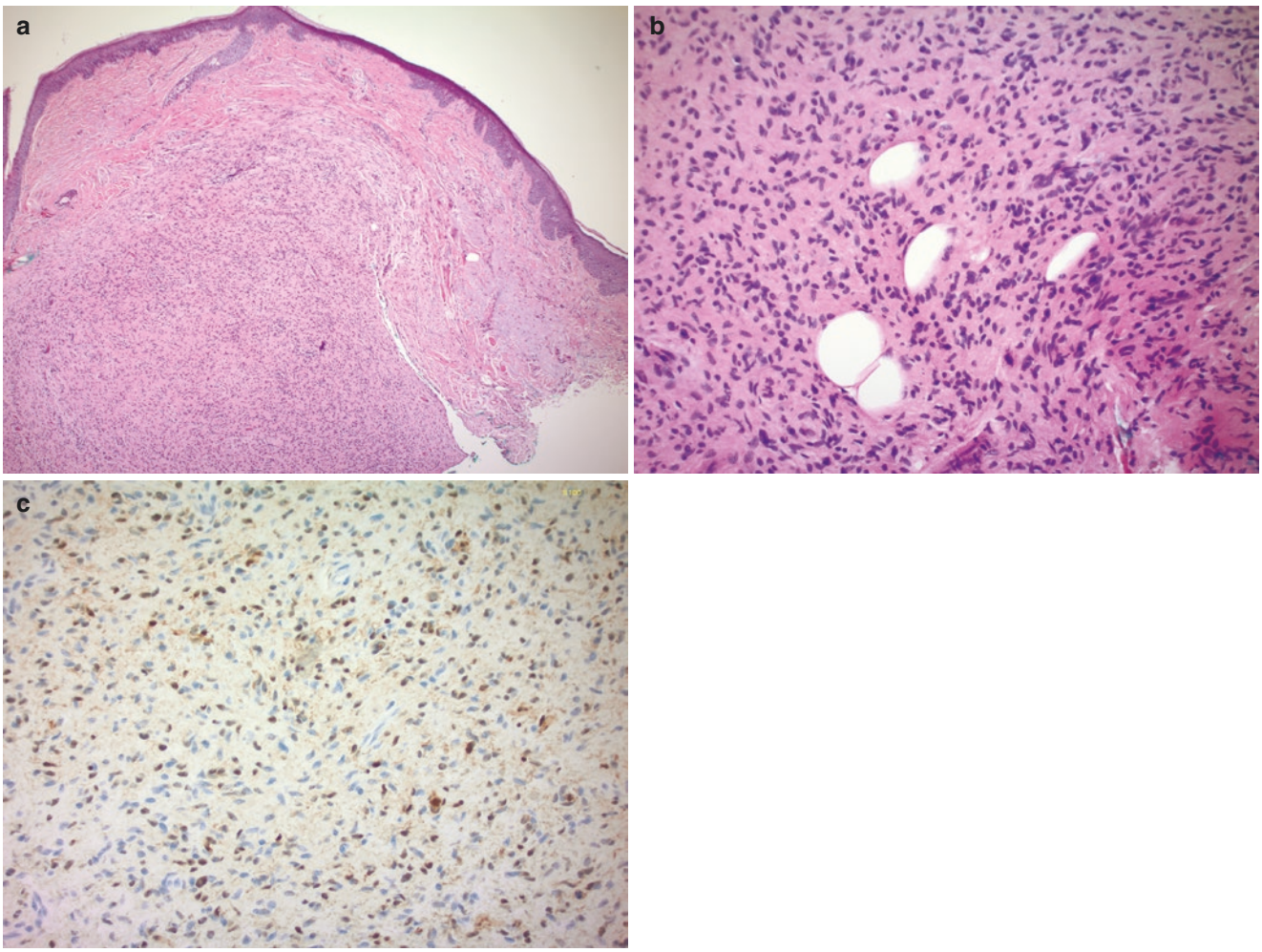


**Fig. 10.20** Neurofibroma. (**a**) A circumscribed, unencapsulated spindle cell tumor is in the dermis. (**b**) Higher magnification shows entrapped fat amidst a proliferation of bland, short spindle cells which are (**c**) focally positive for S100

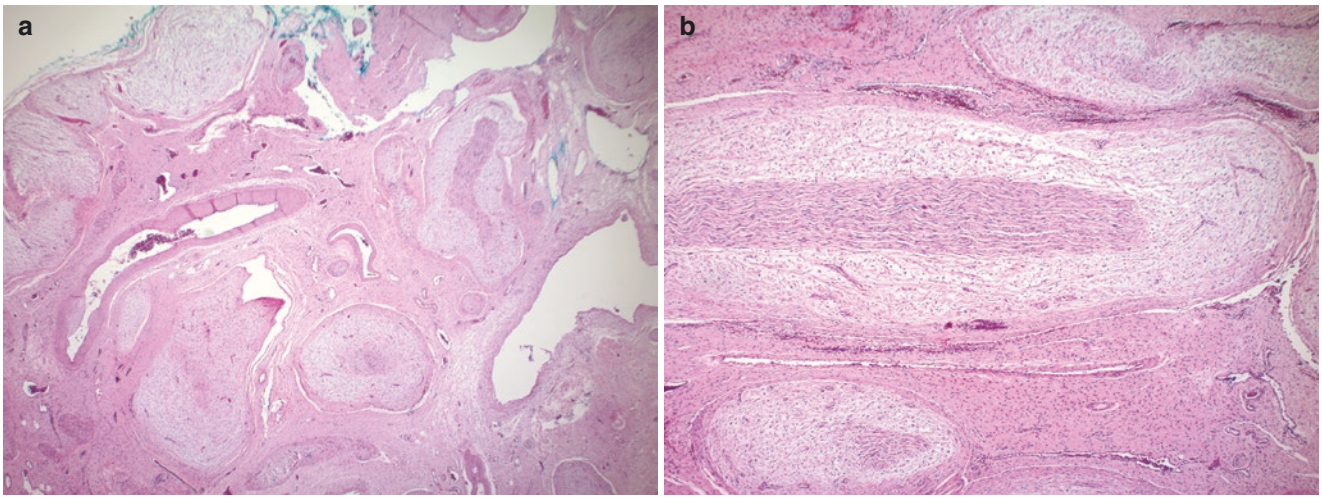


**Fig. 10.21** Plexiform neurofibroma. (**a**) Several nerves are expanded and enveloped by (**b**) a proliferation of short, spindled cells in a myxoid stroma

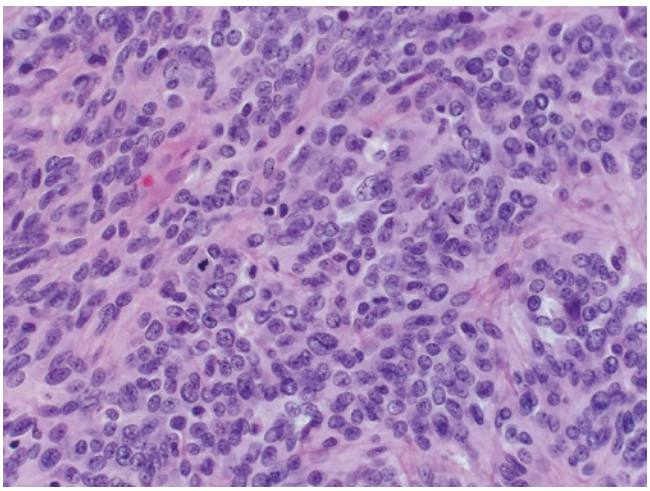

**Fig. 10.22** Malignant peripheral nerve sheath tumor showing short oval to spindled cells with frequent mitoses

- 10% of MPNST are associated with previous radiation therapy
- Average age is in the fifth decade with a wide range from children to the elderly. Patients present with a rapidly enlarging, often painful mass.
- Common head and neck sites include maxilla, mandible, and soft tissues of the neck followed by major salivary glands.
- MPNST is a hypercellular tumor (Fig. 10.22) composed of monomorphic, spindled cells arranged in sweeping, intersecting fascicles. Tumor nuclei are oval, hyperchromatic with inconspicuous nucleoli.
  - The overall fascicular pattern may alternate with more myxoid areas or whorled arrangements.
  - Necrosis and frequent mitoses in excess of 10 per 10 high-power fields can be seen.
  - Heterologous elements including cartilage, bone, and skeletal muscle (Triton) differentiation may be present.
  - A significant proportion of MPNSTs demonstrate homozygous inactivation of polycomb repressive complex 2 (PRC2) which leads to loss of trimethylation at lysine 27 of histone 3.
- This inactivation can be detected with IHC for H3K27me3. Mutated cases are negative. (Of note, melanoma may also show this finding).
- Loss of H3K27me3 is more sensitive in sporadic and radiation-induced MPNSTs.
- Positive IHC: Sox10, S100 (usually not strong).
- Variable IHC staining: Cytokeratin, CD34, EMA.
- Negative IHC: Desmin, INI-1 (epithelioid type), SMA.

References: [150–161]

32. *How are the common muscle tumors of the head and neck categorized?*

Muscle tumors are categorized by their cell of origin and divided into tumors of smooth muscle and skeletal muscle derivation.

- Rhabdomyomas are benign smooth muscle tumors of skeletal muscle origin. Among the extracardiac rhabdomyomas, over 90% occur in the head and neck.
  - There is a 3:1 male predominance.
  - The most common head and neck sites include tongue base, pharynx, and floor of mouth.
  - A detailed description of rhabdomyomas is given in Chap. 1.
- Rhabdomyosarcoma is of skeletal muscle origin and accounts for 4% of all sarcomas.
  - 40% of all rhabdomyosarcomas occur in the head and neck.
  - Almost 70% of rhabdomyosarcomas occur in patients18 years old and younger; it is the most common sarcoma in children.
  - The most common head and neck locations of RMS, in order of frequency, are:
    1. Orbit
    2. Nasopharynx
    3. Sinonasal tract (nasal cavity>maxillary, ethmoid)
  - There are four morphologic subtypes (Table 10.29) of RMS: embryonal, alveolar (Fig. 10.23), pleomorphic, and spindle cell.
- The embryonal type has subtypes including botryoid variant.
- The pleomorphic type is more common in the extremities and rarely occurs in the head and neck.
- In the pediatric age group, botryoid and spindled types have the best prognosis, and the alveolar type has the worst prognosis.
- Adult RMS has a uniformly poor prognosis with 5-year survival rates ranging from 35% to 50%.
- Sinus tumors carry the worst prognosis when compared to other sites, and the orbit carries the best prognosis.
- Smooth muscle tumors of the head and neck are primarily derived from the smooth muscle of vessel walls or erector pili muscles in the skin. Benign smooth muscle tumors are leiomyomas. Common head and neck sites include the larynx, lips, tongue, and palate. Chapter 1 includes a description of angioleiomyomas.
- Leiomyosarcoma (LMS) is a malignant smooth muscle tumor. They are uncommon tumors, constituting approximately 5% of all sarcomas with only 4% occurring in the head and neck. The most common sites within the head and neck are the oral cavity,

**Table 10.29** Clinicopathologic features of rhabdomyosarcomas

| | Embryonal | Alveolar | Spindle cell |
|---|---|---|---|
| Patient | Children | Children | Adults |
| % of all H/N RMS | 50% | 25% | 5% of adult cases |
| Most common H/N sites | Nose, NP, ear, eye | Sinonasal | Deep soft tissues |
| Variants | Classic, botryoid, anaplastic | Classic, solid | Sclerosing |
| Morphology | Primitive, small oval to spindle or stellate cells with hyperchromatic nuclei, scant cytoplasm<br>Rhabdomyoblasts ±strap cells<br>Myxoid stroma<br>Botryoid: hypercellular zone subjacent to epithelium (cambium layer)<br>Anaplastic: large, severely atypical cells with lobulated nuclei | Primitive, small oval to spindle cells with hyperchromatic nuclei, scant cytoplasm<br>Nests of dyshesive cells form central, pseudoglandular spaces separated by fibrous septa<br>Rhabdomyoblasts present, strap cells rare<br>Solid variant is commonly translocation negative | Thin spindled cells with cigar-shaped nuclei in a collagenous stroma<br>Fascicular growth pattern<br>Sclerosing: nests, cords, trabeculae of cells separated by hyalinizing stroma<br>Rare rhabdomyoblasts |
| Desmin | Positive | Positive | Focal |
| MyoD1 | Variable | Positive | Strong |
| Myogenin | Variable | Diffuse, strong | Negative/focal |
| Other positive IHC | MSA | PAX5 (only alveolar type) | MSA |
| Negative IHC | S100, CK, SMA, CD99, CD45, FLI-1 | | |
| Genetics | Trisomy 8 | t(2;13) PAX3-FOXO1 | MyoD1 p.L122R mutations |
| | LOH at 11p15.5 | t(1;13) PAX7-FOXO1 | ±PIK3CA mutations |

*H/N* head and neck, *RMS* rhabdomyosarcoma, *NP* nasopharynx, *MSA* muscle-specific actin, *SMA* smooth muscle actin, *LOH* loss of heterozygosity

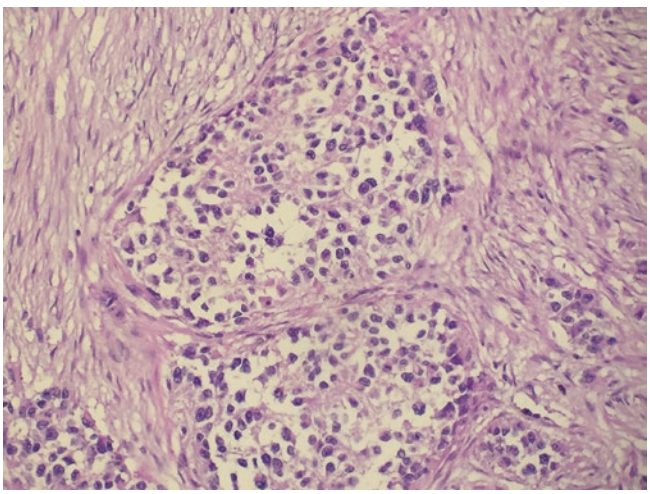

**Fig. 10.23** Alveolar rhabdomyosarcoma. Nests of primitive, small, hyperchromatic cells are loosely cohesive and present in a fibrous stroma

nasal cavity and paranasal sinuses, skin, and larynx. There is no sex predilection and patients are commonly around 50–60 years of age.

- Grossly, leiomyosarcomas are well-circumscribed and unencapsulated, with a smooth cut surface that is tan-white and fibrous.
- Microscopically, they are composed of fascicular bundles of spindle-shaped cells with central cigar-shaped nuclei with blunt ends, perinuclear vacuoles, and eosinophilic cytoplasm. Multinucleated giant cells and nuclear palisading are common. Nuclei may range from monotonous and bland to more pleomorphic.
- Greater than 2 mitotic figures per 10 high-power fields indicates malignancy, especially if atypia or necrosis is present.
- Positive IHC: SMA, desmin, caldesmon.
- Patchy expression for cytokeratin can be seen.
  - Metastases occur via hematogenous spread and most commonly involve the lungs.

References: [148, 160, 162–176]

33. *What are the common sarcomas of the head and neck and which tumors are in the differential diagnosis?*

Malignant fibroblastic tumors of the head and neck include a set of rare entities that together comprise the most common malignant sarcomas of this region. According to the national US cancer databases (SEER) between 1973 and 2010, malignant fibrous histiocytoma (MFH) is the most common sarcoma of the head and neck accounting for 31% of all head and neck sarcomas. We now know this includes tumors diagnosed today as fibrosarcoma and undifferentiated pleomorphic sarcoma (UPS). This group of tumors shows no specific mesenchymal differentiation and are characterized by a cellular, typically spindled cell proliferation. They can show overlapping morphologic and immunohistochemical features (Table 10.30).

**Table 10.30** Malignant fibroblastic tumors of the head and neck

| | MPNST | Synovial sarcoma | Fibrosarcoma | UPS |
|---|---|---|---|---|
| Most common H/N sites | Maxilla, mandible, neck<br>Sinonasal<br>Salivary gland | Neck/parapharyngeal space<br>Pharynx<br>Oral cavity<br>Larynx | Sinonasal<br>Neck | Neck<br>Orbit<br>Sinonasal, oral cavity<br>Temporal bone/ear |
| % of all adult H/N sarcomas | 5% | <1% | nd | 30–40% |
| % which occur in HN | 10–15% | 3–10% | nd | 5–10% |
| Age (years) | 50 | Young, 20–30 | 50–60 | 50–60 |
| Morphology | Variable patterns (herringbone, whorls, fascicles) and cell types (spindle, epithelioid, pleomorphic)<br>Alternating myxoid and cellular areas<br>Perivascular hypercellularity<br>Wavy, elongated nuclei<br>±Mitoses and necrosis<br>±Heterologous elements | Short hypercellular fascicles of small spindle cells<br>Short to elongated oval nuclei, inconspicuous nucleoli, scant cytoplasm<br>Alternating hypocellular areas<br>Minimal atypia<br>Variable myxoid, hyaline, or collagenous stroma<br>Variable amounts of epithelium<br>±Branching vessels, ±nuclear palisading | Hypercellular tumor in herringbone, fascicular pattern<br>Hyperchromatic spindle cells<br>No more than moderate pleomorphism<br>Variable amounts of collagenous stroma | Cells arranged in storiform and haphazard patterns<br>Plump, pleomorphic spindled cells admixed with large histiocytic cells<br>Delicate collagenous stroma<br>Slit-like vessels<br>Numerous mitoses<br>±Giant cells |
| Positive IHC | Focal S100, SOX10, focal TLE1, var EMA, var CK | EMA, CK7, CK19, str (n) TLE, diffuse BCL12, var (c)CD99, var CD56, var S100 | str vimentin, wk SMA only | Vimentin |
| Negative IHC | CK7, CK19, H3K27me3 | Desmin, SMA, S100, CD34, SOX10 | CD34, S100, CK, EMA | All lineage-specific markers |
| Genetics | Loss of H3K27me3 | SSY-SSX1, 2, or 4 t(X;18) | nd | nd |

*EMA* epithelial membrane antigen, *CK* cytokeratin, *diff* diffuse, *str* strong, *wk.* weak, *var.* variable, *n* nuclear, *c* cytoplasmic, *nd* no data

- Synovial sarcoma (SS) is largely a tumor of young patients. It has two histomorphologic types.
  - 3–10% arise in the head and neck (hypopharynx and retropharynx).
  - Monophasic SS is composed of monotonous spindled cells and is the most common subtype.
  - Biphasic SS shows epithelial differentiation in addition to the spindled component.
- The epithelioid cells may form pseudoglandular cavities filled with mucin, which stains positively with Alcian blue, mucicarmine, and periodic acid-Schiff (PAS) stains.
  - Calcifications are present in over half of the cases and may be a helpful radiographic clue.
- Malignant peripheral nerve sheath tumor (see question 31) is not a fibroblastic tumor but is considered here in the differential diagnosis.
- Fibrosarcoma is largely a diagnosis of exclusion. There is an adult type and a fetal type. Over the years, the literature describes several cases that are best classified into MPNST, solitary fibrous tumor (SFT), or synovial sarcoma. As a result, its true incidence is not clear.
  - Infantile fibrosarcoma presents as a fast-growing mass in children less than a year old. The soft tissues of the distal extremities, head, and neck are commonly affected.
- Sheets of spindle-shaped, monomorphic fibroblasts in a fascicular or herringbone pattern with thin-walled hemangiopericytoma-like vessels (Fig. 10.24)
- Negative IHC: neural, epithelial, and muscle markers
- Genetics: t(12;15)(p13;q25) producing ETV6-NTRK3 fusion gene
- Prognosis is favorable with recurrence occurring in a minority of cases
- Undifferentiated pleomorphic sarcoma (UPS) is a high-grade sarcoma which by definition lacks evidence of lineage-specific differentiation. It is the most common soft tissue sarcoma in adults. It is associated with previous radiation therapy.

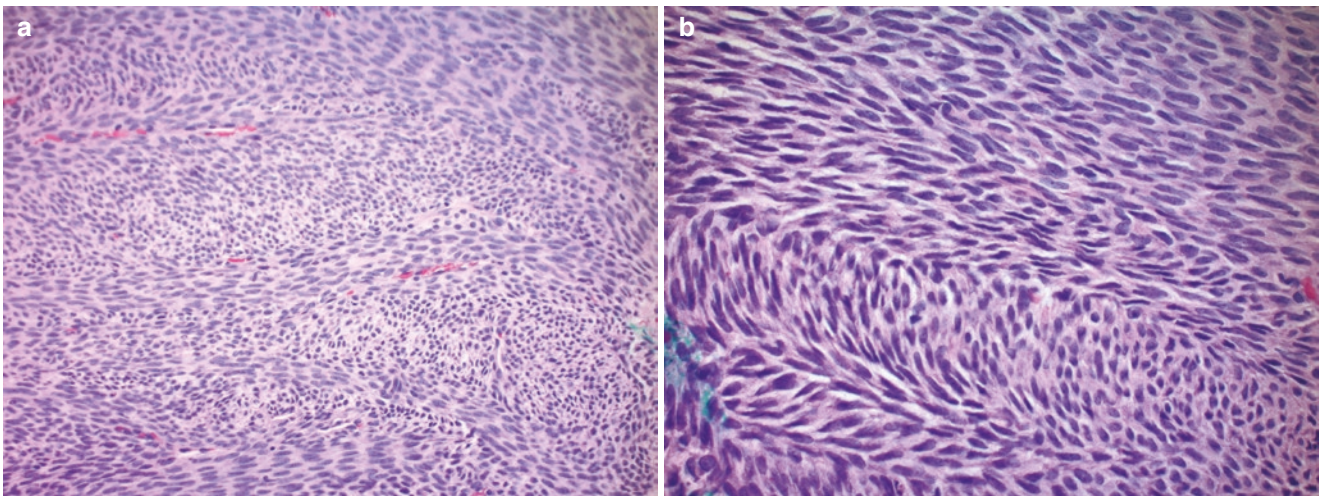


**Fig. 10.24** Fibrosarcoma. (**a**) The tumor is densely cellular and arranged in narrow, intersecting fascicles with a vague herringbone pattern. (**b**) The neoplastic cells contain oval nuclei with blunt ends, fine chromatin, and scant, eosinophilic cytoplasm

- Spindle cell carcinoma and spindle cell melanoma should be considered in the differential diagnosis of spindle cell malignancies of the head and neck. Keratins and melanocytic markers should be included in the immunohistochemical workup of spindle cell tumors of the head and neck.

References: [151, 155, 177–183]

34. *What are the clinicopathologic features of the common benign fibroblastic lesions of the head and neck?*

Benign fibroblastic lesions include a range of neoplastic and nonneoplastic entities. They are all characterized by a bland spindle cell proliferation with no specific mesenchymal differentiation.

- Fibromas of the head and neck (Table 10.31) occur at various sites and clinical settings. They are reactive, nonneoplastic, bland fibroblastic proliferations with a tendency to occur in superficial, subcutaneous, and mucosal locations. Most are thought to represent reactive, fibroinflammatory, and variably scarring processes. Their growth is usually self-limited. Fibromas are also discussed in the chapters corresponding to their specific sites.
- The fibroblastic tumors discussed here also occur in various locations throughout the head and neck. These lesions usually present as an enlarging mass and may show infiltrative growth. Features of solitary fibrous tumor (Fig. 10.25), nodular fasciitis (Fig. 10.26), aggressive fibromatosis, and inflammatory myofibroblastic tumor (Fig. 10.27) are summarized in Table 10.32.

References: [184–208]

35. *Which fatty tumors are found in the head and neck and how are they diagnosed?*

The most common fatty tumor of the head and neck is a lipoma. While there are several histologic types of lipomas, the ordinary and spindle cell lipomas are the most common.

**Table 10.31** Fibromas of the head and neck

| Site | Fibroma |
|---|---|
| Subcutaneous posterior neck | Nuchal fibroma |
| Tongue, cheek, gingiva | Irritation/traumatic fibroma<br>Giant cell fibroma |
| Buccal vestibule, floor of mouth | Epulis fissuratum |
| Gingiva | Peripheral ossifying fibromas |
| Nasal vestibule, floor, septum | Nasal fibromas |

- Approximately 15% of all lipomas occur in the head and neck.
  - Most tumors arise in the subcutaneous tissues and rarely intramuscularly.
- Ordinary lipomas are the most common subtype and consist of variably encapsulated mature adipose tissue.
- Spindle cell/pleomorphic lipoma (Fig. 10.28) is the second most common type of lipoma seen in the head and neck. These are most commonly seen in the posterior neck/upper back of older men.
  - Histologically, spindle cell lipomas vary from largely adipocytic to predominately spindled. The spindle cells have long cytoplasmic processes, with bland nuclei in a variably myxoid stroma often containing ropey collagen bundles. Variable amounts of adipocytes are admixed with the spindle cells.
  - Pleomorphic lipomas are composed of small, round to spindled cells with hyperchromatic nuclei. Scattered multinucleated giants cells with nuclei arranged in a floret-like configuration are the clue to the diagnosis.
  - Mitoses and necrosis are absent. These two entities are on a spectrum and one lesion may show both classic histologies.

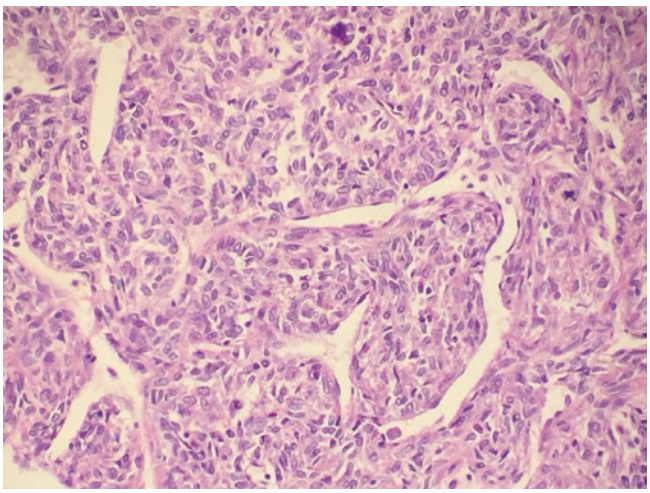

**Fig. 10.25** Solitary fibrous tumor. The tumor cells are ovoid to spindle-shaped fibroblastic cells with vesicular nuclei. The vasculature shows a branching "staghorn" pattern

- Liposarcoma (LPS) represents about 35% of all sarcomas, and 2–9% of them occur in the head and neck. Patients are typically male in the fourth to fifth decades of life, slightly younger than LPS patients with infraclavicular tumors.
  - The most common sites are:
    - Skin, face, neck 85%
    - Pharynx, larynx 5%
    - Oral cavity 4%
  - The four main subtypes of LPS (Table 10.33) are well differentiated (WDLPS), myxoid (including round cell), pleomorphic, and dedifferentiated.
- Lipoblasts are intermediate to small cells with distinct cell borders, a central hyperchromatic nucleus, and a vacuolated cytoplasm. The vacuoles may be rare or numerous and typically indent the nucleus. They are neither required nor specific for the diagnosis of liposarcoma.

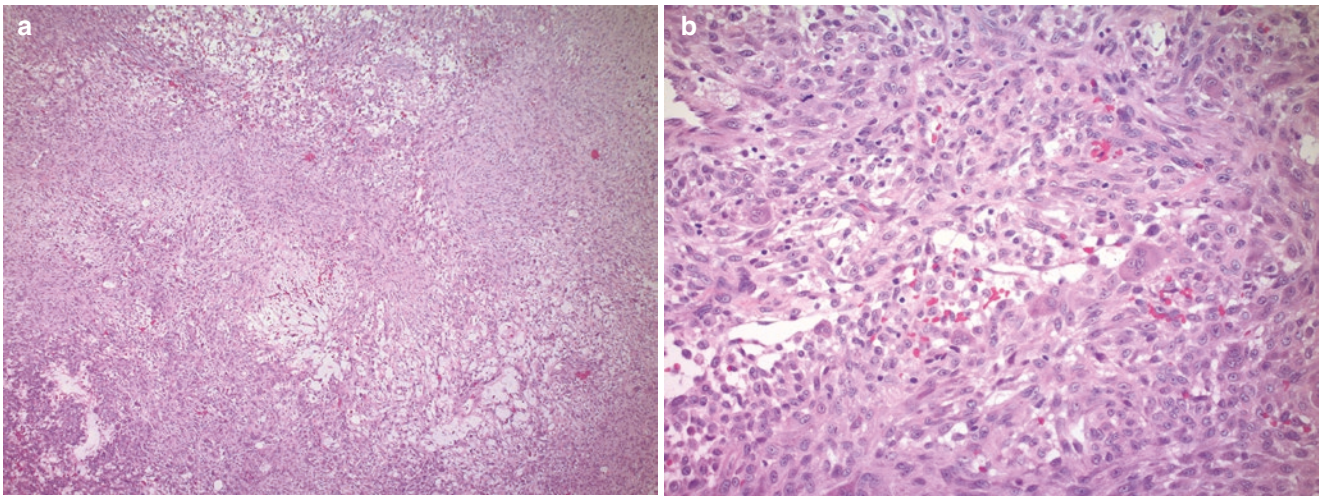


**Fig. 10.26** Nodular fasciitis. (**a**) The heterogeneous pattern of haphazardly arranged spindled cells with alternating hyper- and hypocellular areas and foci of myxoid change are present. (**b**) The cells are plump with vesicular nuclei, conspicuous nucleoli, and scattered mitoses. Chronic inflammation and extravasated red blood cells are also present

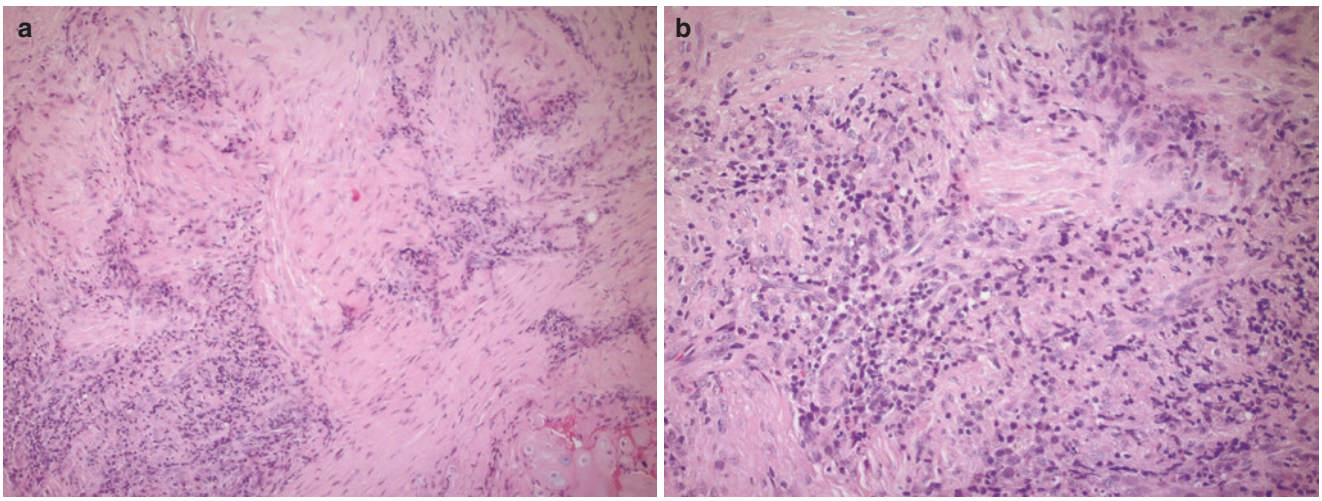


**Fig. 10.27** Inflammatory myofibroblastic tumor of the larynx. (**a**) Dense, sclerotic fibroinflammatory process focally involves cartilage (lower right). (**b**) The inflammatory infiltrate is predominantly lymphoplasmacytic with scattered neutrophils and eosinophils

**Table 10.32** Benign fibroblastic tumors of the head and neck

| | Solitary fibrous tumor | Nodular fasciitis | Aggressive fibromatosis | Inflammatory myofibroblastic tumor |
|---|---|---|---|---|
| H/N sites | Sinonasal<br>Orbit<br>Oral cavity<br>Salivary gland | Soft tissues<br>Oral cavity<br>Sinonasal tract | Mandible, maxilla, neck<br>Oral cavity<br>Sinuses | Larynx (glottis)<br>Oral cavity (cheek, tongue)<br>Sinonasal tract (maxilla)<br>Pharynx |
| % which occur in H/N | 5–6% | 15% | 12–20% of extra-abdominal cases | 10% of extrapulmonary IMFT |
| Clinical | Infiltrative growth | Rapidly growing mass, circumscribed<br>May superficially involve skeletal muscle<br>H/N sites are rarely related to trauma | Presents with a painless mass | Presentation depends on site: stridor, congestion, mass |
| Patient | Fifth decade | Median 37 years | Mean 17 years<br>20–25% of extra-abdominal cases occur in children | M > F, children, and adults, 30–50 years old |
| Morphology | Bland, oval to spindled cells arranged haphazardly in a patternless pattern<br>Low to moderate cellularity<br>Hypo-/hypercellular areas<br>Mild atypia, variable mitoses <4/10 hpf<br>Hyalinized, collagenous stroma | Plump spindle to stellate cells arranged in short fascicles or haphazard pattern<br>Moderate amount of cytoplasm, feathery appearance<br>Loose, myxoid stroma<br>Alternating hyper-/hypocellular areas<br>Minimal or no atypia<br>Mitoses may be frequent<br>Inflammation and extravasated RBCs<br>±Giant cells | Monotonous spindle cells in a dense collagenous stroma<br>Nuclei are small, bipolar, with pointed ends<br>Cells are arranged in broad, sweeping fascicles<br>Low cellularity<br>No mitoses, necrosis, or pleomorphism | Bland, stellate to plump spindled cells in a variably inflamed background<br>May have nodular fasciitis-like areas or fascicular pattern<br>Plasma cells, lymphocytes, neutrophils, eosinophils<br>Stroma may be myxoid or collagenous with scar-like areas<br>Variable mitotic activity usually <10/hpf |
| Behavior | Up to 25% of H/N cases recur<br>Malignant forms have more pleomorphism and increased mitoses | Rarely recurs | High recurrence rates<br>Oral and sinonasal tumors may be lethal<br>Associated with familial adenomatous polyposis | Up to 20% recurrence rate |
| Positive IHC | STAT6, CD34, focal BCL2, focal CD99 | SMA, vimentin, MSA, KP-1 | (n)ß-catenin, vimentin, focal SMA | Variable ALK-1, CK |
| Negative IHC | S100, SMA, EMA | Desmin, CD34, S100 | Desmin, S100 | Caldesmon, CD34, S100, desmin, myoglobin |
| Genetics | Fusion NAB2-STAT6 | None | Trisomy 8 and 12, mutations on chr. 5, ß-catenin, APC genes | 50% have ALK rearrangements |

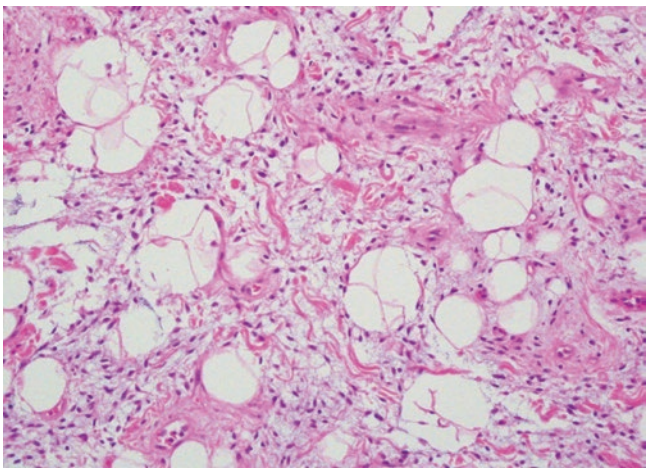

**Fig. 10.28** Spindle cell lipoma. Bland spindle cells in a variably myxoid and collagenous stroma with a variable amount of mature adipocytes and ropey collagen

- In contrast to infraclavicular tumors, the dedifferentiated subtype is among the least common in the head and neck.
  - Disease-specific and overall 5-year survival rates for LPS range from 73% to 83% and 63–66%, respectively.
- Gerry et al. noted that head and neck LPS patients were generally younger, presented at a lower stage, and had better overall and disease-specific survival when compared to infraclavicular counterparts.
- Worse overall survival rates were noted for patients with laryngeal and salivary gland LPS.

References: [150, 209–221]

**Table 10.33** Pathologic features of liposarcomas

| | WDLPS | Myxoid/round cell | Pleomorphic |
|---|---|---|---|
| % H/N LPS | 40% | 30–35% | 10% |
| Morphology | Mature-appearing adipocytes and prominent fibrous bands, scattered adipocytes and stromal cells with atypical, hyperchromatic nuclei<br>Areas of myxoid change may be present<br>Lipoblasts or fat necrosis with or without pseudolipoblasts may be seen<br>Metaplastic bone, cartilage, or muscle may be seen | Lobules of uniform mesenchymal cells admixed with signet ring-like adipocytes in a myxoid background with plexiform capillary network<br>Round cell areas have solid sheets of uniformly small, round blue cells with infrequent lipoblasts and scant myxoid stroma (>5% round cell areas = high grade) | UPS-like tumor with scattered mono- and multinucleate giant cells and extremely bizarre pleomorphic cells. Adipocytes may be only focal |
| IHC positive | MDM2+, CDK4+, p16+, S100+, CD34+ in fibrous portions | Vimentin+, S100+, MDM2–, CD34– | Var S100+, CD34+, CD68+, SMA+ |
| Survival rates | >90%, unless dedifferentiation occurs | >90%/60% | 50% |
| Genetics | Amplification of MDM2+ | t(12;16) (q13;p11) (results in a FUS/DDIT3 fusion protein) | High chromosome counts and complex structural rearrangements<br>MDM2– |

**Table 10.34** Vascular lesions of the head and neck by site

| | Lesion | Site |
|---|---|---|
| Benign | Vascular malformations/hemangiomas | Skin of head and neck, larynx, face |
| | Lobular capillary hemangioma | Oral cavity, nasal cavity |
| | Glomus tumor | Nasal cavity, exceedingly rare in H/N |
| | Angiofibroma | Nasopharynx |
| | Glomangiopericytoma | Sinonasal tract |
| Malignant | Kaposi sarcoma | Tongue, skin, |
| | Angiosarcoma | Scalp |

**Table 10.35** Classification of benign vascular lesions

| | Hemangioma | Vascular malformation | |
|---|---|---|---|
| Age at presentation | Neonatal period, 30% at birth | Always at birth but may present later in life | |
| | F > M | F = M | |
| Clinical course | Proliferates in first year of life then typically involutes | Slow expansion as patient grows | |
| Histogenesis | Neoplasms with endothelial hyperplasia | Developmental anomalies | |
| Clinical classification | Classified by depth:<br>Superficial – papillary dermis<br>Deep – reticular dermis/subcutis<br>Compound – have both superficial and deep components | Low flow | Classified by vessel type and flow parameters: |
| | | | Capillary/Cavernous – postcapillary venules of the dermis. Graded according to amount of ectasia |
| | | | Venous – no uniform muscular layer, flat endothelium, ±phleboliths<br>Lymphatic – multiple, fluid-filled spaces which communicate with larger lymphatics |
| | | High flow | Arteriovenous – dilated capillary bed that gets increased flow causing hypertrophy of nearby arteries and veins |

36. *What are the common benign vascular tumors of the head and neck and how are they characterized?*

In the head and neck, vascular lesions show a strong preference for specific sites (Table 10.34). Benign vascular lesions in this location include congenital and perinatal lesions (Table 10.35), acquired lesions, and neoplasms (Fig. 10.29).

- Hemangiomas are vascular tumors characterized by the proliferation of vessels and endothelium. Most hemangiomas of the head and neck are congenital or develop in the perinatal period.
  - They are the most common tumor of infancy and show a 3:1 female predominance.
  - 60% of hemangiomas occur in the head and neck.
- Vascular malformations are developmental anomalies classified by the type of vessel and the flow characteristics.
  - The arteriovenous malformation is the least common type and may show shunting of blood flow and pulsatile masses. They are common in the midfacial region, ears, and cheek.

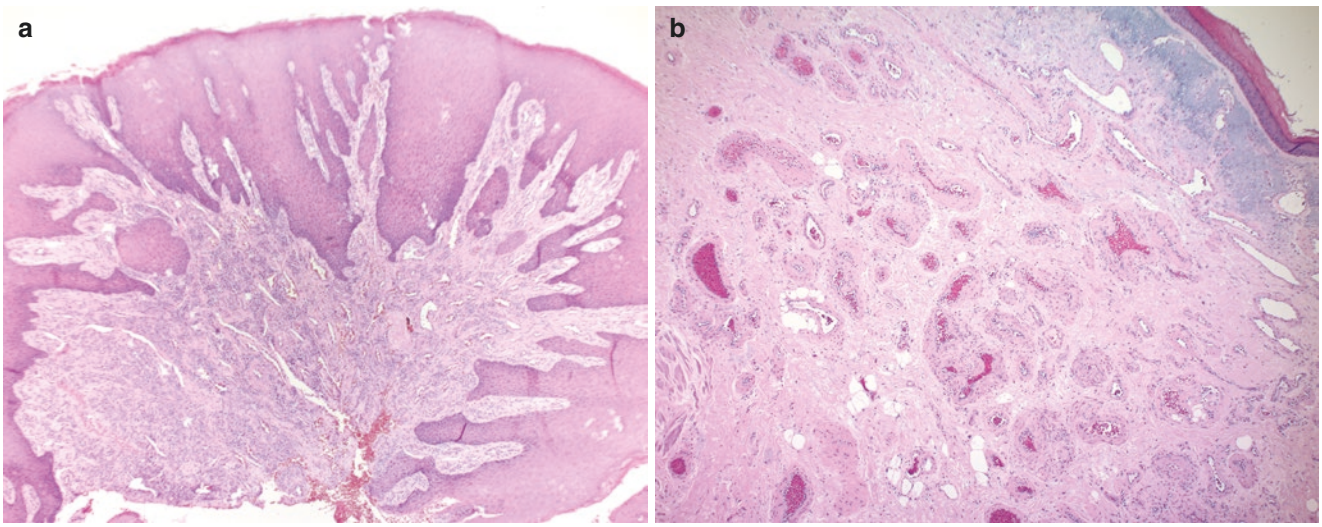


**Fig. 10.29** Benign vascular lesions. (**a**) Lobular capillary hemangioma of the oral cavity shows an endothelial proliferation creating small vessels arranged in a lobular architecture with chronic inflammation. (**b**) Vascular malformation of lip with variably sized muscular vessels

- Lobular capillary hemangiomas are acquired vascular tumors primarily of adults. There is a 2:1 female predominance in adults with an average age of 40 years old. Pediatric cases show a striking male predominance.
  - Tumors are characterized by a lobular proliferation of capillaries with bland, plump endothelium in a loose, collagenous stroma. Vascular spaces may be ectatic or indistinct. Mitoses may be seen, but atypical forms and necrosis are absent. Inflammation is common, and the overlying skin or mucosa may be ulcerated.
  - 30% occur in the head and neck with the remainder arising in the trunk and extremities.
- Common head and neck sites in order of frequency include lip, cheek, other intraoral sites, and nasal cavity.
- Mucosal lobular capillary hemangiomas are common in pregnant women.
- Glomus tumors are exceedingly rare tumors derived from pericytic myoid cells. They are rare in the head and neck and are more commonly seen in the skin of the extremities.
  - The tumors are composed of nests and sheets of small, bland, epithelioid cells with round nuclei and a scant to moderate amount of pale to eosinophilic cytoplasm. Variably sized vessels are scattered throughout the tumor.
- Angiofibromas occur almost exclusively in the nasopharynx and are discussed in detail in Chap. 2.
- Glomangiopericytomas occur almost exclusively in the sinonasal tract and are discussed in detail in Chap. 4.

References: [222–225]

37. *Which are the common malignant vascular tumors of the head and neck?*

Angiosarcoma (AS) is a malignant vascular tumor. In the head and neck, cutaneous angiosarcomas and Kaposi sarcoma are the most common malignant vascular tumors.

- The head and neck region is the most common site among cutaneous angiosarcomas (40%).
- The skin of the scalp and neck are the most frequent sites accounting for over 80% of cases. There is a slight male predominance, and the mean age is 60 years old.
  - Non-cutaneous sites are very rare, and reported cases include the larynx and sinonasal tract.
- Various risk factors for angiosarcoma have been identified:
  1. Prior radiation
  2. Polyvinyl chloride, arsenic, and thorium dioxide exposure
  3. Chronic lymphedema
  4. Familial syndromes
  5. Possible ultraviolet light exposure
- AS is grossly classified as nodular, ulcerative, or macular. Histologic findings show a highly infiltrative proliferation of spindle or epithelioid cells with variably abortive to well-developed, complex vascular channels (Fig. 10.30). Intracytoplasmic lumina with red blood cells may be seen. Cells can show mild atypia to marked pleomorphisms with increased mitotic activity and necrosis. Higher-grade lesions may show minimal vascular differentiation.
  - Positive IHC: CD31, CD34, fVIIRA, D2-40 (podoplanin), FLI-1, ERG.

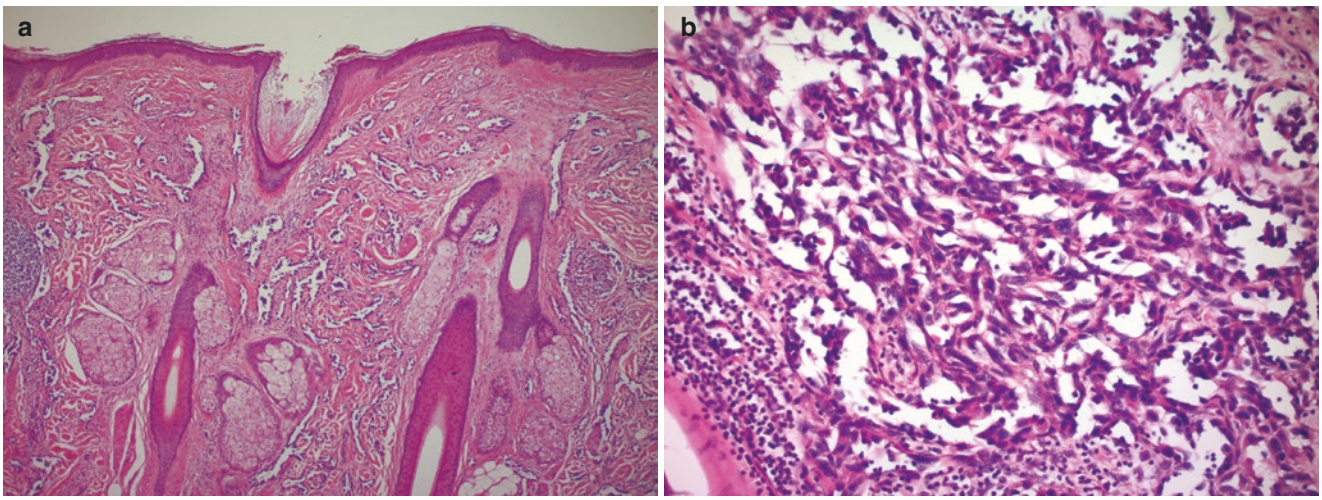


**Fig. 10.30** Angiosarcoma of the scalp. (**a**) The tumor is characterized by anastomosing, slit-like vascular spaces infiltrating the dermis, separating collagen bundles and wrapping around adnexal structures. (**b**) Higher magnification shows the vascular spaces are lined by atypical cells with a high N:C ratio

**Table 10.36** Clinical features of different types of Kaposi sarcoma

| Type of KS | Patients | Sites | Distribution |
|---|---|---|---|
| Classic | Male, 40–70-year-old Ashkenazi Jewish or Mediterranean | Skin of lower extremities>>>visceral and mucosal sites | Multiple |
| African/endemic | Children and middle-aged adults in equatorial African | Skin of lower > upper extremities, ±draining lymph nodes, visceral | Multiple |
| AIDS | IVDA, homosexual males, African children | Mucocutaneous and visceral | Disseminated |
| Iatrogenic immunosuppression | Transplant, drug-induced, or autoimmune disease | Mucocutaneous and visceral | Localized or disseminated |

*IVDA* intravenous drug abusers, *LE* lower extremities

  - Focal keratin expression in epithelioid variants can be seen.
  - MYC amplification is seen in lymphedema and radiation-associated tumors.
  - Cervical lymph node metastases occur from lesions arising in the scalp. Distant metastases occur in 30–50% of cases, usually to the lungs, bone, and liver.
- Prognosis is poor with late recurrence and metastases. Overall 5- and 10-year survival for cutaneous AS is 51% and 43%, respectively. Among those of the scalp and neck, the rates are much worse at 34% and 14%, respectively.

  Kaposi sarcoma (KS) is a unique vasoproliferative sarcoma caused by human herpesvirus type-8 (HHV8) infection, also known as KS herpes virus (KSHV). It occurs in specific clinical settings (Table 10.36).
- KS of the head and neck are most commonly seen in mucosal sites (oral cavity, tonsils, and palate) among patients with AIDS and iatrogenic immunosuppression, although cases with no apparent immunosuppression may occur.
- There are several histologic variants of KS, but typical KS is characterized by a spindle cell proliferation with round to oval, hyperchromatic nuclei with minimal to moderate nuclear atypia. The cells are arranged in short fascicles and admixed with inflammatory cells, hemosiderin-laden macrophages, and extravasated red blood cells (Fig. 10.31). The tumor cells are typically plumper than traditional angiosarcoma. Intervening slit-like vascular spaces are present within the spindle cell proliferation. Periodic acid-Schiff-positive intra- and extracellular globules are resistant to diastase.
  - Positive IHC: nuclear HHV8, diffuse D2-40 (podoplanin), VEGFR-3, and PROX-1.
  - Variable IHC: CD31, CD34, and fVIIIRA.
  - The bland morphology and inconsistent expression of vascular markers can complicate the diagnosis. Clinical history is important in this setting.

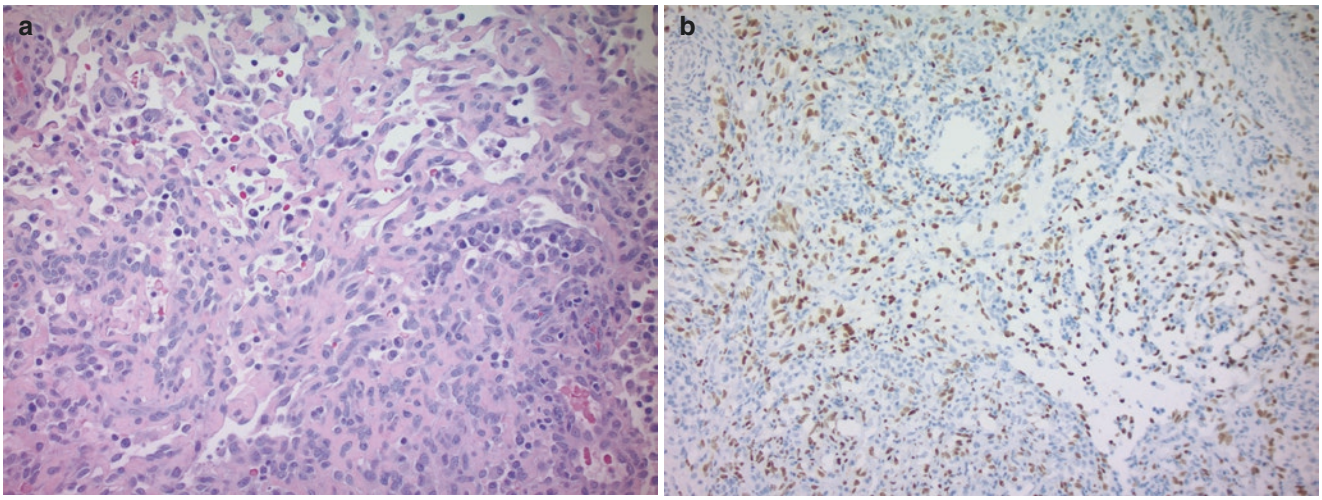


**Fig. 10.31** Kaposi sarcoma. (**a**) Spindle cell proliferation forming anastomosing vascular channels. The tumor cells have oval nuclei with fine chromatin, eosinophilic cytoplasm, conspicuous nucleoli and (**b**) express HHV8

- The differential diagnosis includes several benign vascular lesions including pyogenic granuloma, hemangiomas, bacillary angiomatosis, spindle cell carcinoma, and melanoma.

References: [226–232]

38. *Which chondroid tumors are common to the head and neck?*
    - Benign cartilaginous tumors of the head and neck are rare lesions restricted primarily to case reports and small series. Table 10.37 summarizes the chondroid tumors encountered in the head and neck.
    - Chondromas in the head and neck are rare with a few reported cases occurring in the larynx and discussed in more detail in Chap. 3.
    - Chondrosarcomas (CS) are malignant tumors that demonstrate cartilaginous differentiation. CS represent only 4% of all sarcomas. Head and neck CS account for 2–10% of all CS. The reader is referred to Chaps. 3 and 6 for a more detailed discussion of CS.
      - Approximately two-thirds of CS in the head and neck develop in the bones of the skull, face, and skull base. An additional 28% arise in the laryngotracheal region.
    - 10% of CS arise in soft tissues of the head and neck.

    References: [233–240]

39. *Which non-mesenchymal and unclassified soft tissue tumors can be found in the head and neck?*

    Paragangliomas are neuroendocrine tumors that arise from the extra-adrenal paraganglia. Paragangliomas (PGL) of the head and neck are derived from the parasympathetic nerves in this region and are named according to their anatomic location. PGL of the head and neck (HNPGL) are generally nonfunctioning tumors that come to clinical attention incidentally or as a result of nerve compression symptoms. There is a female predominance and patients present in the fifth to sixth decades.
    - The head and neck paragangliomas are from the following sites, in decreasing order: carotid body, jugulotympanicum, vagus nerve, and larynx. The genetics and morphologic details of PGL are discussed in Chap. 7. Regardless of site, PGL shows identical morphologic features. Here we will focus on PGL of the neck.
      - Vagus and carotid body tumors account for almost 70% of HNPGL.
    - PGL syndrome 1 (PGL-1) is the most common inherited syndrome associated with HNPGL and is the result of mutations of succinate dehydrogenase D protein (SDHD) encoded on chromosome 11.
      - Approximately a third of carotid and vagal PGL are familial.
      - The majority of patients with an SDHD mutation have carotid body PGL and tend to have multiple PGL.
    - Vagal PGL demonstrates the highest rates of malignancy (up to 16%), followed by carotid tumors.
      - In two small series of malignant PGL, carotid body tumors accounted for as much as 50% of all malignant PGL.
      - There are no definitive histologic features for malignancy; only the presence of metastases confirms malignancy (Fig. 10.32).
    - However, findings that favor malignancy include perineural invasion, lymphovascular invasion, and infiltrative growth.

    Alveolar soft part sarcoma (ASPS) is a tumor or probable myogenic or neurogenic derivation. It accounts

**Table 10.37** Benign chondroid tumors of the head and neck

| | Ectomesenchymal chondromyxoid tumor | Chondroblastoma | Chondromyxoid fibroma |
|---|---|---|---|
| % of cases arising in HN | n/a – exclusive to head and neck | 6.4% | 2–5% |
| Median/average age (range) | M = F, 34 years (7–78) | M > F, 20 years (2–83) | M ≥ F, second–third decades |
| Site | Dorsum of oral tongue>>>BOT, hard palate | Temporal bone, mandible | Mandible, jaw bones, sinuses |
| Morphology | Sharply demarcated lobules of small cells with scant, pale cytoplasm arranged in nests, cords, or a sieve-like pattern<br>Nuclei are round to oval, slightly irregular, and hyperchromatic<br>Stroma is myxoid or chondroid<br>Entrapped muscle and nerves are common<br>Rare mitoses, necrosis, or invasion | Sheets and ribbons of mononuclear cells with distinct cell borders and moderate to abundant cytoplasm, ±brown granular pigment<br>Nuclei are oval to slightly elongated with a longitudinal groove and fine to vesicular chromatin<br>Calcifications show a lace-like pattern<br>Scant to abundant chondroid stroma<br>Mitoses are present but infrequent<br>±Aneurysmal bone cyst changes or necrosis | Well-circumscribed lobules of chondromyxoid stroma containing loose groups of spindle or stellate fibroblasts<br>Hypercellular areas at periphery of the lobules<br>Aggregates of calcifications are present and occasional giant cells |
| Radiology | Rare reports. U/S: hyperechoic, hypovascular on ultrasound<br>CT: heterogeneous enhancement<br>MRI: low-level signals | Round or oval, expansile radiolucency with a sclerotic rim and sharp borders<br>Intratumoral calcifications are present | Well-defined radiolucent bone lesion with scalloped, sclerotic rim and cortical thinning<br>Scattered calcifications<br>T1: low signal<br>T2: heterogeneous, high signal |
| Positive IHC | S100, GFAP, f. SMA, f. MSA | Vimentin, SMA | Vimentin, SMA, ±CD34, ±S100 |
| Negative IHC | Desmin, var p63, calponin, rare f. CK, synaptophysin, and Cam5.2 | S100, CD34, AE1/3, EMA | CK, EMA, GFAP |

*F* focal, *U/S* ultrasound, *CT* computed tomography; *T1,T2* magnetic resonance imaging (MRI) weighted images, ≥ slight predominance

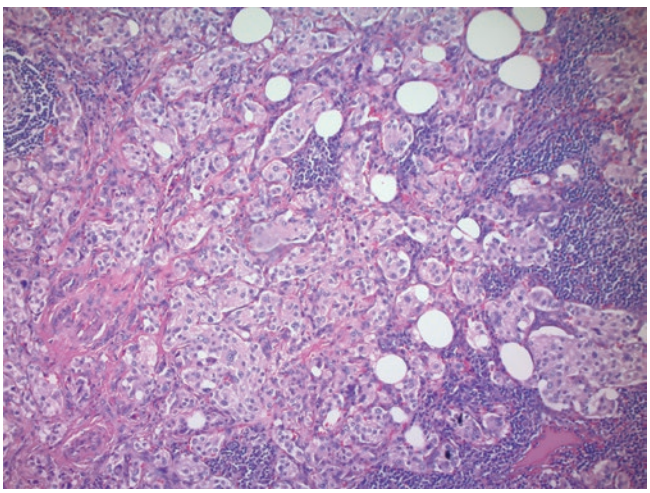

**Fig. 10.32** Malignant paraganglioma. Nests of epithelioid cells with moderate to abundant amounts of cytoplasm are present in cervical lymph node. Note the bland morphology, indistinguishable from a benign paraganglioma

for less than 1% of all sarcomas, and up to 25% occur in the head and neck.

- ASPS is a tumor of the young with a mean age of 23 years old (range: 6–43 years) and a female predominance. Tumors are primarily of the lower extremities.
- Head and neck sites are common in younger patients, and the most common sites are orbit followed by the tongue and soft tissues of the head and neck. Granular cell tumors.
- ASPS is characterized by large nests of tumor cells invested in a delicate fibrovascular stroma. The cells are polygonal with abundant, granular, pale eosinophilic cytoplasm and a central round, vesicular nucleus with conspicuous to prominent nucleoli. Pleomorphism is minimal, mitoses are rare, and necrosis may be present. Granular cell tumors are in the differential diagnosis based on similar morphology (Fig. 10.33) and tumor site. Table 10.38 compares the two tumors.
  - The tumor cells show distinct cell borders and dyshesion that impart an alveolar appearance to the cell nests.
  - Vascular invasion is common.
  - Rhomboid and rod-shaped intracytoplasmic crystals are positive for PAS with diastases resistance.
  - Positive IHC: TFE3, cathepsin K, desmin, variable myoD1, and myogenin.
  - Negative IHC: CK, vimentin, S100, NSE, PAX8, EMA, HMB-45, HepPar-1, chromogranin, and synaptophysin.

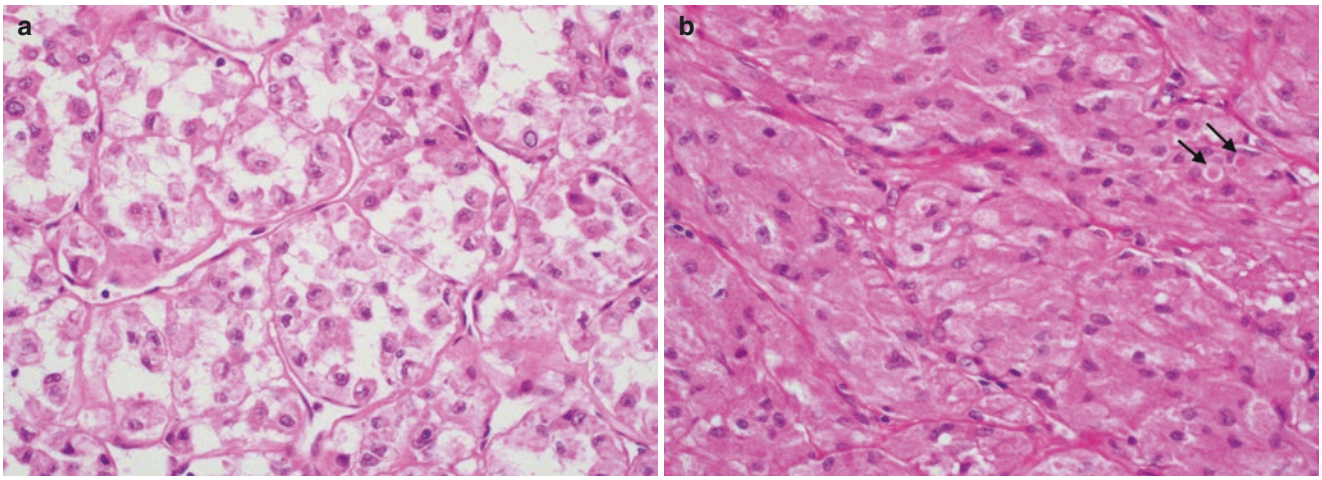


**Fig. 10.33** (**a**) Alveolar soft part sarcoma nests of loosely cohesive, epithelioid cells with abundant granular cytoplasm and nuclear pleomorphism and delicate vasculature. In contrast, (**b**) a granular cell tumor shows bland, cohesive epithelioid cells with abundant granular cytoplasm and scattered intracytoplasmic globules (arrows)

**Table 10.38** Comparison of immunoprofiles of granular cell tumor and alveolar soft part sarcoma

| IHC stain | Granular cell tumor | Alveolar soft part sarcoma |
|---|---|---|
| S100 | Positive | Negative |
| SOX10 | Positive | Negative |
| Inhibin | Positive | Negative |
| Nestin | Positive | Negative |
| Calretinin | Positive | Positive in ~50% |
| TFE3 | Positive (~90%) | Positive |
| PAS-D | Positive, diffuse | Positive, scattered |

  - Genetics: ASPS has a specific chromosomal alteration.
    - Fusion of the TFE3 transcription factor gene on Xp11 with the ASPS critical region 1 on 17q25 results in a transcript (ASPSCR1-TFE3) that can be detected by RT-PCRs.
    - FISH analysis detects the TFE3 rearrangement.
    - Of note, TFE3 IHC is not specific for ASPS and has been noted in granular cell tumors.
- 5-, 10-, and 20-year survival rates range from 65%–83%, 38–59%, and 14–47%, respectively. There is a 7% rate of regional lymph node metastases and a propensity for late, distant metastases (DM).
  - DM sites include, in order of frequency, the lung, bone, and brain.

Granular cell tumor (GCT) is a benign tumor believed to originate from Schwann cells. The most common site of GCT is the tongue. However, the tumor may be found in other locations such as the larynx and trachea and in soft tissues.

- The tumor is discussed in Chap. 1. Briefly, it is composed of sheets of polygonal cells with abundant eosinophilic cytoplasm and coarse granules with small, hyperchromatic, centrally located nuclei. Associated pseudoepitheliomatous hyperplasia is common in mucosal sites. The granules are positive for PAS and diastase resistant (PAS-D). Tumor cells are positive for S100, SOX10, and CD68.

References: [184, 187–189, 241–247]

## Case Presentations

### Case 1

#### Learning Objectives

1. To become familiar with the histologic features of necrotizing lymphadenitis
2. To create a comprehensive immunohistochemical panel to aid in the diagnosis
3. To generate a differential diagnosis of necrotizing lymphadenitis

#### Case History

An 18-year-old male noticed a painless posterior neck mass. Imaging studies revealed a 2.0 cm enlarged posterior cervical lymph node. The patient had no significant past medical history and did not have constitutional or other symptoms.

#### Gross Findings

An enlarged lymph node was bisected to reveal a homogeneous, fleshy tan-white cut surface without obvious nodularity.

**Histologic Finding** (Fig. 10.34a, b)

- Disruption of normal lymphoid architecture by ill-defined areas of necrosis.
- Distinct lack of neutrophils and numerous apoptotic cells within necrotic. Crescent-shaped histiocytes are prominent adjacent to necrosis.

**Differential Diagnosis**

- Kikuchi disease
- Systemic lupus erythematosus lymphadenopathy
- Bacterial or mycobacterial lymphadenitis

**Immunohistochemical Studies** (Fig. 10.34c, d)

- Histiocytes are positive for myeloperoxidase.
- Clusters of CD123-positive plasmacytoid dendritic cells surrounding the necrosis.
- CD8-positive T cells predominant over CD4-positive T cells.

**Final Diagnosis** *Histiocytic necrotizing lymphadenitis, favor Kikuchi disease*

**Take-Home Messages**

1. Kikuchi disease typically presents as painless lymphadenopathy in the cervical region of young adults. Constitutional symptoms such as fever and malaise may occur.
2. The key histologic feature is necrosis without granulomas or neutrophils.
3. Systemic lupus erythematosus lymphadenopathy is similar in presentation but usually has associated constitutional symptoms and positive serologic testing and may have hematoxylin bodies or Azzopardi effect (see question 7).
4. Bacterial lymphadenitis will usually demonstrate a neutrophilic infiltrate with or without a granulomatous component.
5. Immunohistochemical stains are helpful to confirm the diagnosis, including stains for microorganisms when appropriate.

References: [18, 19, 22, 23, 31–36, 38, 248]

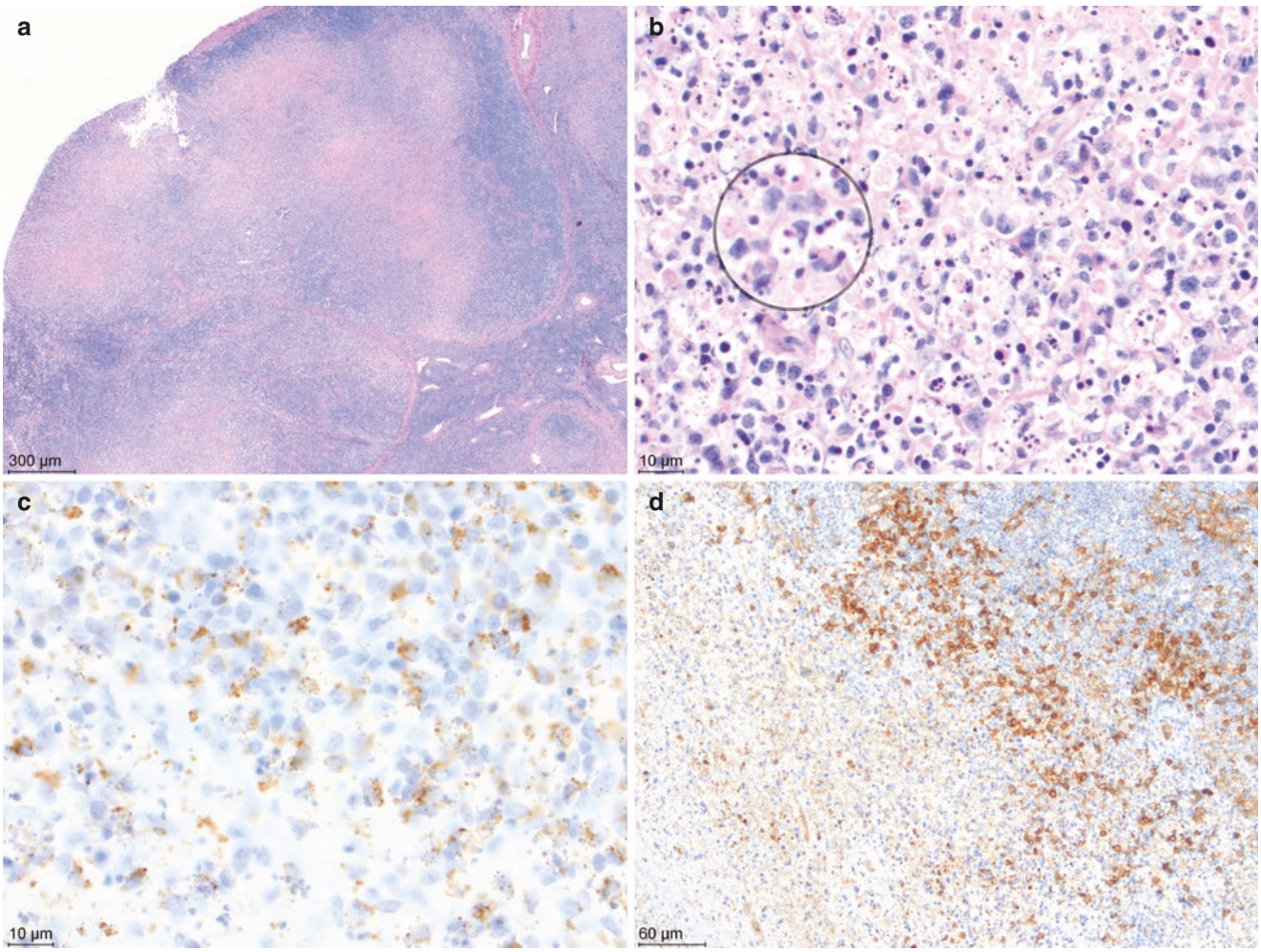


**Fig. 10.34** Case 1. (**a**) Effacement of normal architecture by (**b**) large zones of necrosis comprising few neutrophils and abundant apoptotic cells and rimmed by aggregates of histiocytes with crescent-shaped nuclei. (inset) (**c**) Myeloperoxidase stain is positive in histiocytes. (**d**) A CD123 stain is positive in clusters of plasmacytoid dendritic cells

## Case 2

### Learning Objectives

1. To become familiar with the histologic features of B-cell lymphomas
2. To generate a differential diagnosis of lymphomas composed of large cells
3. To utilize immunohistochemical stains to confirm the diagnosis

### Case History

A 25-year-old female presented with a 3-week history of painless, right cervical lymphadenopathy. She noticed an unintentional, 10-lb weight loss and has experienced a few episodes of drenching night sweats. Imaging showed a conglomerate of enlarged lymph nodes in the right cervical chain, supraclavicular region, and anterior mediastinum.

### Gross Findings (Not Pictured)

A grossly enlarged lymph node was bisected to reveal pale, firm, dense tissue with obvious nodularity.

### Histologic Findings (Fig. 10.35a, b)

- Low-power examination showed nodules of a mixed inflammatory infiltrate separated by thick bands of paucicellular fibrosis.
- High-power examination of the infiltrate demonstrated large, atypical cells, including lacunar and Reed-Sternberg forms, in a background of small lymphocytes, histiocytes, and eosinophils.

### Differential Diagnosis

- Nodular sclerosis classic Hodgkin lymphoma
- ALK-positive anaplastic large cell lymphoma

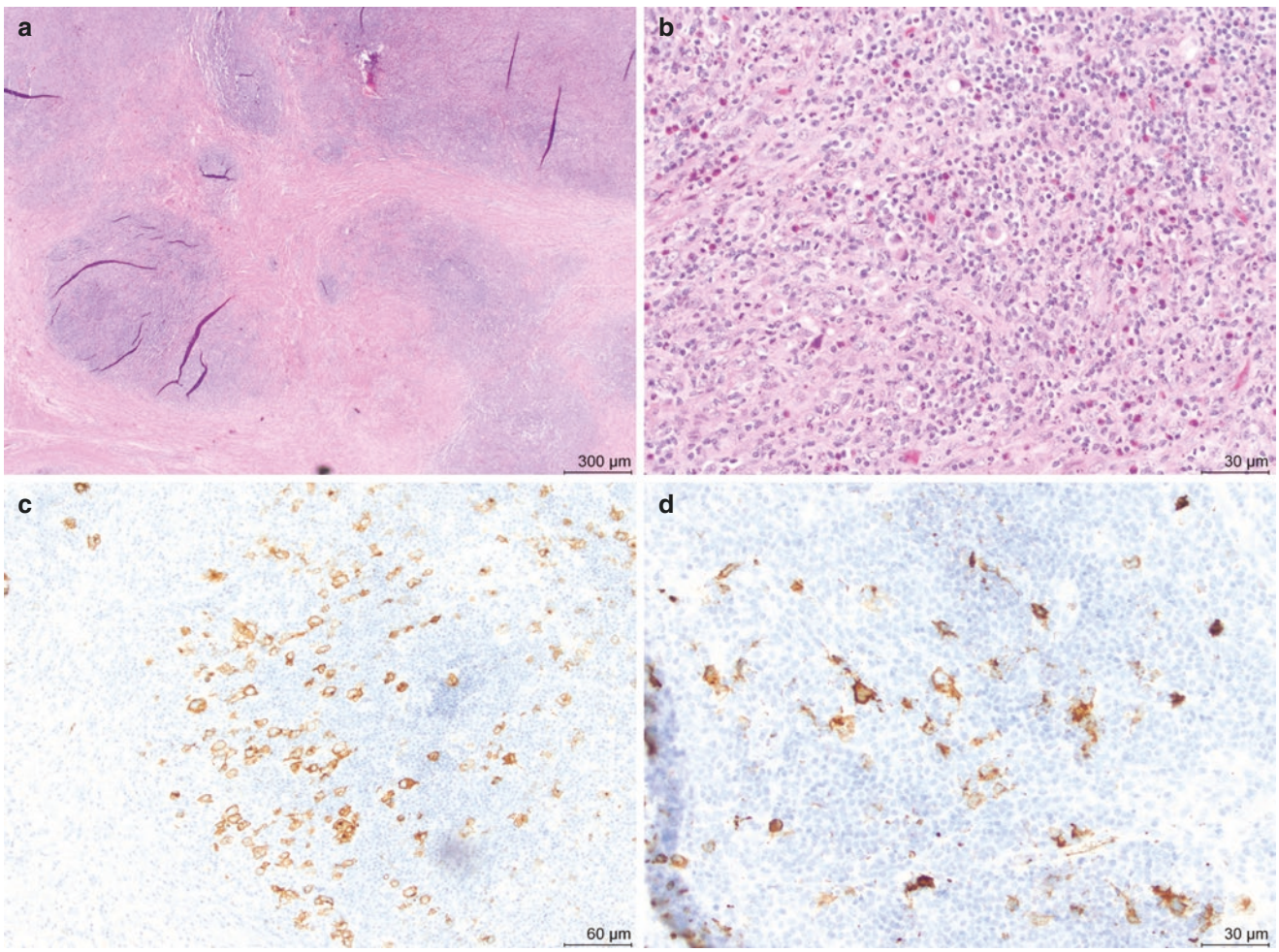


**Fig. 10.35** Case 2. (**a**) Effacement of normal architecture by a nodular infiltrate separated by thick bands of paucicellular fibrosis. (**b**) The center of the atypical nodules shows a mixed inflammatory infiltrate and scattered large, atypical tumor cells which are positive for (**c**) CD30 and (**d**) CD15

- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma ("mediastinal gray zone lymphoma")

**Immunohistochemical Studies** (Fig. 10.35c, d)

- CD30 is uniformly, strongly positive in a membrane and Golgi pattern in the large, atypical cells.
- CD15 is positive in a significant subset of the atypical cells, as well as in background eosinophils.
- CD20 and ALK-1 immunohistochemical stains were negative. PAX5 was dim, focally positive.

**Final Diagnosis** *Nodular sclerosis classic Hodgkin lymphoma*

**Take-Home Messages**

1. Classic Hodgkin lymphoma commonly presents as a painless neck mass, and a subset of patients have constitutional symptoms.
2. Nodular sclerosis classic Hodgkin lymphoma (NSCHL) is the most common subtype and shows dense fibrous bands and prominent lacunar atypical cells which are positive for CD30, CD15, and dim PAX5.
3. The large atypical cells of ALK-positive anaplastic large cell lymphoma will be positive for ALK. Mediastinal gray zone lymphoma typically expresses more B-cell antigens than NSCHL, such as CD20 and strong PAX5.

References: [55, 56, 59, 74, 75, 77, 78, 88, 99, 102, 106, 107]

## Case 3

**Learning Objectives**

1. To become familiar with the histologic features of this low-grade lymphomas
2. To become familiar with the flow cytometric findings used to aid in the diagnosis of lymphoma
3. To generate a differential diagnosis of low-grade, diffuse B-cell lymphomas

**Case History**

A 72-year-old male presented to his primary care physician with complaints of "lumps in my neck and armpits." He had noticed multiple, slowly growing masses but complained of no other symptoms, although he had noticed a few more colds than usual over the past few years. A complete blood count with differential performed at the doctor's office showed an absolute lymphocytosis of 10,000 cells per cubic millimeter. Cross-sectional imaging revealed diffuse lymphadenopathy throughout his body.

**Gross Findings**

A grossly enlarged cervical lymph node was excised, which when bisected showed fleshy, pale tissue without nodules or obvious necrosis.

**Histologic Findings** (Fig. 10.36a, b)

- A low-power examination of the lymph node showed effacement of normal architecture by a diffuse proliferation of predominantly small lymphocytes with a mottled appearance.
- High-power examination showed that the mottled areas represented proliferation centers with somewhat enlarged cells with more abundant cytoplasm (paraimmunoblasts and prolymphocytes). Mitotic activity is not brisk.

**Differential Diagnosis**

- Small lymphocytic lymphoma/chronic lymphocytic leukemia
- Mantle cell lymphoma
- Marginal zone lymphoma
- Diffuse follicular lymphoma

**Flow Cytometric Findings** (Fig. 10.36c)

- Eight-color flow cytometry of the lymph node showed a prominent monoclonal B-cell population, kappa-restricted, positive for CD19, CD20, dim CD5, and dim CD23.

**Additional Ancillary Studies**

- Cyclin D1 immunohistochemistry performed on the lymph node was negative.
- A fluorescence in situ hybridization panel performed concurrently on the peripheral blood showed the deletion 13q commonly seen in CLL, and did not show evidence of a t(11;14)(CCND1/IGH) translocation.

**Final Diagnosis** *Small lymphocytic lymphoma/chronic lymphocytic leukemia*

**Take-Home Messages**

1. CLL/SLL is a common cause of painless, asymptomatic lymphadenopathy in older patients and typically is associated with prominent peripheral blood and bone marrow involvement. It is a clinically indolent lymphoma with symptoms that may progress over years.

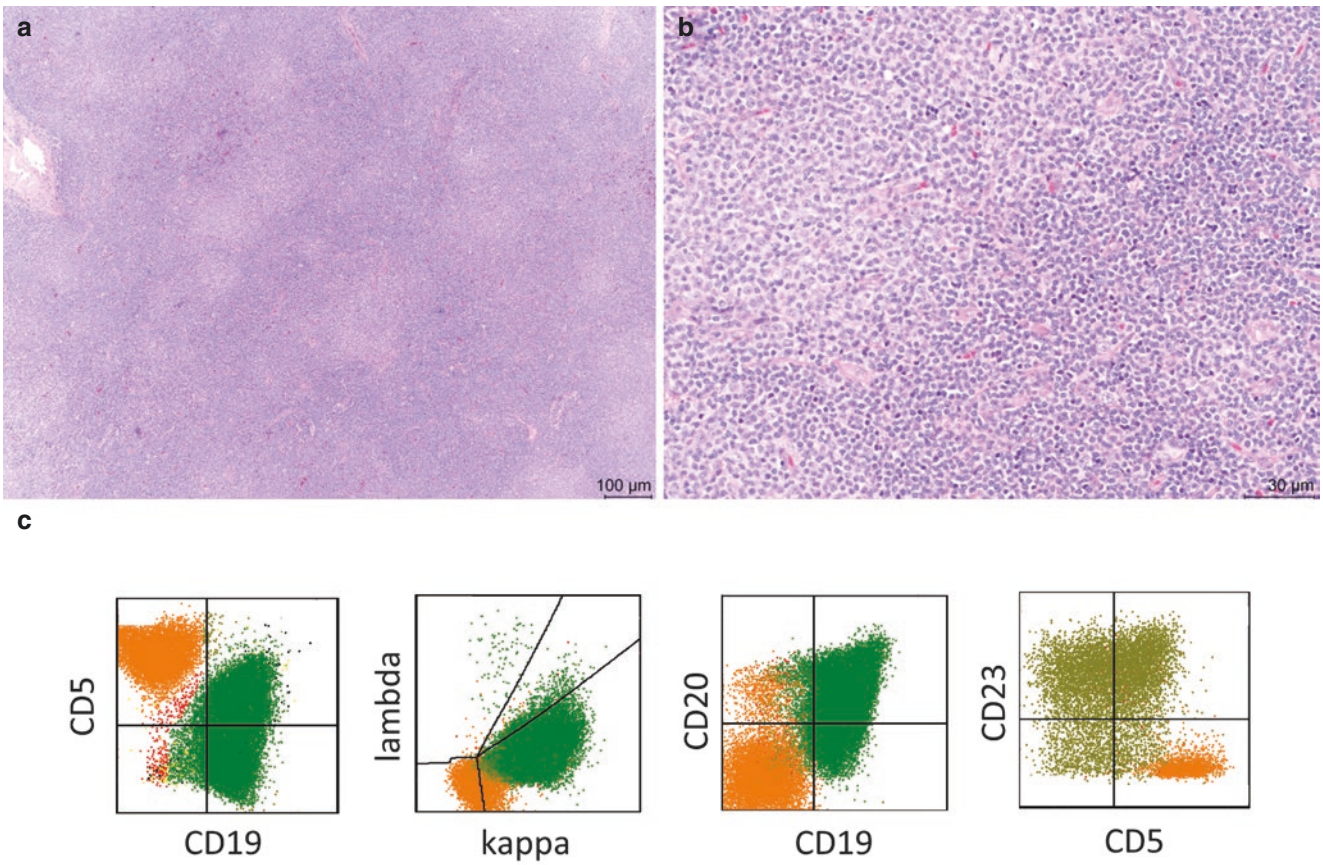


**Fig. 10.36** Case 3. (**a**) Effacement of normal architecture by a diffuse infiltrate of small lymphocytes with a mottled appearance. (**b**) Mottled areas represent proliferation centers. (**c**) Representative flow cytometry plots show a small CD5-positive T-cell population (orange). The neoplastic cells (dark green) are positive for CD19 and CD20 with dim CD5 expression and kappa light chain restriction. The olive green population represents all B cells

2. Histologically, lymph nodes involved by CLL/SLL show diffuse effacement with a mottled appearance due to proliferation centers.
3. The distinction between different low-grade lymphomas relies on the expression of specific antigens which can be demonstrated by flow cytometry or immunohistochemical stains.

References: [2, 6, 249–254]

## Case 4

### Learning Objectives

1. To become familiar with the histologic features of small round blue cell tumors in soft tissue
2. To generate the differential diagnosis of small round blue cell tumors
3. To create a comprehensive immunohistochemical panel to diagnosis these tumors

### Case History

A 21-year-old female presented with a rapidly, enlarging painless mass on the side of her neck. Physical examination was significant for a nontender, palpable mass in the posterior-lateral neck. Surgical excision of the mass is performed.

### Gross Findings

A gray-tan fleshy soft tissue mass is circumscribed but unencapsulated. The cut surfaces show focal hemorrhage and necrosis.

### Histologic Findings (Fig. 10.37a, b)

- Nests and sheets of monomorphic round blue cells separated by fibrous septa of varying thickness
- High-grade tumor cells with hyperchromatic nuclei and frequent mitotic figures

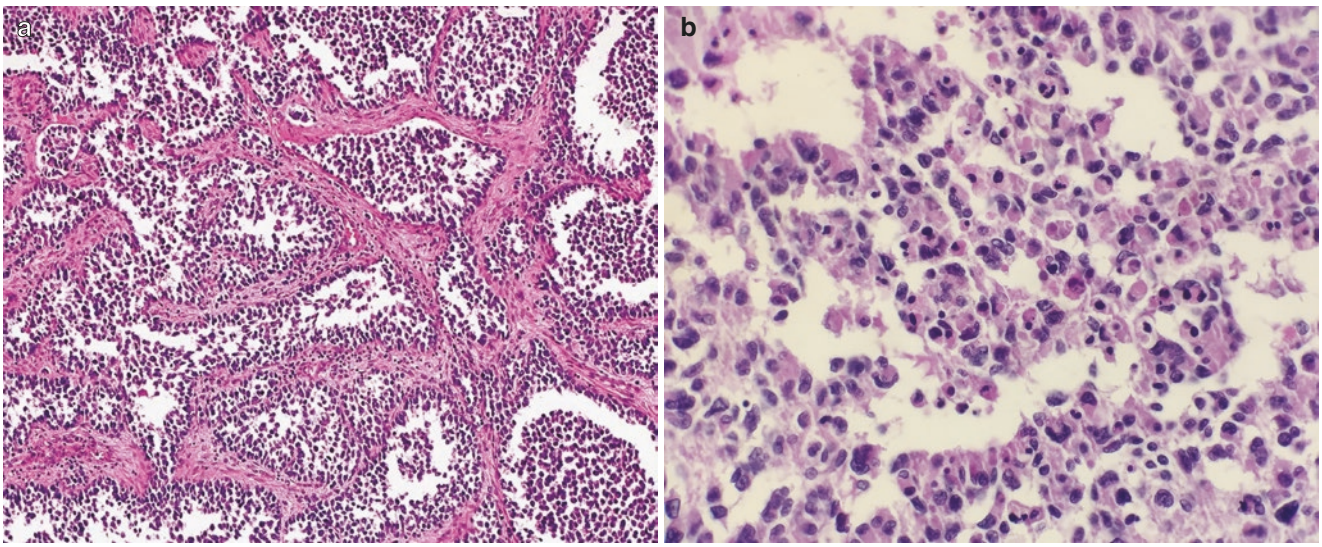


**Fig. 10.37** Case 4. (**a**) Nests and sheets of monomorphic, small round blue cells separated by fibrous septa. (**b**) High-grade tumor cells have hyperchromatic nuclei and frequent mitotic figures

### Differential Diagnosis

- Embryonal rhabdomyosarcoma
- Alveolar soft part sarcoma
- Lymphoma
- Neuroblastoma
- Ewing sarcoma
- Desmoplastic small round cell tumor

### IHC and Other Ancillary Studies

- Positive IHC: strong diffuse MyoD1, desmin, MSA, myogenin
- Positive FISH analysis: t(2;13)(q35;q14)

**Final Diagnosis** *Alveolar rhabdomyosarcoma*

### Take-Home Messages

1. Alveolar rhabdomyosarcoma is a malignant high-grade sarcoma of children and adolescents.
2. Tumor cells are monomorphic round blue cells with hyperchromatic nuclei and frequent mitotic figures. ~15% will be fusion mutation negative. This finding is associated with a solid pattern.
3. Immunohistochemistry and molecular studies are helpful to narrow the broad differential diagnosis. Other tumors in the differential diagnosis are primitive and may show focal expression of lineage-specific markers. However, strong diffuse staining for skeletal muscle markers confirms the diagnosis in this case.

References: [64, 80, 86, 255, 256]

## Case 5

### Learning Objectives

1. To become familiar with the histologic features of lipomatous tumors
2. To generate a differential diagnosis for fatty tumors
3. To become familiar with the immunohistochemical features of different lipomatous tumors

### Case History

A 56-year-old male presented with a painless mass on the back of his neck. The patient reports the mass has been slowly growing and present for several years. On physical examination, a mobile, nontender, subcutaneous mass is palpated on the inferior-posterior aspect of the neck. Surgical excision of the mass was performed.

### Gross Findings

Gross specimen showed a 3.2 cm well-circumscribed, ovoid mass with a yellow, fatty cut surface.

**Histologic Findings** (Fig. 10.38a, b)

- Numerous multinucleated giant cells with eosinophilic cytoplasm and peripherally arranged nuclei (floret cells)
- Bland spindle cells, mast cells, adipose tissue, and "ropey" collagen

### Differential Diagnosis

- Atypical lipomatous tumor/Well-differentiated liposarcoma
- Pleomorphic lipoma

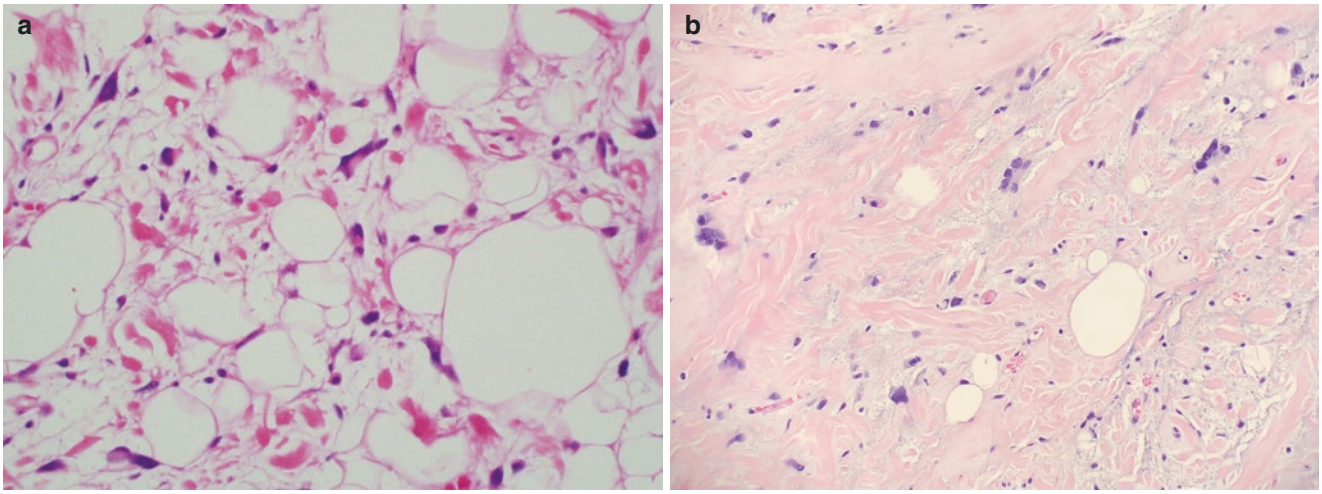


**Fig. 10.38** Case 5. (**a**) Scattered multinucleated giant cells with eosinophilic cytoplasm, and peripherally located, hyperchromatic nuclei (floret cells) are seen. (**b**) Other areas show more bland spindle cells, mast cells, mature adipocytes, and "ropey" collagen

### IHC and Other Ancillary Studies

- Positive IHC: Diffuse CD34
- Negative IHC: S100, CDK4
- Cytogenetics: *RB1* (13q14) deletion

**Final Diagnosis** *Pleomorphic lipoma*

### Take-Home Messages

1. Pleomorphic lipoma is a benign slow-growing adipocytic tumor. It often presents in men greater 50 years of age as a subcutaneous well-circumscribed mass on the posterior neck or upper back.
2. Characteristic floret cells and ropey collagen in conjunction with diffuse expression of CD34 by IHC confirm the diagnosis.

References: [28, 87, 209, 210, 212, 257–260]

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