Pediatric Surgical Pathology of the Nasopharynx and Sella Turcica

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Marie-Anne Bründler and Alfredo Pinto

Introduction

Nasopharyngeal and sellar masses in children are difficult to diagnose because of their location and silent growth. Initially, they may present with nonspecific symptoms often mimicking an upper respiratory infection. Pathological examination is essential for proper classification of nasopharyngeal or sellar masses, which fall mainly into three categories: developmental, inflammatory/reactive, or neoplastic.

Knowledge of the development and anatomy is necessary to understand the pathology of lesions arising in this region. The nasopharynx is derived from the endoderm and divided into three anatomic compartments: the nasopharynx, oropharynx, and hypopharynx. Anteriorly, the nasopharynx extends to the posterior aspect of the nasal turbinates, and the choanae or posterior nares that communicate with the nasal cavity. Posteriorly and superiorly, the nasopharynx is bordered by the skull base including the sella turcica, the body of the sphenoid, and the first and second cervical vertebrae. Inferiorly, it extends to the level of the soft palate, where the oropharynx begins. The lateral wall of the nasopharynx contains the ostium of the Eustachian tube, which communicates with the middle ear and is located anterior to a pharyngeal recess known as the fossa of Rosenmuller [1, 2]. The mucosa of the nasopharynx is separated from the deeper retropharyngeal space by the pharyngobasilar fascia which comprises bilateral openings, the sinus of Morgagni [3, 4].

Lymphoid tissue is found around the opening of the Eustachian tubes (tubal tonsils) and at the junction of the roof and posterior wall (pharyngeal tonsils). This lymphoid tissue forms part of the Waldeyer's ring [5, 6], which further includes the palatine and lingual tonsils. The Waldeyer's ring is part of the mucosa-associated lymphoid tissue (MALT). Microscopically, squamous mucosa lines the inferior half of the anterior and posterior wall, and the anterior half of the lateral wall of the nasopharynx. Ciliated pseudostratified respiratory epithelium covers the area around the nasal choanae and the roof of the posterior wall. The remainder of the nasopharynx contains irregular patches of ciliated and squamous epithelium. Further, there are areas with an intermediate or transitional-type epithelium. The submucosa contains seromucinous glands and lymphoid aggregates [3, 4, 6].

The sella turcica is located in the sphenoid bone where the pituitary gland is found [7].

Tumors of the nasopharynx and the sellar region are rare in children, and in most instances, they are benign. Malignant tumors albeit very rare are associated with a significant morbidity and mortality. This chapter discusses the pathology and differential diagnosis of the commonest benign and malignant tumors and tumor-like lesions of the nasopharynx and sellar region in children [8].

Benign Tumors and Cysts

Tornwaldt's Cyst

Definition

Tornwaldt's or Thornwaldt's cyst is a benign submucosal developmental cyst located in the midline of the posterior nasopharynx. It is thought to arise from a persistent pharyngeal bursa, a tubular invagination of the endoderm at the junction of the posterior nasopharyngeal wall and nasopharyngeal vault [9].

Clinical Presentation

Tornwaldt's cysts mostly are an incidental finding in older individuals [10]. Infected or larger cysts may present with nasopharyngeal discharge, halitosis, or dull headache [9, 10].

M.-A. Bründler (✉) · A. Pinto
Departments of Pathology and Laboratory Medicine and Paediatrics, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
e-mail: Marie-Anne.Brundler@albertaprecisionlabs.ca; Alfredo.Pinto@albertaprecisionlabs.ca

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Pathologic Features

As excision is infrequently performed, there is only scant literature documenting pathologic findings. A case showing a pseudo-stratified cylindrical-ciliated epithelial lining is described in a series of nasopharyngeal cysts published by Nicolai et al. [11].

Differential Diagnosis

Other foregut derived developmental cysts of the head and neck, namely Rathke's cleft cyst, neuroenteric cysts, and branchiogenic cysts, in rare cases show extension into the posterior or posterolateral nasopharynx [9, 12]. These cysts are lined by mucinous, ciliated, and/or squamous epithelium. Mucus retention cysts are distinguished by the presence of a prominent foam cell reaction and absent epithelial lining [10].

Rathke's Cleft Cyst

Definition

Rathke's cleft cyst is nonneoplastic epithelial-lined cystic lesion occurring in the sellar or suprasellar region. They are thought to develop from embryonal remnants of the Rathke's pouch [13].

Clinical Presentation

Rathke's cleft cysts are slow growing and generally asymptomatic. Larger cysts (> 2cm) may cause headache, diplopia, or endocrine disturbances through compression of the optic chiasm or the pituitary stalk [14–16].

Macroscopic Features

Rathke's cleft cysts present as unilocular thin-walled cyst containing clear or xanthochromic fluid or mucus [14, 15].

Microscopic Features

The cyst lining variably consists of a simple cuboidal, mucinous, or ciliated epithelium (Fig. 9.1). Focal squamous metaplasia can be present in up to 31% of cases and is associated with an increased risk of recurrence [15–17].

Immunohistochemistry

In cases that demonstrate squamous metaplasia or a xanthogranulomatous reaction, especially if only small biopsies are received, immunohistochemistry for BRAF 600VE and β-catenin may aid in the differentiation of a Rathke's cyst from craniopharyngioma [18–20].

Differential Diagnosis

Rathke's cleft cyst needs to be differentiated from other cystic epithelial lesions of the sellar region, most importantly craniopharyngioma. In rare instances, coexistence of a Rathke's cleft cyst with craniopharyngioma or other tumors of the sellar region is reported [21–23].

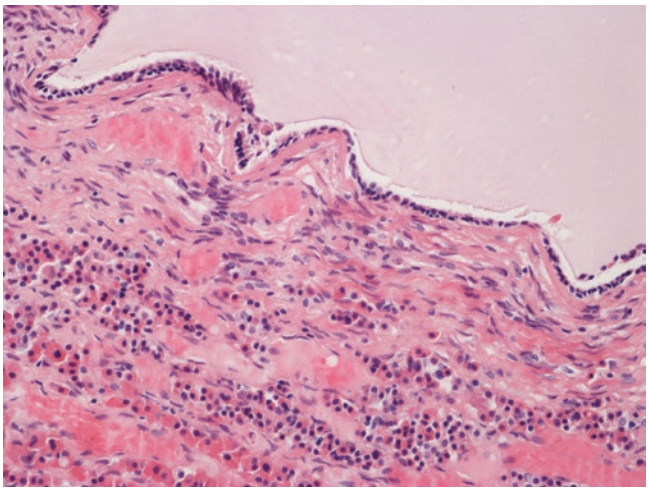

Fig. 9.1 Rathke's cleft cyst. The cyst is lined by ciliated epithelium and contains proteinaceous fluid. Adjacent pituitary gland tissue is seen in the lower half of the image. H&E × 200. (Courtesy Dr Lothar Resch, Calgary)

Adenoid Hypertrophy

Definition

Clinically, adenoid (or adenotonsillar) hypertrophy refers to chronic enlargement of the lymphoid tissue in the nasopharynx. Adenoid hypertrophy commonly is associated with recurrent viral and bacterial infections.

Clinical Presentation

Chronic enlargement of adenotonsillar tissue results in airway obstruction, snoring, sleep apnea, and middle ear effusions associated with hearing problems.

Pathological Examination of Adenoids and Tonsils

Routine pathological examination of all adenoidectomy or tonsillectomy specimens is of limited clinical value and thus not recommended [24, 25]. Main indications for pathological examination are tonsillar asymmetry and a clinical suspicion of lymphoma. Tonsillar examination also is recommended in children at increased risk for lymphoproliferative disorders and lymphomas. This includes children with genetic/metabolic problems, primary immune deficiencies, or post bone marrow or solid-organ transplantation. Adenoids and tonsils, like lymph nodes, should be submitted unfixed and without delay to the pathology department. Excisional biopsy is recommended in children, because adenoidal or tonsillar involvement by lymphoma may be focal. Moreover, this is to ensure that sufficient tissue is available for examination by light

microscopy as well as for ancillary tests required for a diagnosis of lymphoma, namely immunohistochemistry, flow cytometry, cytogenetics or FISH, and molecular studies. Touch preparations provide a useful initial impression.

Macroscopic Features

On macroscopic examination, the tonsils may reveal asymmetry, and on sectioning, localized areas of ulceration of the surface may be noted. Tonsillar crypts typically are preserved in tonsillar hypertrophy, but may reveal small punctate yellow areas corresponding to abscesses. Adenoid hypertrophy or asymmetry may be difficult to appreciate as the tissue often is fragmented.

Microscopic Features

In most cases, microscopic examination reveals florid reactive follicular hyperplasia (Fig. 9.2). At low magnification, the architecture of the lymphoid tissue is preserved. The lymphoid follicles are of variable shape and size with retained polarization of germinal centers and a well-defined mantle zone. The interfollicular areas reveal a proliferation of small, intermediate, and large lymphocytes.

Differential Diagnosis

Differentiation of reactive follicular hyperplasia from lymphoma may be difficult based solely on microscopic features and normally requires immunohistochemistry, flow cytometry, and molecular techniques.

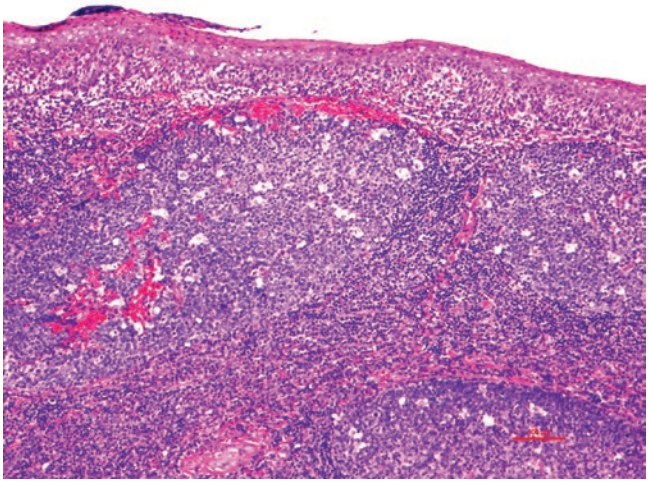

Fig. 9.2 Adenotonsillar hypertrophy. Reactive lymphoid follicles with tingible macrophages in germinal centers and a well-defined mantle zone are noted. Overlying nonkeratinized squamous epithelium is also present. H&E 10X

Nasopharyngeal Teratoma

Definition

Nasopharyngeal teratomas are extragonadal germ cell tumors that contain elements of all three embryonic germ cell layers: endoderm, mesoderm, and ectoderm. The etiology of extragonadal teratomas is not fully understood. However, the thought is that they likely occur when individual pluripotent germ cells fail to complete migration and continue to divide in an aberrant location typically along the midline. Extragonadal germ cell tumors can arise in a midline location anywhere along the axis of the body [26, 27].

Clinical Presentation

Most nasopharyngeal teratomas are congenital or manifest in early infancy. They rarely are encountered past 1 year of age [28, 29]. Tumors identified prenatally, by prenatal ultrasound or MRI, may be complicated by polyhydramnios due to impaired fetal swallowing or stillbirth. In neonates, the principal and most serious clinical symptoms are related to respiratory distress due to obstruction. Nasopharyngeal teratomas typically present as sessile or pedunculated mass protruding into the oral cavity. They may be associated with other cranial or skull base anomalies and show intracranial extension. Epignathus is an extreme form of oropharyngeal teratoma that presents as large disfiguring congenital oronasopharyngeal tumor that protrudes through the mouth and may cause severe airway obstruction [30, 31].

There is inconclusive evidence for a genetic link for extragonadal teratomas. Cytogenetic studies have shown that somatic malignancies can develop in teratomas and show the same genetic abnormalities detected in the corresponding teratoma [32]. Deletions on chromosome 1 and 6 have been observed [26]. Moreover, mosaic tetrasomy 1q has been reported [33]. Teratomas can occur in isolation or in association with congenital cardiac, urogenital, or CNS anomalies, with chromosomal anomalies, specifically Klinefelter syndrome, trisomy 13 and trisomy 21, or in the context of overgrowth syndromes, such as Beckwith-Wiedemann syndrome, Proteus syndrome, or Schinzel-Giedion syndrome [26, 27, 34].

Germ cell tumors are divided into tumors arising from gonadal (testis or ovary) and extragonadal sites. Further, they are separated into benign teratomas and malignant germinomatous and nongerminomatous germ cell tumors. Most nasopharyngeal germ cell tumors are benign teratomas [35, 36]. Mature teratomas are characterized by an absence of immature neuroectodermal elements, while such elements are identified with varied abundance in immature teratomas. Teratomas containing a malignant germ cell tumor component, most commonly Yolk sac tumor or germinoma, are classified as malignant mixed germ cell tumors. In exceptional cases, teratomas may also comprise a malignant nongerm cell tumor component, such as neuroblastoma or rhabdomyosarcoma [37].

Macroscopic Features

Macroscopic appearances vary considerably with tumors presenting as lobulated masses that can be solid encapsulated, multiloculated, or variably cystic. On cut sections, various tissue types such as adipose tissue, hair, bone, and teeth can be appreciated.

Microscopic Features

Teratomas consist of a mixture of tissues derived from the three germ cell layers. The degree of organization and the relative abundance of the different tissue types vary considerably between cases. Skin, hair, and sebaceous glands, and neural or glial tissue are most consistently observed. Extensive sampling is recommended to identify possible malignant germ cell tumor elements, most commonly yolk sac tumor, or other malignant components. The clinical outcome of congenital extragonadal teratomas is primarily determined by whether complete resection is achieved. The prognosis does not appear to correlate with the grade of immaturity of the teratoma or the presence or absence of foci of yolk sac tumor [29, 38]. There is an isolated report of a neonate who had a mature teratoma excised that recurred 3 years later as yolk sac tumor with disseminated disease and death within 18 months [39].

Immunohistochemistry

Immunohistochemistry is not usually necessary unless a malignant component is identified on microscopic examination that requires further characterization. AFP serum levels are used to monitor residual disease or recurrence if yolk sac tumor is identified.

Differential Diagnosis

The pathological diagnosis of resected teratomas usually is straightforward. Difficulties may arise if a lesion is biopsied and there is sampling bias.

Hairy Polyp

Definition

Hairy polyps are benign congenital malformations of the nasopharynx that usually present at birth or in early infancy. Hairy polyps have been variably described in the literature as dermoid, hamartoma, teratoma, or choristoma [40–44]. The latter appears to be a more appropriate designation since hairy polyps are composed of heterotopic, ectodermal, and mesodermal derivatives. Hairy polyps are slow growing with no reported cases of malignant transformation. Slow regrowth over 6-year period has been documented in one case [45].

Clinical Presentation

Hairy polyps most frequently present as a pedunculated polypoid mass on the lateral wall of the nasopharynx but can also arise from other sites, including the hard and soft palate, tonsils, tongue, Eustachian tube, and middle ear [41–43]. Moreover, they can be associated with other craniofacial anomalies, such as cleft palate, uvular agenesis, ankyloglossia, bifurcation of tongue, facial hemihypertrophy, low-set ears, agenesis of external auricle, branchial arch sinuses, and left carotid artery atresia. HP usually presents as a visible mass or with symptoms of respiratory obstruction, dysphagia, or both.

Macroscopic Features

Hairy polyps present as broad based or pedunculated mass that is covered by skin that may be focally ulcerated. The cut section shows adipose tissue, and in some cases cartilage or bone (Fig. 9.3).

Microscopic Features

The surface is lined by epidermis with normal adnexal structures including hair follicles, sebaceous, and eccrine glands. The core of the polyp contains mature adipose tissue. Cartilage, bone, and skeletal muscle can also be present. Typically, there is no immature tissue or cellular atypia.

Differential Diagnosis

Clinically, the differential diagnosis is broad and includes meningoencephalocele, teratoma, nasal glial heterotopia, congenital salivary gland anlage tumor, hemangioma, vascular malformations, neuroenteric cyst, and craniopharyngioma [43]. Microscopically, the differential diagnosis does not pose significant challenges.

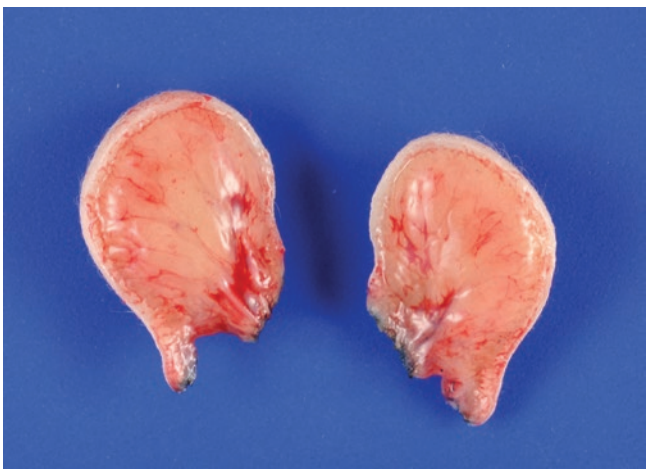

Fig. 9.3 Hairy polyp. Macroscopic examination shows a polypoid lesion covered by intact skin and an adipose tissue core

Nasopharyngeal Angiofibroma

Definition

Nasopharyngeal angiofibroma is a rare locally aggressive fibrovascular tumor involving the posterior nasal cavity and the nasopharynx. The tumor is thought to arise from the pterygopalatine fossa region and develops almost exclusively in adolescent males [46]. Occurrence at atypical extra nasopharyngeal sites, such as nasal septum, maxillary, or ethmoid sinus, is very rare in children and adolescents [46, 47].

Clinical Presentation

Nasopharyngeal obstruction and recurrent epistaxis are the commonest presenting symptoms. Other findings and secondary complications include facial deformities, palatine swelling, visual disturbance, headache, sinusitis, mastoiditis, and dacryocystitis [48]. Recurrence is common and related to incomplete excision or invasive growth [46, 49].

Hereditary/Genetic Features

Activating mutations in CTNNB1, the gene encoding β-catenin, resulting in abnormal nuclear accumulation of β-catenin are identified in a nearly all cases of nasopharyngeal angiofibroma [50, 51]. Most cases are sporadic. Whether nasopharyngeal angiofibroma truly occurs at an increased frequency in patients with familial adenomatous polyposis remains controversial [52–54]. Recurrent chromosomal gains were identified in a series 22 nasopharyngeal angiofibromas by comparative genomic hybridization, and occurred at greater frequency in recurrent tumors [55].

Macroscopic Features

The tumor presents as a firm rubbery lobulated or nodular sessile or pedunculated mass with a smooth and glistening mucosal lining that can be focally ulcerated (Fig. 9.4). Cut sections typically show a spongy appearance due to the abundance of vascular channels [48]. If tumor embolization has been performed prior to surgery, vascular thrombosis and infarcts may be seen.

Microscopic Features

The microscopic features of nasopharyngeal angiofibroma are described in great detail in a series of 25 cases published by *Sternberg* in 1954 [48]. As inferred by its name, nasopharyngeal angiofibroma characteristically comprises of a vascular and a fibrous component (Fig. 9.5A). The vascular channels vary in size, shape, and thickness. They can be of elongated, angulated, or stellate configuration. Simple endothelial-lined vascular channels mimicking lymphatic vessels are characteristic, but vessels showing a complete or incomplete smooth muscle layer and capillary proliferations mimicking reactive vascular granulation tissue are also seen

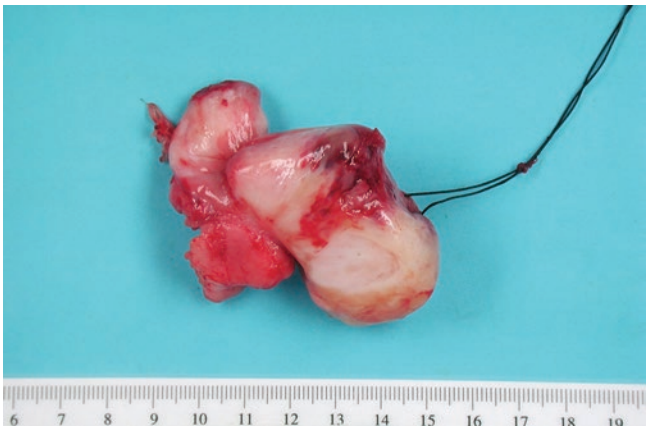

Fig. 9.4 Nasopharyngeal angiofibroma. The resected tumor presents as firm multilobulated mass with a smooth glistening surface

(Fig. 9.5B). The vessels are embedded in a paucicellular fibrillary collagenous stroma. Focally, the stroma may show hyalinization, myxoid change, or coarser collagen fibers arranged in parallel bundles. The stromal cells are haphazardly arranged and stellate or spindle shaped (Fig. 9.5C). They contain plump oval cytologically bland nuclei with small nucleoli. Mitosis are uncommon.

Immunohistochemistry and Molecular Diagnostic Features

Stromal cells in virtually all cases show strong diffuse nuclear immunoreactivity for β-catenin (Fig. 9.5D) and also are consistently positive for vimentin [50, 56]. In most cases, the stromal cells are negative for fibroblast/myofibroblast or myoid markers (CD34, actin, smooth muscle actin, desmin, or myogenin). CD117 (c-kit) expression is inconsistent [57–59]. Epithelial markers (cytokeratin, EMA), CD99 and S100 are consistently negative. Most cases show expression of androgen receptors, but not estrogen receptors, in the nuclei of stromal and endothelial cells [51, 60]. Endothelial cells stain positive for the vascular endothelial markers CD31 and CD34, but are negative for D2-40, a lymphatic vascular marker, and Glut-1, a marker of infantile hemangioma. Perivascular smooth muscle cells are highlighted by smooth muscle actin. Desmin staining may be observed in larger thick-walled vessels [57].

Differential Diagnosis

Sinonasal polyps, vascular anomalies, fibroblastic/myofibroblastic lesions, rhabdomyosarcoma, lymphoma, and nasopharyngeal carcinoma are the main differential diagnoses in pediatric patients. Pertinent histological, immunohistochemical, and molecular-genetic features that differentiate nasopharyngeal angiofibroma from other tumors or tumor-like lesions are summarized in Table 9.1.

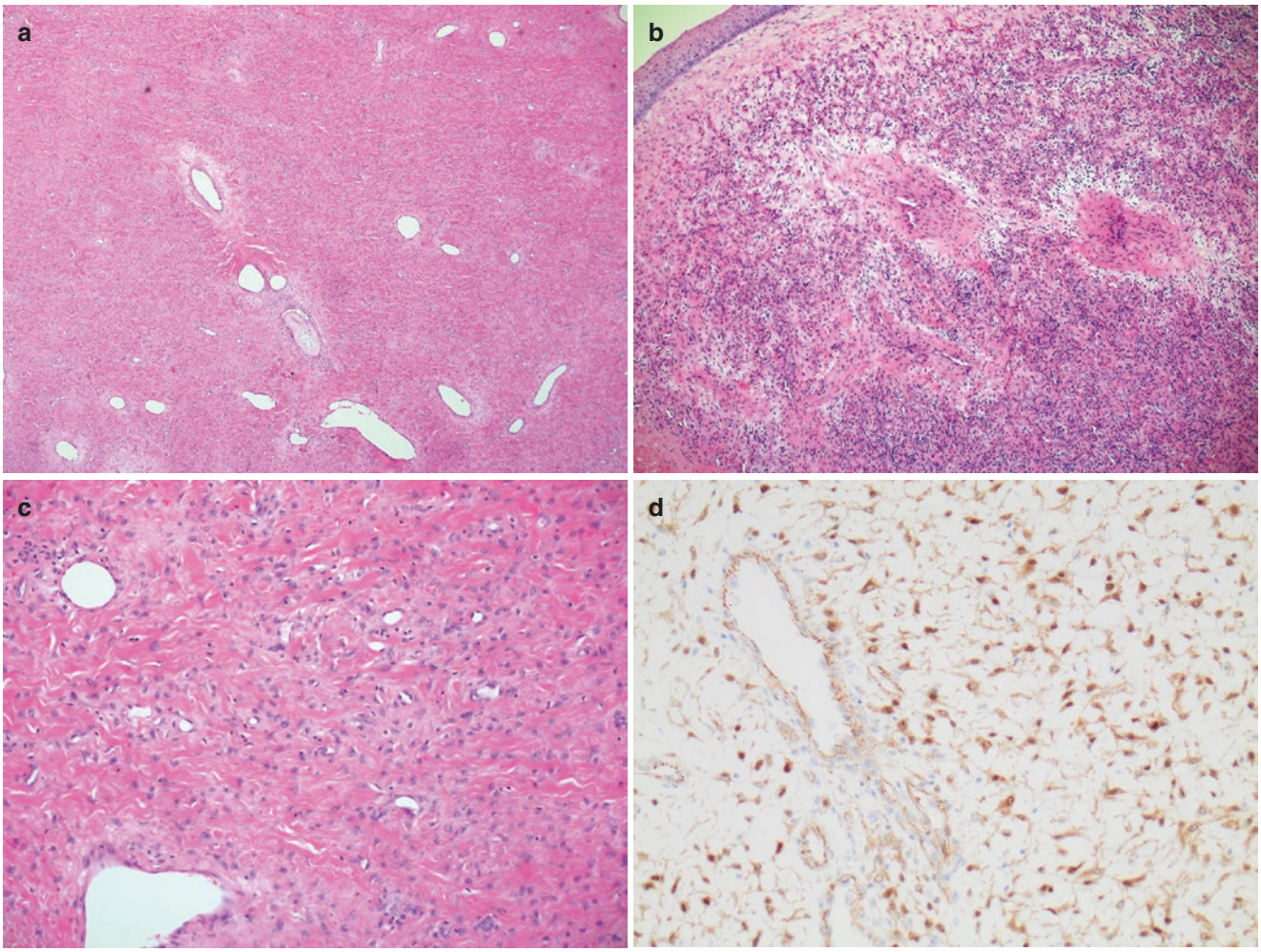

Fig. 9.5 Nasopharyngeal angiofibroma. Microscopic examination at low magnification (**A**) shows scattered ectatic vascular channels surrounded by paucicellular fibrous tissue (H&E × 20). In the superficial portion of the tumor (**B**), thick-walled vessels and capillary proliferations are noted (H&E × 200). Higher magnification (**C**) illustrates the haphazard arrangement of stromal cells with plump oval nuclei (H&E × 400). Diffuse nuclear immunoreactivity of stromal cells for β-catenin (**D**)

Table 9.1 Differential Diagnosis of Nasopharyngeal Tumors: Microscopic, immunohistochemical and molecular findings

Diagnosis	Microscopy	Immunophenotype	Molecular phenotype
Sinonasal polyps	Stromal edema, variable inflammation, ulcer, squamous metaplasia	NA	NA
Vascular anomalies	Clustered lymphatic, venous, or capillary channels	CD31, CD34, D2-40, Glut-1	NA
Cranial fasciitis	Fibroblasts/myofibroblasts arranged in short fascicles, myxoid stroma	Smooth muscle actin, desmin, nuclear β-catenin	*CTNNB1*
Infantile myofibroma	Myofibroblasts, nodular or fascicular architecture, hemangiopericytoma like vasculature	Smooth muscle actin, (desmin)	NA
Rhabdomyosarcoma	Small round blue cells, rhabdomyoblasts	Desmin, myogenin, MyoD1	*FOXO1*, alveolar RMS
Lymphoma	Effacement of normal follicular architecture, atypical lymphoid cells (intermediate or large), Hodgkin or Reed Sternberg cells	CD45, CD3, CD20 CD30, CD15 Ki-67 (Mib1)	*t(8;14 or t(2;8) or t(8;22)*, Burkitt's *IgH* EBV (EBER ISH)
Nasopharyngeal Carcinoma	Cords and sheets of large atypical cells, variable lymphoid infiltrate	Pancytokeratin	EBV (EBER ISH)
Chordoma	Cords and sheets of large vacuolated cells, myxoid matrix, delicate fibrovascular septa, bone destruction	Pancytokeratin, Brachyury, S100 INI1	*INI1/SMARCB1*

Due to the risk of massive bleeding, biopsy generally is not recommended in nasopharyngeal angiofibroma, unless imaging findings are equivocal. Superficial sampling of a nasopharyngeal angiofibroma in addition may render findings that are histologically indistinguishable from those seen in an ordinary sinonasal polyp, especially if the mucosa overlying the tumor is ulcerated. The stroma of a sinonasal polyp more typically is edematous and lacks the vasculature and regular distribution of stromal cells characteristic of nasopharyngeal angiofibroma. Eosinophils and plasma cells are infrequently seen in nasopharyngeal angiofibroma. Even though common in the head and neck region, vascular anomalies, with the exception of lymphangioma, only in very rare instances present as nasopharyngeal mass. Vascular tumors or malformations typically lack a conspicuous fibrous component. Juvenile nasopharyngeal angiofibroma lacks significant cytological atypia seen in rhabdomyosarcoma or nasopharyngeal carcinoma. Moreover, these lesions express markers of skeletal muscle and epithelial differentiation, respectively. Nuclear expression of β-catenin is not specific to nasopharyngeal angiofibroma; it is seen in other mesenchymal and epithelial lesions involving the nasopharynx [61].

Pituitary Tumors

Pituitary Adenoma

Definition

Pituitary adenomas are benign epithelial neoplasm of neuroendocrine differentiation arising from the anterior lobe of the pituitary glands. Clinically, hormonally active or functioning adenomas are separated from nonfunctioning adenomas. These are then further subclassified based on tumor size and histopathological features, including expression of pituitary hormones and transcription factors [62].

Clinical Presentation

Pituitary adenomas are comparatively rare in the pediatric age group; in two large surgical series, they represented only 2–6% of cases [63, 64]. The majority of pediatric cases are diagnosed in the second decade after onset of puberty [63–67]. Most pediatric adenomas are hormone secreting, and of these, more than half are prolactinomas. Prolactinomas are more prevalent in females, and typically manifest with primary amenorrhea or oligomenorrhea and galactorrhea [63–68]. Adrenocorticotropin (ACTH)-secreting tumors and growth hormone (GH)-producing adenomas are less frequent. They represent between 10% and 30% of pediatric pituitary adenomas [62, 64, 66]. ACTH releasing adenomas typically manifest before or at the onset of puberty with stunted growth, excessive weight gain, and delay of pubertal symptoms [63, 64, 66, 67, 69]. Accelerated growth and acromegaly are characteristically seen in association with GH-secreting tumors [69]. The percentage of endocrine inactive tumors in children varies between 5% and 20% of pediatric pituitary adenomas [63, 64]. Inactive tumors tend to be larger at diagnosis and go unrecognized until they elicit neurological deficits.

Hereditary/Genetic Features

Pituitary adenomas in most instances are sporadic and occur in isolation, without other endocrine or nonendocrine tumors or anomalies, and without identifiable germ line mutations in any of the predisposing genes. Approximately 5% of pituitary adenomas are inherited with familial occurrence [69]. Pituitary adenomas can occur as a manifestation of an endocrine neoplasia syndrome, namely multiple endocrine neoplasia type 1, Carney complex, or McCune Albright syndrome [69, 70]. The possibility of a germline mutation in the *AIP* gene should be considered in isolated pituitary adenomas in children and young adults that present with macroadenomas or gigantism [71]. Isolated sporadic adenomas in the very young adults can also be due to *MEN1* mutations [72, 73].

Macroscopic Features

Adenomas present as tan-brown circumscribed noncapsulated lesions. Tumors measuring 1 cm or greater are classified as macroadenomas [62]

Microscopic Features

Adenomas show a loss of the normal lobular architecture of the adenohypophysis and consist of sheets and cords of monomorphic cells with well-defined cell borders and granular cytoplasm. Densely granulated GH-secreting tumors and prolactinomas typically show a strongly eosinophilic cytoplasm (Fig. 9.6A). Basophilic granules are observed in ACTH-producing tumors [62, 74]. Multinucleated cells, focal nuclear pleomorphism, and nuclear pseudoinclusions may be observed. These latter features, however, do not indicate malignancy. Mitosis are rare in adenomas. Regressive changes including necrosis and stromal fibrosis can be seen in larger or treated lesions. Reticulin staining typically shows a loss of the normal trabecular architecture (Fig. 9.6B).

Immunohistochemistry and Molecular Diagnostic Features

The pathological classification of pituitary adenomas is based on a combination of microscopic features and immunostaining for pituitary hormones which should be performed in all cases [62, 75, 76]. Staining for pituitary specific and other transcription factors can be helpful in cases with low or absent staining for pituitary hormones [75]. Immunoreactivity for pituitary hormones does not equate hormonal secretion. Ki-67 and p53 labeling indexes aid in separating proliferative and likely more aggressive lesions

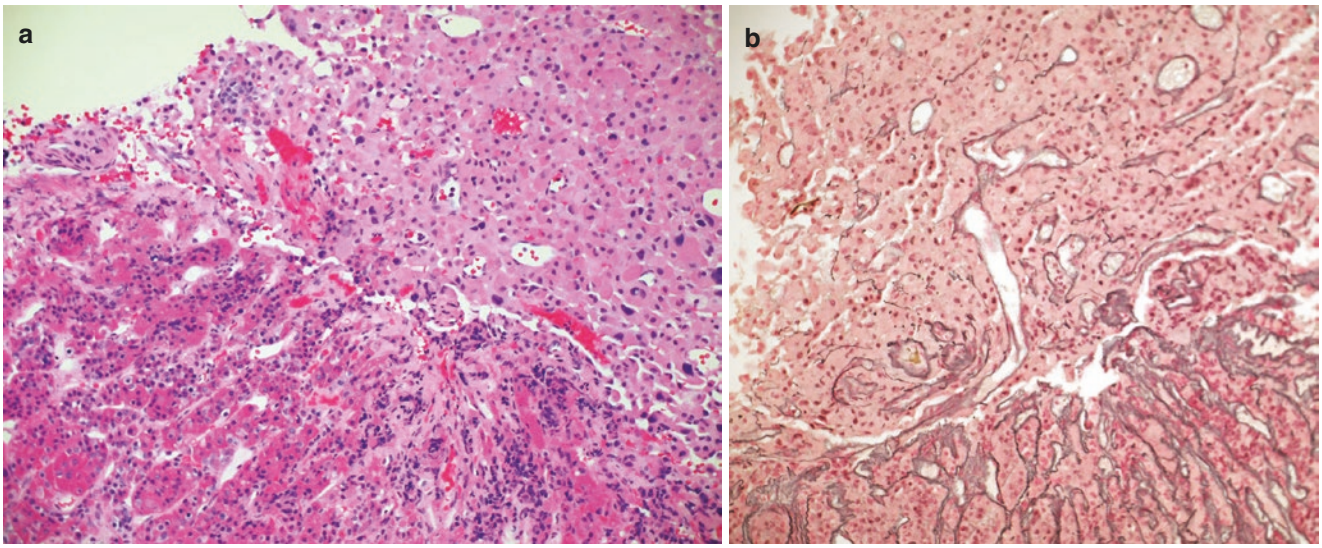

Fig. 9.6 Pituitary adenoma. This prolactin-producing adenoma is comprised of sheets of cells with strongly eosinophilic cytoplasm (**A**, H&E × 400). Reticulin staining (**B**) shows loss of the normal trabecular architecture in the adenoma, while it is preserved in the adjacent pituitary gland (lower half)

from nonproliferative lesions [75, 76]. Nonproliferative lesions show a low Ki-67 index, corresponding to a low proliferation fraction, and are negative for p53 or show only rare positive nuclei. Local tumor expansion or infiltrative growth is assessed on imaging. Presently, there is a lack of molecular markers reliably predicting aggressive behavior.

Differential Diagnosis

Pituitary adenomas need to be distinguished from pituitary hyperplasia and other epithelial or nonepithelial tumors involving the sellar region. In the pediatric age group, the main differential diagnoses are pituitary blastoma, Langerhans cell histiocytosis, germinoma, chiasmatic glioma, and most importantly craniopharyngioma.

Pituitary Hyperplasia

Pituitary hyperplasia occurring in puberty or secondary to hypothyroidism can mimic pituitary adenoma clinically and radiologically. On microscopic examination, a retained trabecular architecture, highlighted by the reticulin stain, and the presence of pituitary cells with normal expression of pituitary hormones allow differentiation from adenoma.

Pituitary Blastoma

Pituitary blastoma is a distinct but very rare and potentially aggressive tumor of the pituitary gland first described by *Bernd W Scheithauer* [77]. Patients typically present in the first two years of life with infantile onset Cushing disease or raised ACTH levels. Microscopically, pituitary blastoma resembles embryonic pituitary tissue [77, 78]. Secretory cells, glandular or tubular elements resembling Rathke's pouch and small primitive cells are present in variable proportions (Fig. 9.7). Germline and somatic loss of function mutations in *DICER1* are critical in the pathogenesis of these tumors which are part of the Dicer1 syndrome [78, 79].

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis involving the suprasellar region most commonly presents with pituitary dysfunction (hypopituitarism or diabetes insipidus) [80, 81]. Involvement usually is seen in conjunction with multisystem disease, and thus biopsy is rarely performed. Langerhans cell histiocytosis consists of a clonal proliferation of histiocytic cells exhibiting a Langerhans cell morphology and immunophenotype [82]. Langerhans cells are round oval and comprise abundant pale eosinophilic cytoplasm and grooved, coffee bean-shaped nuclei. Multinucleated cells can also be identified, and in addition, there is a variable accompanying infiltrate of eosinophils, lymphocytes, and macrophages. Neoplastic Langerhans cells typically express CD1a, CD207, and S100. In addition, more than 60% of cases harbor *BRAF-V600E* mutations [83].

Germ Cell Tumors

Germ cell tumors including teratoma and germinoma can also involve the sellar region either as single site (unifocal) or in conjunction with a pineal tumor (bifocal tumor). Presenting symptoms overlap with those of Langerhans cell histiocytosis and craniopharyngioma, which represents the commonest tumor of the sellar region in the pediatric age group.

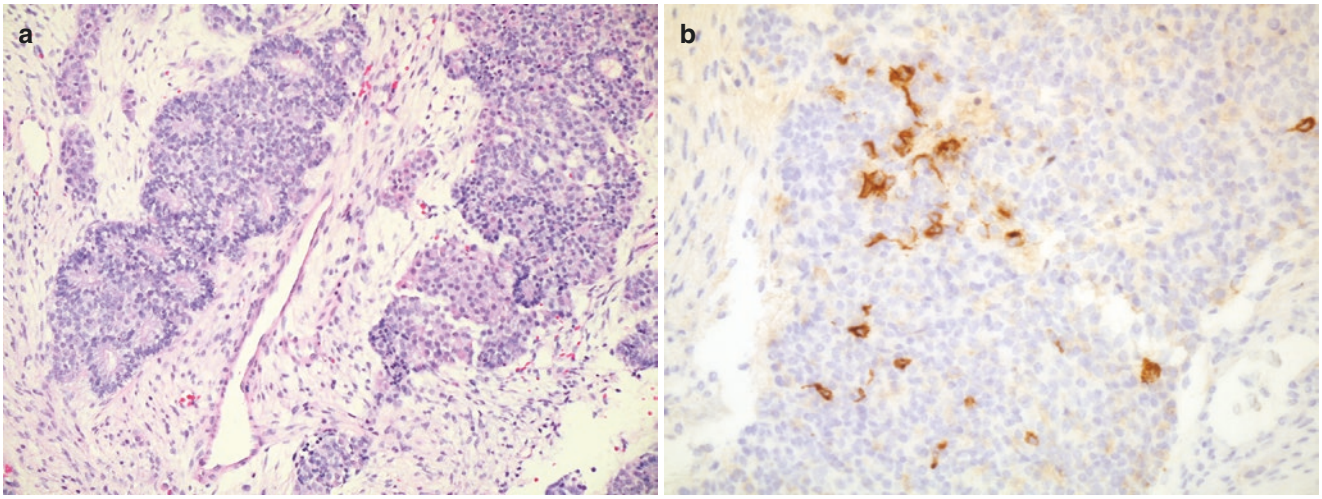

Fig. 9.7 Pituitary blastoma. Secretory cells, glandular or tubular elements resembling Rathke's pouch, and small primitive cells are identified. This lesion also contains a prominent mesenchymal stroma (**A**, H&E x 400). Immunoreactivity for ACTH is observed in larger epithelial cells (**B**)

Craniopharyngioma

Definition

Craniopharyngioma is a benign epithelial tumor of the sellar region that comprises two variants, the adamantinomatous craniopharyngioma and papillary craniopharyngioma, with distinct age distribution, clinical and morphological phenotypes [84]. Major differences also exist with regard to the likely cellular origin and underlying molecular pathogenesis between the two types. Overactivation of the WNT/β-catenin signaling pathway resulting from mutations in *CTNNB1* appears to be the key pathogenic event in adamantinomatous craniopharyngioma, whereas activation of the *Ras/Raf/MEK/ERK* pathway by *BRAF V600E* mutations likely drives the development of papillary craniopharyngioma [85].

Clinical Presentation

Adamantinomatous craniopharyngiomas shows a bimodal age distribution with peak incidences around 5–10 years and in the sixth decade. Congenital presentation is reported in rare cases [86–88]. Papillary craniopharyngioma occurs almost exclusively in adults [89].

Visual disturbances, headache, and cognitive dysfunction are encountered in both types. Endocrine deficiencies, diabetes insipidus, and cranial nerve palsy are more common in the adamantinomatous type. The latter also is associated with a high morbidity and mortality due to the locally aggressive and invasive growth these tumors exhibit with extension into adjacent brain structures, such as the optic chiasm, pituitary gland, and hypothalamus [84, 90]. Adamantinomatous craniopharyngioma infrequently show intrasellar extension. A primary ectopic, intracranial, or extracranial location is very rare [144].

Macroscopic Features

Adamantinomatous craniopharyngioma shows a multilobulated, solid and cystic or multicystic appearance [84]. In addition, there are frequent calcifications and cystic areas with necrotic, hemorrhagic, or cholesterol debris. Adherent neural or vascular tissue may be identified. Papillary craniopharyngioma typically presents as a circumscribed suprasellar or third ventricular mass and lacks calcifications, conspicuous necrosis, or hemorrhage [89].

Microscopic Features

Adamantinomatous craniopharyngioma is formed of anastomosing trabeculae of squamous epithelium that also shows peripheral palisading, loose stellate reticulum, microcystic change and nodules of ghost cells, called wet keratin, that are pathognomonic of this type [84]. Distinct epithelial nodules or whorls are frequently seen in the fingerlike protrusions of tumor tissue extending into the adjacent brain (Fig. 9.8). Microcalcifications, cholesterol clefts, and necrosis may be prominent, and occasionally, a florid granulomatous reaction is noted. Reactive gliosis with prominent Rosenthal fibers may be observed at the invasive edge. Broad proliferations of squamous epithelium with pseudopapillae resulting from epithelial clefting characterize papillary adamantinoma (Fig. 9.9). Moreover, small aggregates of keratinized cells, and mucinous cells or occasionally foci of ciliated epithelium can be observed. Peripheral palisading and ghost cells are consistently absent. The stroma may show mild inflammation and focal hyalinization. Calcifications and cholesterol granulomas are absent or scant [84, 89].

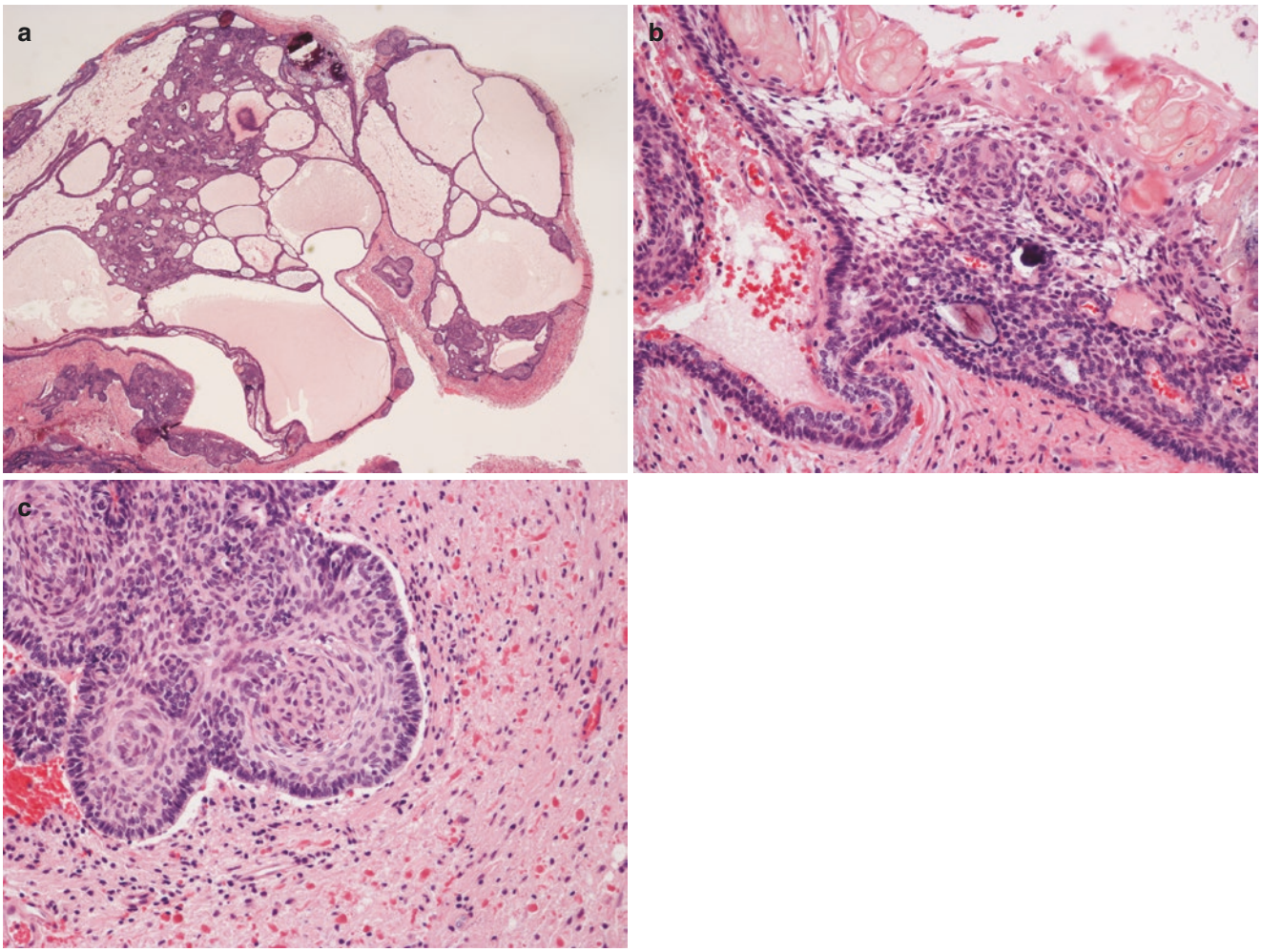

Fig. 9.8 Adamantinomatous craniopharyngioma. Low magnification (**A**) shows a cystic epithelial tumor (H&E × 20). Higher magnification demonstrates a proliferation of squamous epithelium with peripheral palisading, loose stellate reticulum, and nodules of ghost cells ("wet keratin") (**B**) (H&E × 400). Squamous whorls and reactive gliosis with prominent Rosenthal fibers are seen at the invasive tumor edge (**C**) (H&E × 400)

Immunohistochemistry and Molecular Diagnostic Features

Aberrant nuclear expression of β-catenin confined to the whorl-like epithelial clusters at the invasive front of the tumor and epithelial cells adjacent to ghost cells is demonstrated in almost all cases of adamantinous craniopharyngioma. In contrast, the epithelium in papillary craniopharyngioma and Rathke's cleft cyst retains a normal membranous staining pattern for β-catenin [18]. Underlying activating *CTNNB1* mutations or small deletions in exon 3 are identifiable in 76–100% of pediatric and adult adamantinomatous craniopharyngiomas, but are consistently absent in the papillary type and in Rathke's cleft cysts. Conversely, mutations in the *BRAF* oncogene (*BRAF V600E*) appear specific for papillary craniopharyngioma [85, 90–93].

Differential Diagnosis

Appropriate morphological classification of craniopharyngioma and distinction from Rathke's cleft cyst with squamous metaplasia, or in exceptional cases from other cystic or cystic and solid nonadenomatous epithelial lesions of the sellar region, may be challenging on small biopsies due to partly overlapping microscopic features, and not be achievable without further immunohistochemical and/or molecular testing. In such cases, immunohistochemical staining for BRAF V600E and β-catenin and molecular testing may assist in proper classification [94].

Epidermoid and dermoid cysts, thought to derive from ectodermal inclusions during neural tube closure, are distinguished from craniopharyngioma by their lining which consists of a keratinizing squamous and that they contain hair

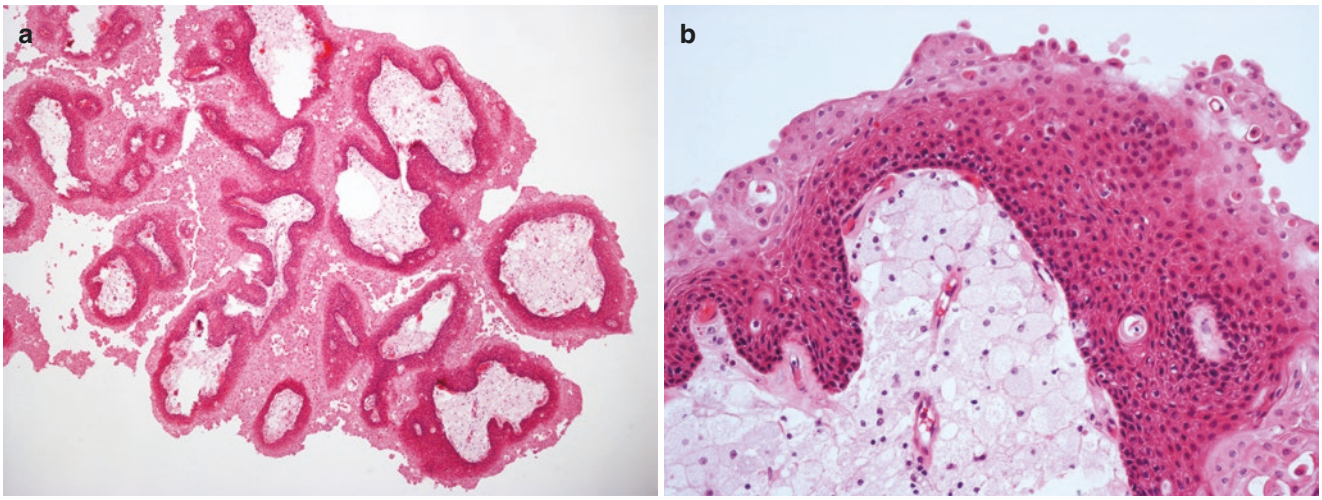

Fig. 9.9 Papillary craniopharyngioma. Low magnification (**A**) shows the pseudopapillary architecture of the tumor (H&E × 20). At higher magnification (**B**), the squamous epithelium lacks peripheral palisading and keratinization. The fibrovascular stroma in this case contains abundant foam cells (H&E × 400). (Courtesy Dr Lothar Resch, Calgary)

and other skin appendages in their wall. Teratomas typically comprise a mixture of tissues derived from more than one germ cell layer.

Finally, on small biopsies, the glial reaction in the adjacent brain tissue may raise concerns for a low-grade glial tumor [84]. Glial tumors of the optic chiasma can involve the sellar region through local extension.

Malignant Tumors

Non-Hodgkin Lymphoma

Definition

Non-Hodgkin lymphomas are malignant clonal proliferations of lymphoid cells. Extranodal non-Hodgkin lymphomas in the head and neck region develop most commonly in the lymphoid tissue of the Waldeyer's ring. In the pediatric population, diffuse large B-cell lymphoma and Burkitt's lymphoma are the commonest types. Pediatric-type follicular lymphoma and marginal zone lymphoma, both typically exhibiting a follicular architecture, are very rare [95].

It is thought that lymphomas of the nasopharynx, nasal/paranasal sinuses, and salivary glands are distinct from their respective nodal counter parts, and that they reflect the unique underlying biology and function of the lymphoid cells of the particular site involved [96].

Clinical Presentation

Diagnosis of lymphoma of the nasopharynx is challenging because it is rare, and symptoms may mimic adenotonsillar hypertrophy or infection.

Hereditary/Genetic Features

Populations at increased risk of developing NHL include children with congenital immunodeficiency disorders, such as Wiskott–Aldrich syndrome, ataxia telangiectasia, X-linked lymphoproliferative disorders, common variable immunodeficiency, Nijmegen syndrome, or autoimmune lymphoproliferative syndrome.

Classification/Subtypes

The vast majority of non-Hodgkin lymphomas arising from the nasopharynx in children are aggressive or high-grade Burkitt's lymphoma or diffuse large B-cell lymphoma. Primary adenotonsillar involvement by lymphoblastic lymphoma is very rare. Similarly, pediatric-type follicular lymphoma and nodal marginal zone lymphoma are exceedingly rare [97–99].

The lymphoid tissue of the Waldeyer's ring may also be involved by a nodal diffuse large B cell or by Burkitt's lymphoma, anaplastic lymphoma, sinonasal NK/T-cell lymphoma, and Hodgkin lymphoma. These are discussed in detail in Chap. 12.

Accurate classification of lymphomas requires comprehensive microscopic, immunophenotypic, cytogenetic, and molecular studies. Therefore, as emphasized earlier, adenotonsillar tissue should always be submitted unfixed and without delay for pathological examination.

Pediatric-Type Follicular Lymphoma

Classification

Follicular lymphoma in children are clinically and genetically different from follicular lymphomas occurring in

adults. Previously a provisional entity, the 2016 Revision of the World Health Organization (WHO) classification of lymphoid neoplasms recognizes pediatric-type follicular lymphoma as definite entity [97]. Pediatric-type follicular lymphoma (PTFL) occurs predominantly in male patients with a median age of 15 years (age range from 5 to 18 years) and shows a predilection for the head/neck. They are usually localized and display an indolent behavior [97–100].

Microscopic Features

Microscopic examination reveals at least partial effacement of the normal architecture of the lymphoid tissue with a follicular pattern of growth. The latter is characterized by expanded follicles without polarization and a thin mantle zone. These follicular infiltrates are composed of medium to large blastoid follicular center cells showing round/oval nuclei, a finely clumped chromatin and scant cytoplasm (Fig. 9.10). The architecture is entirely follicular; any diffuse component or areas of diffuse large B-cell lymphoma (DLBCL) exclude a diagnosis of PTFL.

Immunohistochemistry

PTFL is of germinal center B-cell origin and positive for CD20, CD79a, BCL6, and CD10, but negative for BCL2. The follicular infiltrates also show staining for follicular dendritic cells (CD21 and CD23). CD10 is only weakly expressed in residual reactive follicles. Ki67 demonstrates a high proliferation index. PTFL lacks the t(14;18) translocation seen in the usual, adult-type follicular lymphoma. Clonal immunoglobulin heavy chain (IGH) rearrangement is detected in 97% of cases. PTFL shows recurrent loss of heterozygosity in 1p36 and somatic mutations in the gene TNFRSF14 (tumor necrosis factor receptor superfamily) [101]. Also somatic mutations and deletions in the MAPK pathway (MAK/ERK pathway) have been reported [102]. These data suggest that PTFL has a different pathogenesis from usual follicular lymphomas with t(14;18) and has an indolent behavior.

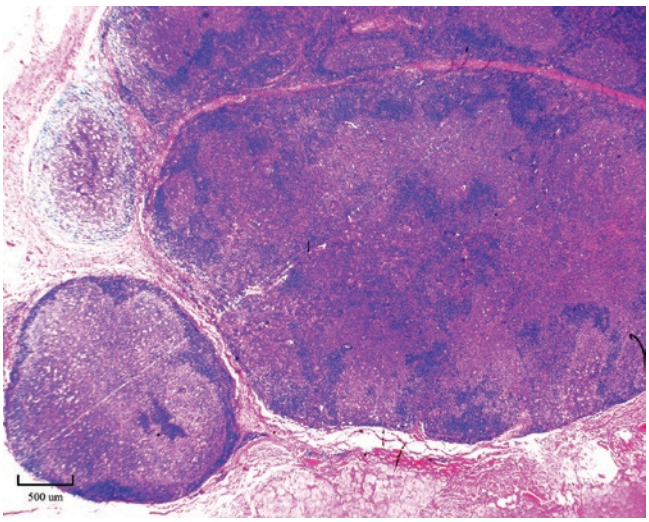

Fig. 9.10 Pediatric-type follicular lymphoma. Microscopic examination at scanning magnifications shows partial effacement of the normal architecture of the lymphoid tissue by confluent nodular infiltrates. H&E × 10. (Courtesy Dr B Ngan, Toronto)

Recently, another distinct type of lymphoma involving primarily the Waldeyer's ring has been described. Originally thought to represent a subtype of PTFL, the growth pattern is more variable and may be purely follicular, purely diffuse, or mixed diffuse and follicular. The neoplastic cells show strong and uniform positivity for MUM1 and BCL6. CD10 and BCL2 positivity is observed in greater 50% of cases, despite that these tumors do not harbor a t(14:18) translocation [95, 101, 103, 104]. In most cases, a novel translocation (IG/IFR4) with juxtaposition of the interferon regulatory factor super family (IRF) of transcriptions factors (IRF4) next to one of the immunoglobulin (IG) loci is identified. The most recent WHO classification categorizes this type of lymphoma as a provisional entity designated as large B-cell lymphoma with IRF4 rearrangement [97, 103, 105, 106].

Differential Diagnosis

The differential diagnosis of PTFL includes reactive follicular hyperplasia, progressive transformation of germinal centers, and other types of lymphoma that can show a follicular or nodular architecture, like marginal zone lymphoma, classical Hodgkin's lymphoma, and nodular lymphocyte predominant Hodgkin's lymphoma. Infectious mononucleosis also can mimic lymphoma.

Morphological features of marginal zone lymphoma can overlap with those of PTFL, but residual follicles in marginal zone lymphoma with expansion and fragmentation of germinal centers, as seen in progressive transformation of germinal centers, are often present [107, 108]. Unlike PTFL, the neoplastic CD20-positive cells in marginal zone lymphoma show co-expression of CD43. Moreover, CD10 and BCL6 are usually negative in marginal zone lymphoma. BCL2 may be positive in up to half of the cases [109]. The most frequent genetic aberration is trisomy 18 and rarely trisomy 3 and monosomy 20 [108, 110, 111].

Progressive transformation of germinal center (PTGC) is a nonspecific reactive pattern in which small mantle zone B cells infiltrate germinal centers leading to expansion and fragmentation of germinal centers and the follicular dendritic cell network which can be demonstrated by CD21 or CD23 immunohistochemical staining [112, 113]. Mitotic figures and tingible body macrophages are still apparent in the transformed follicle consistent with germinal center remnants (Fig. 9.11). PTGC is most often seen as focal change in association with reactive follicular hyperplasia, but can rarely be the primary reactive feature within an enlarged lymph node. PTGC has been reported in association with

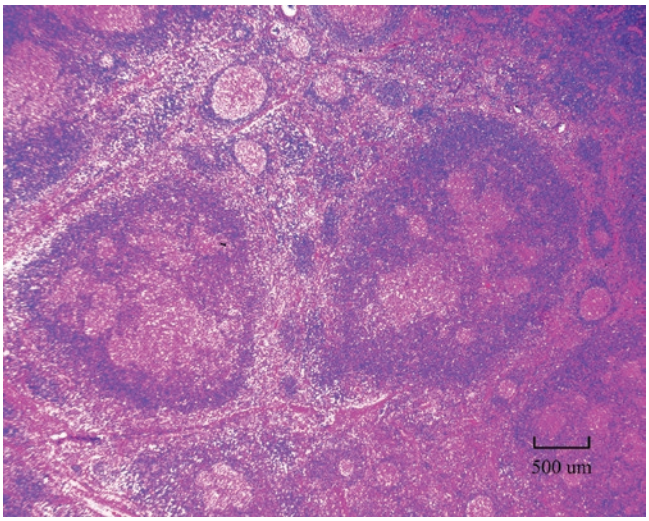

Fig. 9.11 Progressive transformation of germinal centers. Scanning magnification shows markedly enlarged follicles with fragmentation of germinal centers and infiltration by small mantle zone lymphocytes. H&E × 10. (Courtesy Dr B Ngan, Toronto)

autoimmune diseases [114]. Although the presence of PTGC should alert one to the possibility of a concurrent lymphoma, specifically nodular lymphocyte predominant Hodgkin's lymphoma, the vast majority of lymph nodes with PTGC are seen in patients without lymphoma.

Involvement of the nasopharynx by Hodgkin lymphoma is very rare [115, 116].

The diagnosis of infectious mononucleosis, or acute Epstein-Barr virus (EBV) infection, is usually made on the basis of clinical and laboratory findings. However, an atypical clinical presentation occasionally results in a lymph node or tonsillar biopsy. The morphological features of EBV-infected lymphoid tissue can easily mimic lymphoma [117]. The presence of an atypical lymphoid infiltrate with numerous CD20 and MUM1 positive, CD10, and BCL-6-negative immunoblasts should raise the suspicion of a reactive process, such as infectious mononucleosis, and warrants additional consideration such as EBER in situ hybridization before a diagnosis of lymphoma is made.

Posttransplant lymphoproliferative disorder (PTLD) most commonly is of B-cell type and associated with the Epstein-Barr virus (EBV) infection after solid-organ or bone marrow/stem cell transplantation. The majority of cases develop in the first 2 years following the transplantation. Young children are at increased risk. PTLD presents with a spectrum of morphological patterns ranging from nodular lymphoid hyperplasia to diffuse large cell lymphoma. A study of the utility of head and neck biopsies in the evaluation of posttransplant lymphoproliferative disorder in post liver, heart, and kidney transplant patients from a single institution showed that of the 22 cases of PTLD diagnoses, 16 cases were made from biopsies of tonsils and adenoids, 2 were from the soft palate, 1 was from the nasal turbinate, and the remaining 3 diagnoses from cervical lymph node biopsies [118].

Rhabdomyosarcoma

Definition

Rhabdomyosarcoma arises from primitive mesenchymal cells that are destined to differentiate into striated muscle cells. Rhabdomyosarcoma is the most common sarcoma of the nasopharynx in children.

Clinical Presentation

Rhabdomyosarcoma of nasopharynx, like most other masses occurring in children, frequently mimics upper respiratory tract infection and usually presents with nasal obstruction and mucopurulent discharge. More ominous signs pursuant to involvement of cranial nerves are diplopia and impaired ocular movements. Headache and papilledema may occur if there is intracranial involvement. Most cases arise before 5 years of age. Early diagnosis is important as localized tumors have a much better outcome. Nasopharyngeal location is classified as parameningeal site which is associated with a poor prognosis because of the high propensity for bony erosions and intracranial extension [119–121].

Hereditary/Genetic Features

Most cases have a sporadic presentation. In a small subset of patients, rhabdomyosarcoma is associated with the following genetic tumor predisposition syndromes: Li-Fraumeni syndrome, Rubinstein-Taybi syndrome, Gorlin-Goltz syndrome, Beckwith-Wiedemann syndrome, Costello syndrome, neurofibromatosis type I, constitutional mismatch repair deficiency syndrome, nevoid basal cell carcinoma syndrome, Noonan syndrome, and Dicer1 syndrome [119].

Classification/Subtypes

There are three histological variants of rhabdomyosarcoma (Table 9.2).

Embryonal rhabdomyosarcoma occurs in younger patients and no single genetic abnormality prevails. A small subset of cases harbors LOH at 11p15 or mutations of *FGFR4*, *P53*, *BCOR*, *ARID1A*, and *RAS*.

Alveolar rhabdomyosarcoma shows a predilection for older children and young adults. The genetic hallmark of alveolar rhabdomyosarcoma is the *FOXO1* translocation resulting in *PAX3-FOXO1* or *PAX7-FOXO1* fusions.

The rare spindle/sclerosing rhabdomyosarcoma can have *NCOA2* and *VGLL2* related fusions in congenital/infantile setting associated with a favorable outcome [122, 125]. *MYOD1* mutations are identified in older children and adults, and associated with a poor outcome [123, 124, 126].

Table 9.2 Rhabdomyosarcoma Classification [119, 121–125]

Type	Age	Histology	Genetics/Molecular
Embryonal	<5 years	Resembles fetal skeletal muscle	LOH 11p15 Mutations: *FGFR4*, *P53*, *BCOR*, *ARID1A*, *RAS*
Alveolar	>5 years, adolescents	Small round blue cells Alveolar or solid alveolar pattern	*FOXO1* translocation *PAX3* and *PAX7* fusion partners
Spindle Cell/Sclerosing	Any age	Spindle cells Hyalinizing stroma	*NCOA2* AND *VGLL2* fusions *MYOD1* mutations (poor prognosis)

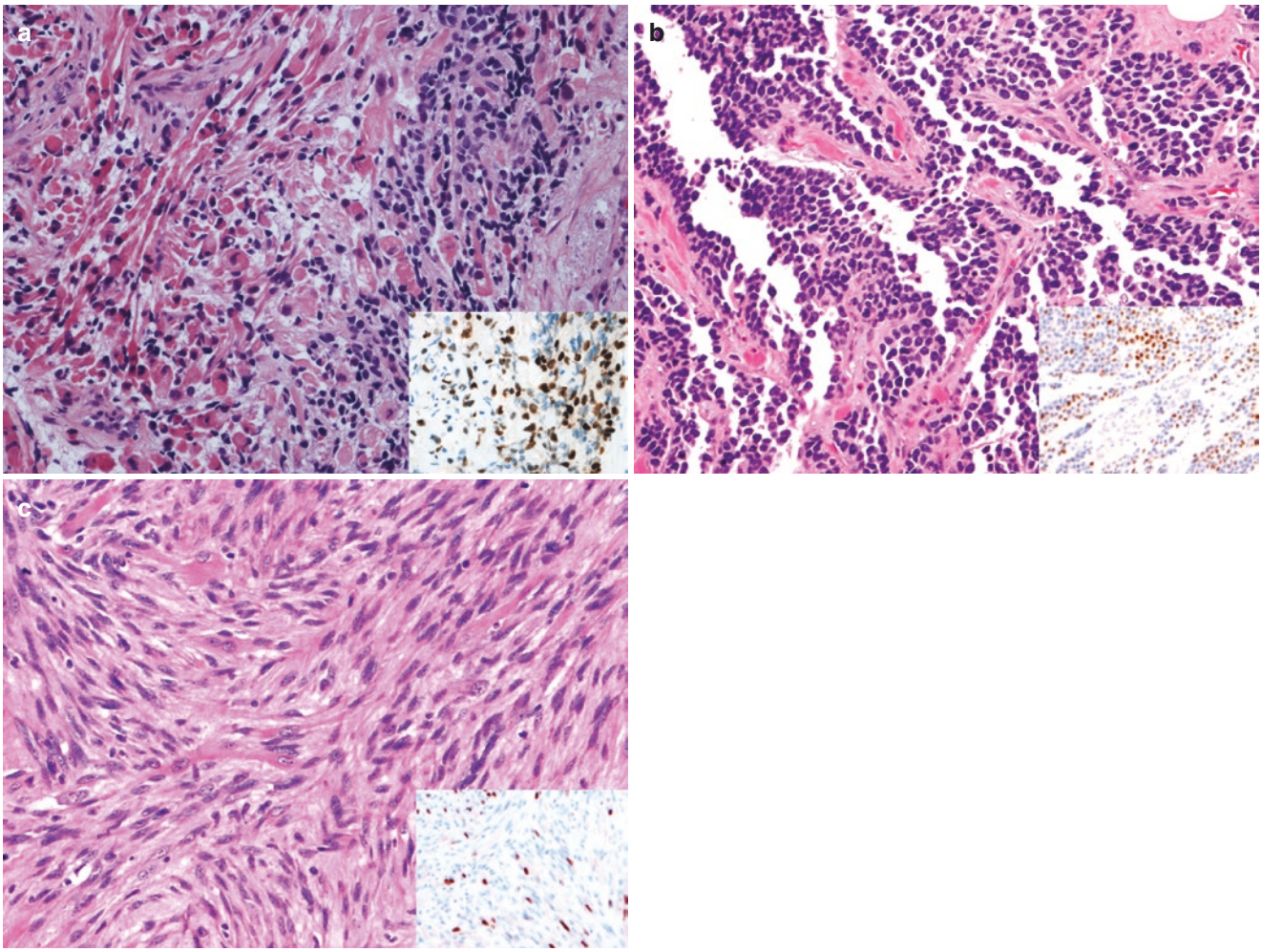

Fig. 9.12 Rhabdomyosarcoma (**A**). Embryonal (**B**). Alveolar (**C**). Spindle cell type H&E × 40. Insert, myogenin immunostain (×40)

Macroscopic Features

Nasopharyngeal rhabdomyosarcoma, if resected, appears as a poorly circumscribed, infiltrative pale fleshy tumor in the nasopharynx that can extend into the oropharynx, meninges, and brain.

Microscopic Features

Embryonal rhabdomyosarcoma shows a microscopic resemblance to embryonal skeletal muscle. It shows a myxoid stroma often with alternating hypocellular and hypercellular areas. Focal stromal hyalinization can be present. Tumor cells range from primitive-appearing stellate cells with sparse amphophilic cytoplasm to spindle and polygonal cells with brightly eosinophilic cytoplasm often showing cross striations (Fig. 9.12A). The botryoid variant of embryonal RMS typically occurs at mucosal sites and is characterized by an exophytic multi nodular growth. On microscopic examination, the tumor cells condense underneath an epithelial surface (referred to as the "cambium layer"). Cytological atypia varies from mild to severe.

Alveolar rhabdomyosarcoma, on the other hand, is composed of undifferentiated small round blue cells. The tumor cells appear discohesive and cluster around fibrovascular structures resulting in an alveolar pattern (Fig. 9.12B).

Rhabdomyoblasts are sparse and when present are small with minimal eosinophilic cytoplasm. Multinucleated wreath-like tumor giant cells are common. Some tumors show solid nested growth, called a solid alveolar pattern.

The classical spindle cell rhabdomyosarcoma is composed of monomorphic spindle cells that are arranged in intersecting fascicles and lack rhabdomyoblastic differentiation (Fig. 9.12C). A subset of spindle cell rhabdomyosarcoma displays areas of hyaline sclerosis, suggesting a morphological overlap with the even less common sclerosing rhabdomyosarcoma. The latter may show in addition an undifferentiated round cell pattern with cells arranged in a pseudovascular pattern associated with a hyalinized stroma [127].

Immunohistochemistry/Molecular Diagnostic Features

A combination of immunohistochemical stains is required to differentiate RMS from other small round cell tumors. This includes myogenin or MyoD1, desmin, sarcomeric actin, CD56, CD45, CD99, NSE, S100, and INI1. Rhabdomyosarcoma typically are positive for myogenin, MyoD1, desmin, and CD56. Myogenin belongs to a group of myogenic regulatory proteins whose expression determines commitment and differentiation of primitive mesenchymal cells into skeletal muscle. Alveolar rhabdomyosarcoma shows a stronger and more widespread nuclear staining than embryonal rhabdomyosarcoma. Identification of a *FOXO1* rearrangement confirms alveolar rhabdomyosarcoma.

Differential Diagnosis

In the nasopharynx, rhabdomyosarcoma, especially the alveolar variant, must be distinguished from other small round blue cell tumors, such as Ewing sarcoma, mesenchymal chondrosarcoma, olfactory neuroblastoma, or lymphoma. Classic Ewing sarcoma shows diffuse membranous expression of CD99, and translocations involving the *EWSR1* gene are typically identified. Olfactory neuroblastoma usually shows positivity for neuroendocrine markers (synaptophysin, chromogranin) and S100 staining of sustentacular cells. Mesenchymal chondrosarcoma can show spindle cells and cartilaginous foci as well as variable staining for CD99 and desmin. Recently, a recurrent translocation (*HEY1-NCOA2*) has been identified [128–130]. Staining for CD45 and other lineage-specific lymphoid markers may be required to exclude the possibility of lymphoma.

Chordoma

Definition

Chordoma is a midline bone tumor thought to arise from remnants of the fetal notochord (axial mesoderm) in the craniovertebral canal.

Clinical Presentation

Chordoma is very rare in the pediatric population with cases reported from the neonatal period to adolescence [131, 132]. The clivus is the site of origin in 70% of pediatric chordomas [132]. Nasopharyngeal or retropharyngeal involvement can be seen but is more commonly due to secondary tumor involvement. Symptoms relating to compromise of adjacent anatomic structures include headaches, torticollis, cranial nerve palsy, and brain stem compression. Rare familial cases have been reported [133, 134].

Macroscopic Features

Chordoma presents as gelatinous or myxoid mass and typically causes destruction of the bone.

Microscopic Features

Classical chordoma is formed of cords, nests, and sheets of polygonal cells with a pale eosinophilic vacuolated cytoplasm set in a myxoid or mucoid stroma with delicate fibrovascular septa (Fig. 9.13). Cellular pleomorphism and focal necrosis are frequently observed. Microscopic variants include the chondroid variant with focal areas resembling hyaline cartilage and the aggressive sarcomatoid (dedifferentiated) variant. In a series of 12 pediatric patients, the latter variant was present in half of the cases, leading the authors to suggest that a greater histological variability compared to adults may account for a more aggressive clinical course in children [131].

Immunohistochemistry and Molecular Diagnostic Features

Chordomas strongly express cytokeratins [131]. A vast majority of cases also is positive for vimentin and epithelial membrane antigen. Expression of S100 is more variable [131, 135]. More recently, consistent nuclear expression of brachyury has been demonstrated [136]. In a recent series of 8 cases, 4 cases showed lack of INI1 expression by immunohistochemistry. *SMARCB1* mutations were found in 3 cases, including one case with retained INI1 expression [137]. This suggests that SMARCB1/INI1-negative chordoma may represent a distinct group of chordomas.

Differential Diagnosis

Immunohistochemistry assists in differentiating chordoma from chondrosarcoma arising from the skull base, and from rhabdomyosarcoma or nasopharyngeal carcinoma which may show microscopic features that overlap with those of chordoma.

Chondrosarcoma lacks expression of brachyury and also is negative for cytokeratins and EMA. Immunoreactivity for markers of skeletal muscle differentiation (desmin and myogenin or MyoD1) confirms rhabdomyosarcoma. Nasopharyngeal carcinoma in almost all cases is positive for

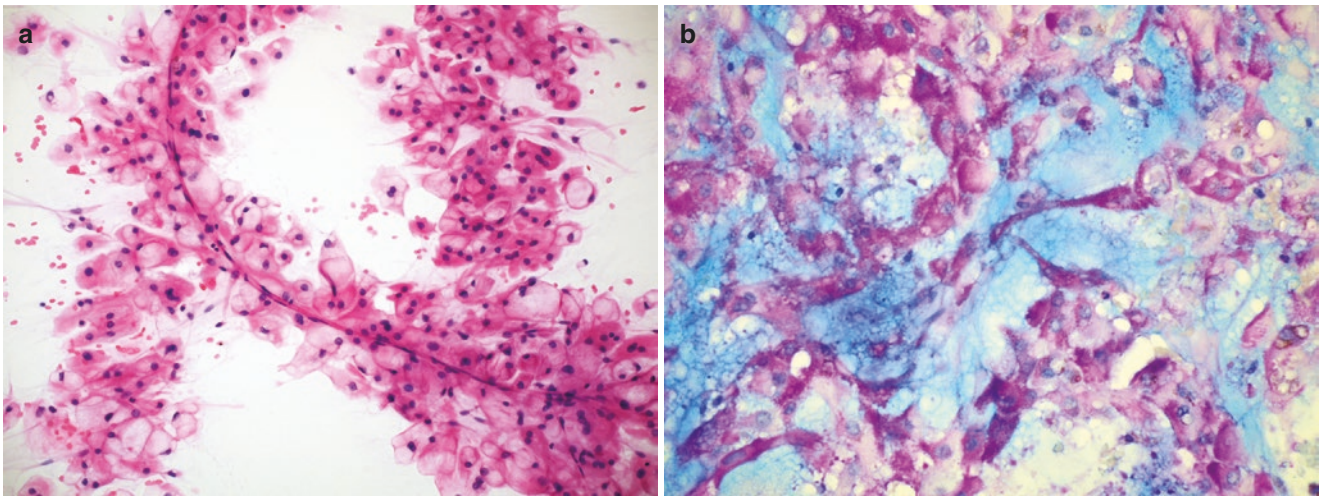

Fig. 9.13 Chordoma. A cytological smear preparation (**A**) shows large vacuolated cells with small bland nuclei and delicate fibrovascular septa (H&E × 400). Cords and nests of tumor cells are surrounded by a prominent myxoid matrix (Alcian blue-PAS, × 400) (**B**)

EBV using EBER in situ hybridization. Tumors arising from the pituitary region may also need to be considered if extending into adjacent bony structures. Pituitary (macro) adenomas, craniopharyngioma, and Langerhans cell histiocytosis can usually readily be identified by their distinct microscopic features and immunohistochemical staining characteristics.

Nasopharyngeal Carcinoma

Definition

Nasopharyngeal carcinoma is a rare aggressive type of cancer that arises from the nasopharyngeal mucosa and shows epidermoid differentiation. Nasopharyngeal carcinoma moreover shows a distinct racial and geographic distribution with endemic areas in South East Asia, the Mediterranean, and Alaska. Almost all cases are associated with serological and molecular evidence of EBV infection [138]. The WHO classification distinguishes between three types of nasopharyngeal carcinoma: the keratinizing squamous cell carcinoma (WHO grade 1), the nonkeratinizing squamous carcinoma, including the differentiated subtype (WHO grade 2) and the undifferentiated subtype (WHO grade 3), and the basaloid carcinoma [139].

Clinical Presentation

The incidence of nasopharyngeal carcinoma in children is significantly lower compared to adults (0.5 vs 8.4 per million person years) [140]. Among children, a higher incidence is noted in black children and those from endemic regions. Moreover, there is a male preponderance. Nasopharyngeal carcinoma frequently presents with advanced locoregional disease and lymph node metastases. Consequently, painless cervical lymphadenopathy is a very common presenting sign [140, 141]. Other symptoms include signs of nasal obstruction, bloody discharge and epistaxis, diminished hearing, recurrent ear infections, and cranial nerve dysfunction. In exceptional cases, patients may present only with cervical lymphadenopathy.

Macroscopic Features

Most tumors develop from the lateral wall of the nasopharynx and present as exophytic mass. [138].

Microscopic Features

The undifferentiated carcinoma (WHO grade 3) is the commonest histological type encountered in children [140, 142]. It consists of cords and sheets of large cells with amphophilic cytoplasm and poorly defined cell borders. The nuclei are large and appear vesicular with prominent nucleoli (Fig. 9.14). Characteristically, the epithelial cells are intermixed with inflammatory cells, including lymphocytes, plasma cells, and eosinophils. If prominent, the inflammatory component may obscure the epithelial component. Granulomas can also be seen. Microscopic features of undifferentiated nasopharyngeal carcinoma may overlap with those of Grade 2 tumors that are characterized by squamous differentiation without overt keratinization. WHO grade 1 tumors are indistinct from keratinizing squamous cell carcinoma at other sites and exceedingly rare in children. Also, grade 1 tumors usually are not associated with EBV infection [139].

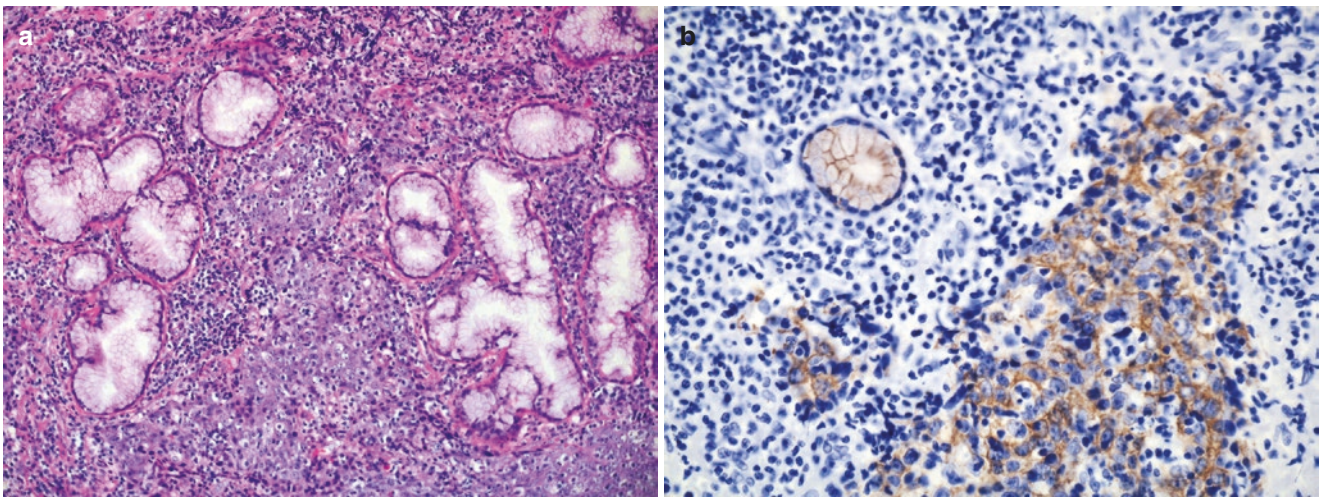

Fig. 9.14 Nasopharyngeal carcinoma. Sheets of large undifferentiated epithelial cells which are partly obscured by the accompanying dense inflammatory infiltrate extend in between normal submucosal mucinous glands. The cells show large vesicular nuclei and prominent nucleoli (**A**, H&E × 400). Immunohistochemical staining for keratin creates a meshwork-like pattern (**B**, × 400)

Immunohistochemistry and Molecular Diagnostic Features

Nasopharyngeal carcinoma is immunoreactive for pancytokeratins and high-molecular-weight keratins (AE1/AE3, CK5/6, 34βE12) but negative for CK7 and CK20 [138]. EBV-encoded early RNA (EBER) can be demonstrated in virtually all cases of undifferentiated nasopharyngeal carcinoma by means of in situ hybridization. Immunohistochemistry for EBV-LMP is much less sensitive [139].

Differential Diagnosis

The differential diagnosis of undifferentiated nasopharyngeal carcinoma is broad but usually can be resolved using immunohistochemistry and molecular genetic testing. It includes the very aggressive undifferentiated carcinoma associated with *BRD4-NUT* rearrangement [143], anaplastic large cell lymphoma, Hodgkin's lymphoma, rhabdomyosarcoma, and less commonly other types of sarcomas. Prominent germinal center cells or plump endothelial cells in reactive lymphoid hyperplasia also can be confused with undifferentiated NPC especially on small or crushed biopsies.

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