7 Pediatric Surgical Pathology of the Nasal Cavity, Paranasal Sinuses, and Skull Base

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Benign Conditions:

1. Chronic Eosinophilic Rhinitis or Chronic Rhinitis with Nasal Polyps or Without Nasal Polyps and Noneosinophilic Chronic Rhinosinusitis

Definition

A common inflammatory condition of the paranasal sinuses and nasal passages. This condition is classified into two subtypes, those associated with polyps and the remaining without polyps. Definition/subclassification is best by the incorporation of the basic pathogenic mechanism where the immune system has a major role in both the initiation and sustaining phases. Loss of the immune barrier is common to all types and the subsequent manifestations by a very heterogeneous group of inflammatory mediators from the immune system on tissue remodeling lead to positive or negative polyp formation. Recently, cytokines interleukin (IL)-5 and IL3 coming from Th2 cells, type 2 innate lymphoid cells, and probably mast cells (IgE-positive mast cells) are reported to be associated with chronic rhinosinusitis with polyps [1, 2]. A histopathological study found that those with polyp formation had statistically significant increase in basement membrane thickening, subepithelial edema, fibrosis, eosinophilia, and in particular eosinophil aggregates [3]. Eosinophil aggregates are found to be associated with significantly worse disease [3]. In noneosinophilic chronic rhinosinusitis, the inflammatory cells are dominated by Th1 types of T cell [2].

Microscopic Features

For chronic eosinophilic rhinitis, the edematous respiratory mucosa of the polypoid mucosa is infiltrated by chronic inflammatory cells with a prominent population of eosinophils (Fig. 7.1). Charcot–Leyden crystals are present. The basement membrane of the epithelium is thickened (Fig. 7.2). Acute inflammation is light and no vasculitis and no fungi are found.

For chronic rhinitis, eosinophils are not the major component of the inflammatory infiltrates. For inflammatory polyps, mucosal edema is significant. Without eosinophils, both forms likely represent a milder form of disease (Fig. 7.3).

Differential diagnosis for chronic eosinophilic rhinitis is that of Langerhans cell histiocytosis where atypical histiocytes with nuclear grooves are admixed with histiocytes and

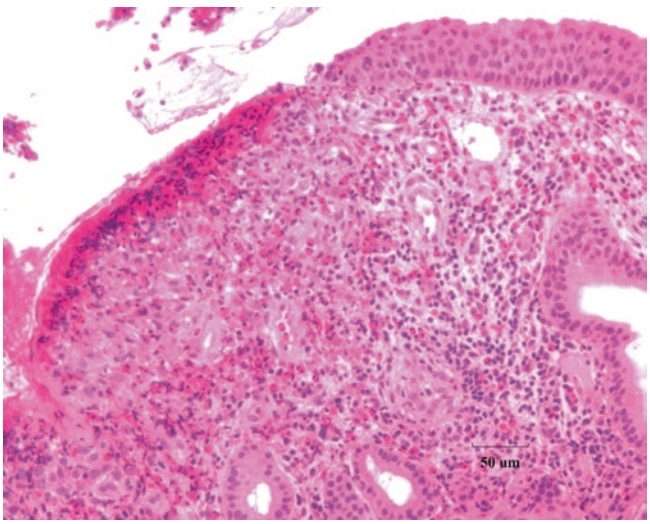

Fig. 7.1 Chronic eosinophilic rhinitis. H&E. Mucosa with ulcer, profuse chronic inflammatory cellular infiltrates with prominent eosinophils

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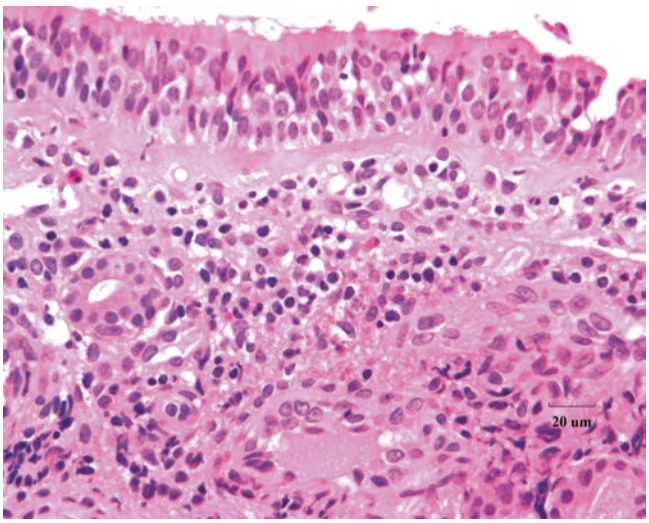

Fig. 7.2 Chronic eosinophilic rhinitis. H&E. Mucosa with chronic inflammation. Hyaline changes in the region of the epithelial basement membrane indicates early stages of basement membrane thickening

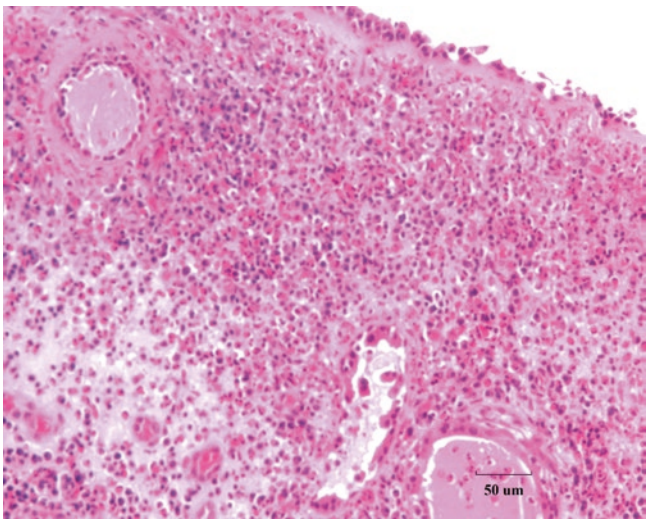

Fig. 7.4 Allergic fungal sinusitis. H&E. Marked infiltrates of chronic inflammatory cells with large numbers of eosinophils. Fungal stains are positive (by GMS stain, not shown)

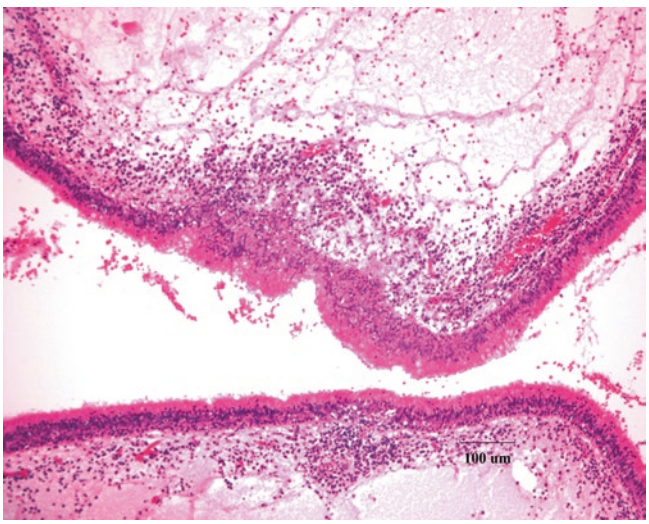

Fig. 7.3 Inflammatory polyp. H&E. Superficial mucosal chronic inflammation with marked mucosal edema

eosinophils. For polyps with eosinophilia, aberrant arachidonic acid metabolism (such as aspirin) can be the cause. For polyps with surface infiltration of neutrophils, cystic fibrosis can be the underlying cause.

2. Allergic Fungal Sinusitis and Invasive Fungal Sinusitis

Definition

Five diagnostic criteria for allergic fungal sinusitis was proposed by Bent and Kuhn are: Type 1 IgE-mediated hypersensitivity; nasal polyposis; characteristic computed tomography findings such as bony erosion in the skull base and orbit and remodeling with a pushing border in the lamina papyracea and the skull base; and eosinophilic mucus and positive fungal smear [4]. Studies on tissues show a range of observations from increase in IgE levels to increase in fungal-specific IgE mast cells in the sinus epithelium and subepithelium [5].

Nasal polyposis is classically seen in the initial presentation as well as during recurrence.

Microscopic Features

For allergic fungal sinusitis, the respiratory mucosa and submucosa is edematous to convey a polypoid appearance and the mucosa has inspissated and laminated mucin. Necrotic foci with neutrophil infiltrates, some intra-epithelial, some within mucinous debris can be present. The mucosa is infiltrated by lymphocytes, plasma cells, eosinophils, and scattered Charcot–Leyden crystals can be found (Figs. 7.4 and 7.5). Leukocytoclastic vasculitis is absent.

Special stains for fungi, namely Grocott methenamine-silver nitrate stain (GMS) will stain the fungal elements black. Typically, if aspergillus is the cause, the organisms have septate hyphae with branching at acute angles, they are nested within the acellular necrotic tissues and the adjacent inflamed polypoid mucosa.

For Invasive Fungal Sinusitis

The respiratory mucosa shows injuries secondary to the inflammatory infiltrates in response to the infection. A mixed inflammatory infiltrate of neutrophils, lymphocytes, plasma cells, and numerous eosinophils are present. The glands within the soft tissue are distended and contain deeply eosinophilic-impacted secretion. Lamellated necrotic tissue, associated with heavy, mixed inflammation can be seen.

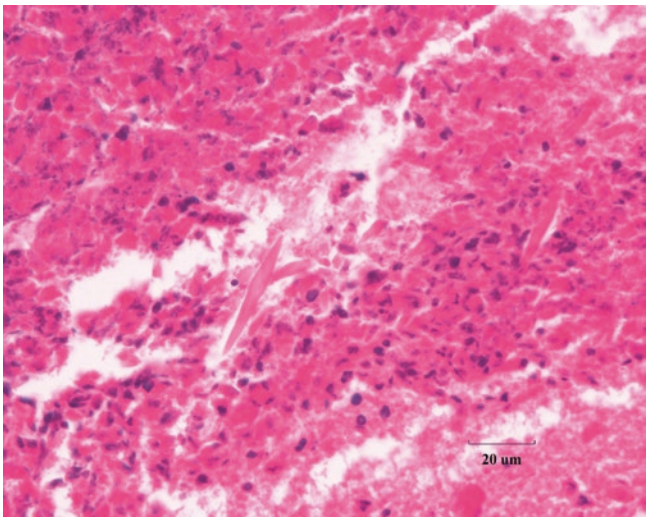

Fig. 7.5 Allergic fungal sinusitis. H&E. Marked infiltrates of chronic inflammatory cells with large numbers of eosinophils. A Charcot–Leyden crystal is deposited among the inflammatory infiltrate

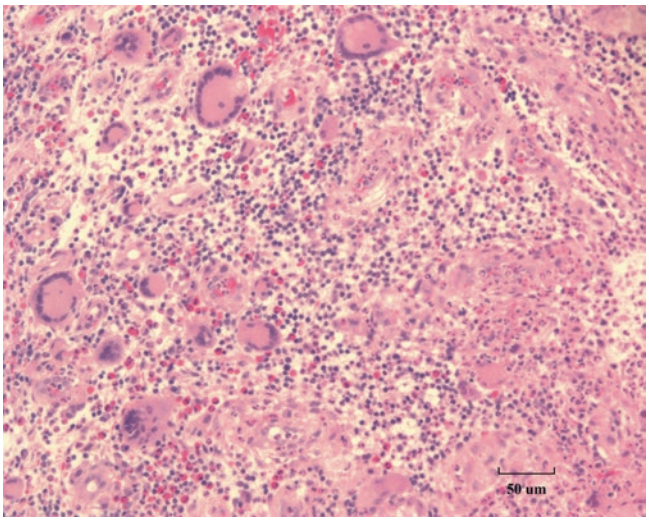

Fig. 7.6 Wegener's granulomatosis in the turbinate. H&E. Numerous multinucleated giant cells are present within infiltrates of lymphocytes, plasma cells, and some eosinophils. The small blood vessels have features of acute vasculitis. Specific histochemical stains for fungi and acid fast bacilli are negative (not shown)

Infection can infiltrate into the sinus bone matrix and it is accompanied by lymphoplasmacytic chronic inflammatory cells.

Special stains for fungi, GMS stain, will stain the fungal elements black. Typically, if aspergillus is the cause, the organisms have septate hyphae with branching at acute angles, they are nested within the acellular necrotic tissues and the adjacent inflamed polypoid mucosa.

3. Wegener's Granulomatosis (Now Known as Granulomatosis with Polyangiitis)

Definition

Granulomatosis with polyangiitis formally known as Wegener's granulomatosis is a clinical pathological syndrome of unknown etiology with multiorgan histopathological findings of necrotizing granulomatous inflammation, vasculitis, and parenchymal necrosis and positive serology for antineutrophil cytoplasmic antibodies. Pulmonary, otologic, and ocular manifestations are common along with glomerulonephritis. Gastrointestinal, genital urinary, and central nervous system manifestations can occur [6]. Nasal disease is common and manifests as crusting, discharge, ulcers, septal perforations, and destruction of nasal cartilage leading to saddle nose deformity [7].

Microscopic Features

Multiple nasal biopsies larger than 5 mm in at least one dimension had been identified as a useful means of diagnosing Wegener's granulomatosis [6, 8]. The important features in the nasal tissues are: active vasculitis and foci of fibrinoid necrosis/microabscesses, vasculitis, epithelioid granulomas, giant cell infiltrates (Fig. 7.6), and vasculitis involving small arteries and veins in a majority of cases. Some nasal biopsy cases may not have granulomatous vasculitis while extravascular necrosis or fibrinoid necrosis is usually present. Some samples may also exhibit nongranulomatous vasculitis at this site perhaps as early lesions. Intimal fibrosis, stromal inflammation, and presence of giant cells are the most frequent features [8].

4. Nasal Xanthogranuloma

Definition

Nasal juvenile xanthogranuloma (JXG) is a non-Langerhans cell histiocytic lesion. It usually presents as a solitary cutaneous lesion, most often in the head and neck region. Multiple skin lesions can be seen and a subset of patients have widespread systemic involvement.

Macroscopic Features

Skin papules or nodules are usually yellow to reddish brown and range from 0.1 to 1.0 cm in diameter. There are deep variants that extend into the subcutis and even into skeletal muscle.

Microscopic Features

JXGs are characterized by a dense dermal infiltrate of histiocytes. Several cell types have been identified including vacuolated or foamy, scalloped, and oncocytic [9–11]. Small histiocytes with moderate faintly vacuolated, pale eosinophilic cytoplasm predominate in early lesions. The nuclei are round to oval and may be indented. Xanthomatous cells

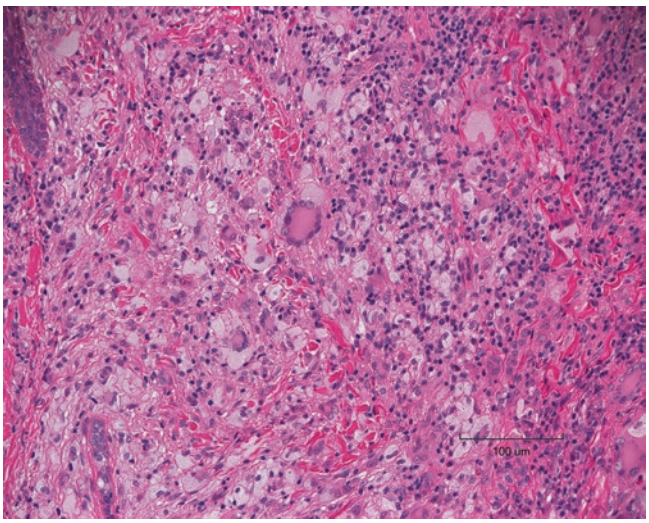

Fig. 7.7 Nasal juvenile xanthogranuloma, H&E, with an infiltrate of histiocytes including xanthomatous cells and Touton-type giant cells

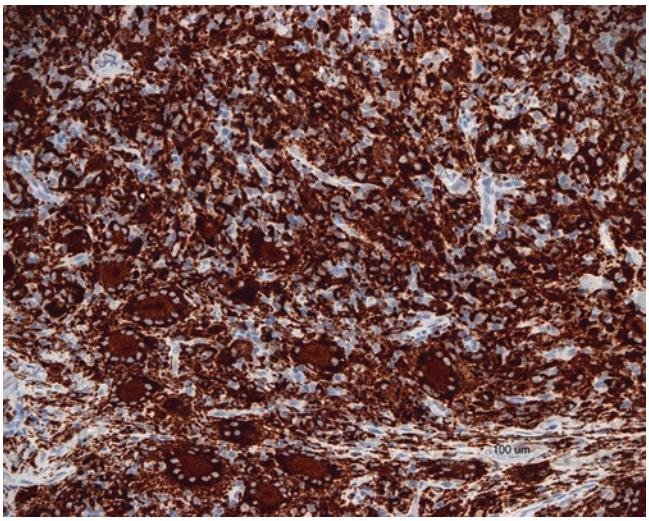

Fig. 7.8 Juvenile xanthogranuloma, immuno stain for CD68 for macrophages shows abundant macrophages in the lesion

increase with the age of the lesion. Multinucleated giant cells including foreign body and Touton type are common. Touton giant cells are a histologic hallmark of JXG but are not required for the diagnosis as they may be absent in early- or late-stage lesions. Present in approximately 85% of JXGs, Touton giant cells consist of a wreath of nuclei around a core of eosinophilic cytoplasm and an outer xanthomatous layer (Fig. 7.7). Background inflammatory cells, including eosinophils and lymphocytes, may be present. A proliferation of fibroblasts with fibrosis replacing the cellular infiltrate characterizes late-stage lesions. Mitoses may be seen, particularly in early lesions.

Ancillary Tests

The lesional cells express macrophage markers including CD68 (Fig. 7.8), CD163, and CD14. CD4 is positive in the histiocytes. There is strong staining for fascin. Factor XIIIa (Fig. 7.9) staining is typically seen at the periphery of the lesion. There is variable staining with S100. CD1a and Langerin are negative.

Differential Diagnosis

Recognition of the varying morphology of JXG is important for making the correct diagnosis. Early lesions can resemble Langerhans cell histiocytosis especially when there is scant lipidization and eosinophils are prominent. In Langerhans cell histiocytosis, the nuclei are more reniform and the cells are positive for CD1a and Langerin. JXGs with a prominent spindle cell component may resemble dermatofibroma.

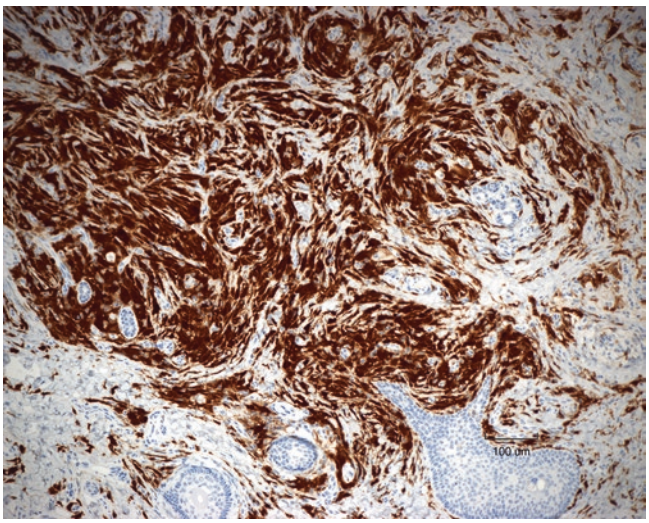

Fig. 7.9 Juvenile xanthogranuloma, immuno stain for Factor XIIIa shows many positively stained histiocytes

Benign Mid-Line Masses

5. Nasal Dermoid Cyst

Definition

A congenital developmental disorder that belongs to the category of benign teratoma (germ cell neoplasm) [12]. Its presentation varies in degrees of severity. Midline congenital anomalies occurs one out of 20,000–40,000 births

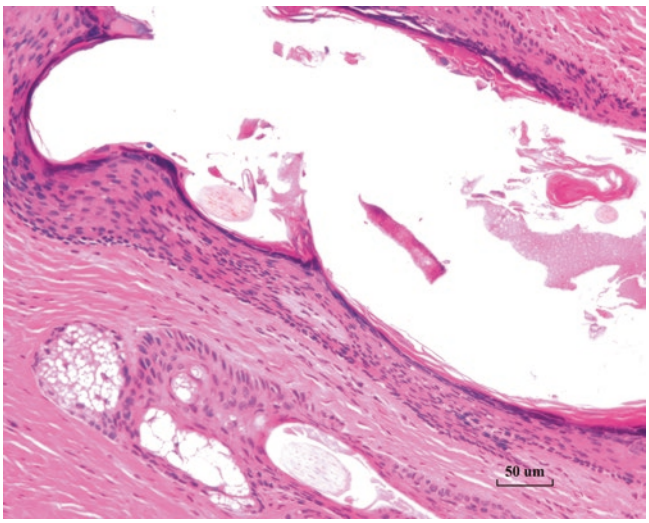

Fig. 7.10 Dermoid cyst. H&E. Cyst wall is lined by keratinizing squamous epithelium with adnexal glandular components. Hair and degenerated desquamated keratinized squamous cells accumulates within the cyst lumen

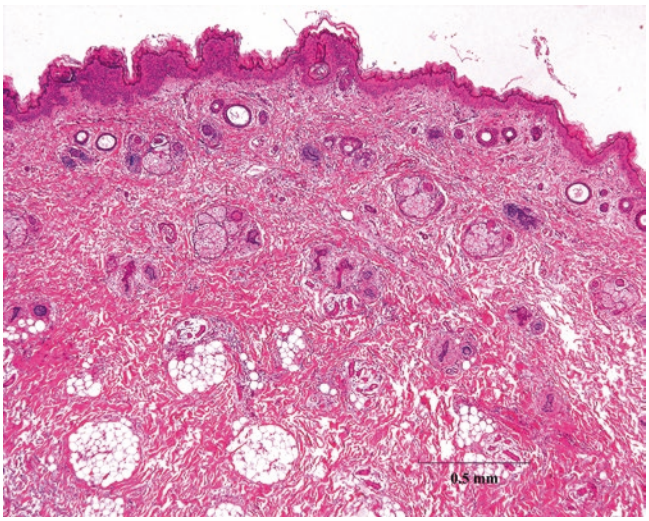

Fig. 7.11 Hairy polyp. H&E. Surface of the polyp is lined by epidermal and dermal tissues. The squamous epithelium contains fully developed hair follicles with sebaceous glands

and nasal dermoids are most common [13]. According to a proposed classification from the Great Ormond Street Hospital, the types of nasal dermoids are: superficial, intraosseous, intracranial extradural, and intracranial and intradural [14, 15]. Dermoid cysts are ectodermal in origin located along the lines of embryonic fusion. Histologically, they are lined by keratinizing squamous epithelium with attached pilosebaceous structure (Fig. 7.10). Eccrine and apocrine glands and smooth muscles may be present in the wall of 25% of these cysts. The sebaceous glands empty into the cyst lumen which is often filled with hair shafts and keratinous debris.

6. Hairy Polyp

Definition

A benign polyp composed of ectoderm and mesoderm. At this location it is exceedingly rare. Nevertheless it has been reported [16]. Most common location is the nasopharynx with a female predominance.

Microscopic Features

The surface of the polyp is a keratinized squamous epithelium containing pilosebaceous units. The polyp stroma is fibroadipose tissue (Fig. 7.11). The histological differential diagnosis includes lipo-epithelial polyp where the stroma of the polyp is predominantly mature adipose tissue (Fig. 7.12).

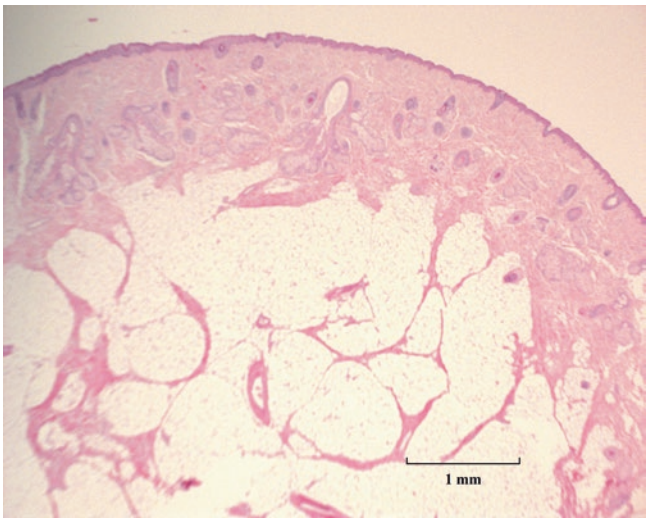

Fig. 7.12 Lipo-epithelial polyp. H&E. Epidermal and dermal tissues occupy the surface with a mature lipocyte rich stroma

7. Polyp Associated with Cystic Fibrosis

Definition

Cystic fibrosis (CF) is an autosomal recessive disorder affecting approximately 30,000 children in the US. It is associated with mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel that affects mucociliary transport. The most deleterious effect is to the lungs and the GI tract. CF patients have thick tenacious

mucin and chronic rhinosinusitis is ubiquitous. Nasal polyps are seen in up to 86% patients [17]. Neutrophil inflammation in the polyp mucosa is mediated by IL-8 [18]. Infection by *Pseudomonas aeruginosa* or *Staphylococcus aureus* are common.

Microscopic Features

The mucosal polypoid structure is lined by pseudostratified ciliated columnar epithelium with focal squamous metaplasia. The stroma is edematous and infiltrated by mixed inflammatory cell infiltrate composed of lymphocytes, eosinophils, plasma cells, mast cells, and scattered neutrophils (Fig. 7.13). Mucicarmine or Alcian blue-periodic acid Schiff (AB-PAS) stain shows mucin deposit within the stroma (Fig. 7.14). Focally, the epithelium is infiltrated by neutrophils. These findings are important to distinguish this polyp from fibro-inflammatory nasal polyps which are the commonest in this region.

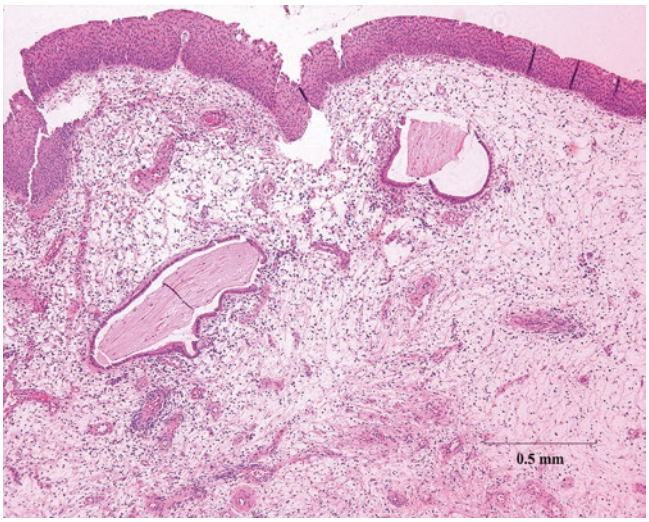

Fig. 7.13 Polyp in cystic fibrosis. H&E. Mucosa of the polyp lined by non-keratinizing squamous epithelium exhibit mild chronic inflammation mimicking an inflammatory polyp. The edema-like mucosa, however, contains abnormal sulfated mucopolysaccharides from abnormal and excessive production caused by the underlying cystic fibrosis (mucoviscidosis) disease, see Fig. 7.14

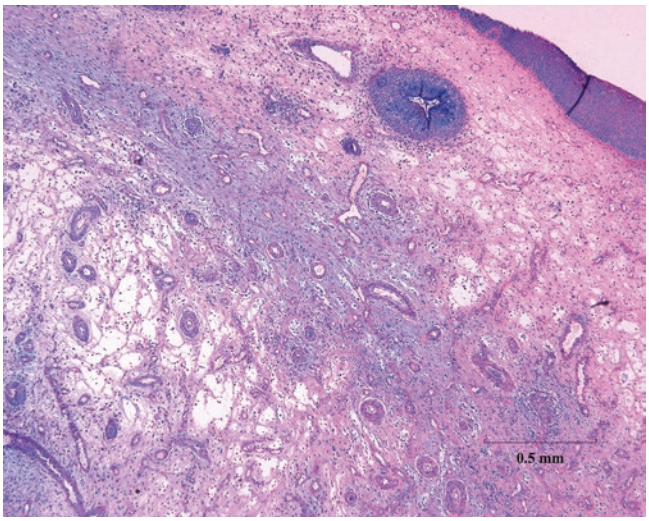

Fig. 7.14 Alcian Blue-PAS stain of polyp in cystic fibrosis. Positive staining generates a magenta/blue color to the mucopolysaccharides and mucin deposited within the polyp stroma

8. Nasal Encephalocele

Definition

Encephaloceles are formed by a defect in the neural tube, characterized by a herniation of the brain and meninges through structural weakness in the bony structures of the skull [19]. A developmental disturbance in the separation of surface ectoderm and the neuroectoderm in the midline just after the closure of the neural folds occur during the fourth gestational week results in this late neurulation defect [20]. If this occurs in the skull base (basal encephalocele) and ethmoid bone (frontoethmoidal encephalocele), the encephalocele so formed may herniate into nasal structures causing obstruction. Both entities are rare with an incidence that ranges from 1 in 5000 to 1 in 40,000 live births around the world [19] and frontoethmoid encephaloceles have the highest incidence in Southeast Asia affecting 1 in 5000 births [20]. Histopathologically, one expects to find both tissue components, that is, brain tissue and meningeal tissue with normal histological features with the tissue mass (Figs. 7.15 and 7.16).

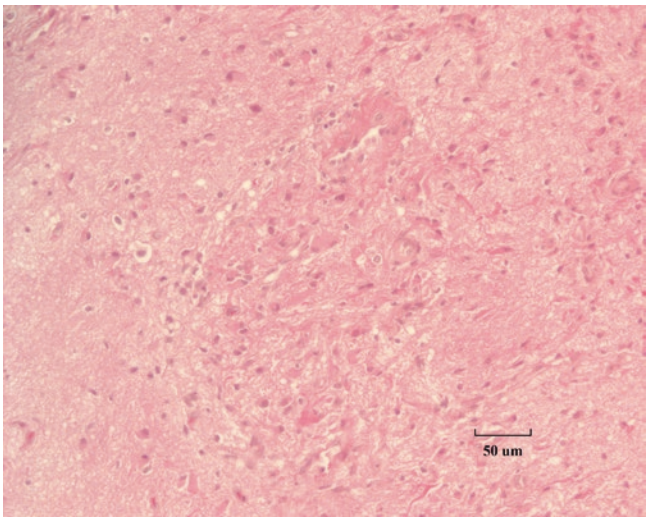

Fig. 7.15 Nasal encephalocele. H&E presence of brain tissue with reactive astrocytes within a neurofibrillary matrix

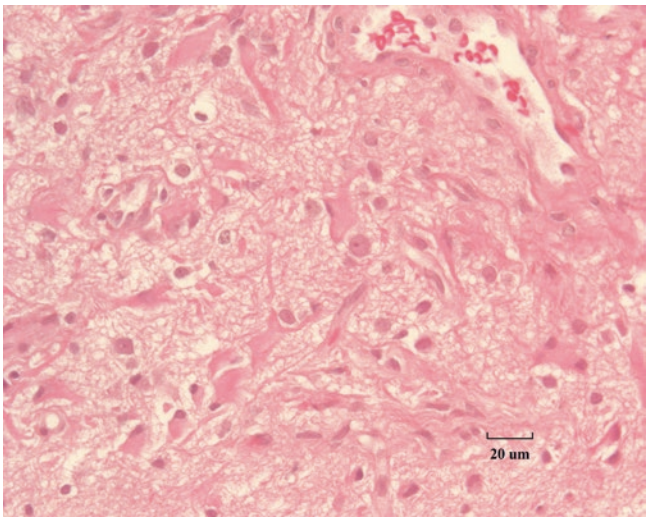

Fig. 7.16 Stroma of nasal encephalocele. H&E. Neurofibrillar matrix with astrocytes and glial tissues

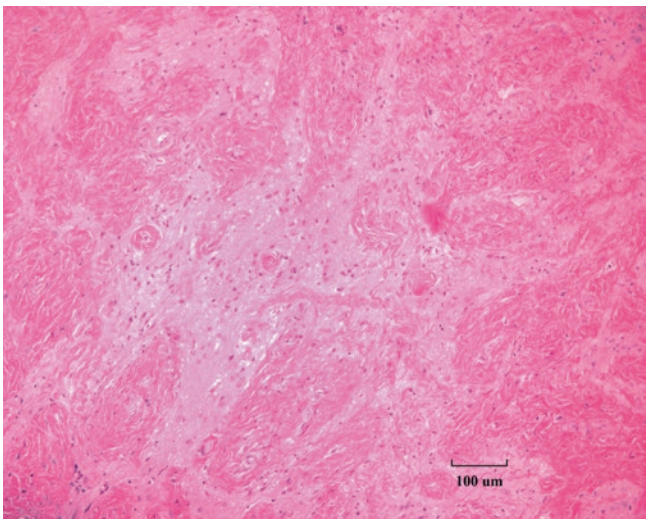

Fig. 7.17 Glial heterotopia. H&E. Patchy glial tissue mingled within a fibrous connective tissue matrix

9. Nasal Glioma/Glial Heterotopia

Definition

Glial heterotopia are rare, benign, congenital midline, and nonteratomatous extracranial glial tissues. Most patients develop a mass either in the nasal cavity or on the nasal bridge. Mean size was reported to be 2.4 cm (range: 1 to 7 cm) [1]. Histopathology findings typically are components of astrocytes (including gemistocyte type) and neuroglial fibers mixed with a fibrovascular connective tissue stroma (Fig. 7.17). Neurons and ependymal cells may be present. Immunostains for glial fibrillary acidic protein (GFAP) and S100 are positive [21].

10. Nasal Schwannoma

Definition

A tumor of Schwann cells first described by Verocay in 1908 [22]. It is a rare tumor at this site and most reported cases occur in adults. A review in year 200 reported 11 cases and there was one infant and two young adults (20–21 year old) [23]. Since then there are sporadic cases, 2 occurred in a 12-year-old boy [24, 25] and the other in a 17-year-old boy [26].

Microscopic Features

As described by Antoni in 1920, the lesions can have two histological patterns: Antoni type A (fasciculated with high cellularity) and type B (reticular, with low cellularity). Antoni A has areas with spindle cells that contain twisted nuclei, indistinct cytoplasmic borders, and occasional nuclear vacuoles. In the high cellularity areas, the cells are arranged in short interlacing fascicles. They may also show

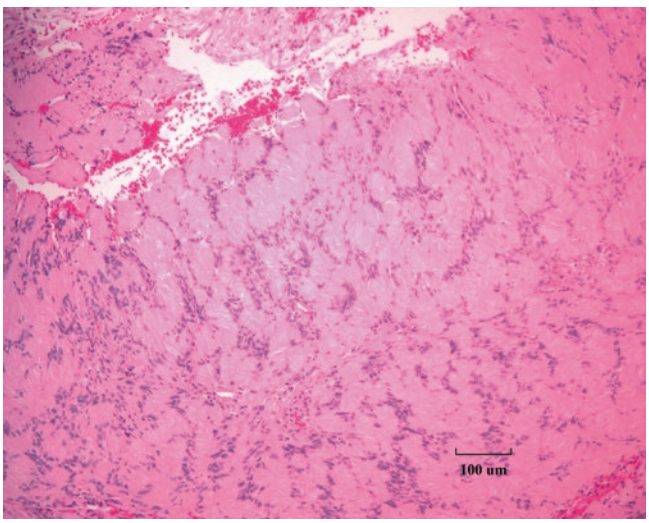

Fig. 7.18 Nasal Schwannoma. H&E. Nasal mucosa is replaced by palisading fascicles of schwann cells where their elongated wavy nuclei characteristically align in parallel next to each other (Antoni A pattern) separated by anuclear zones to form Verocay bodies

nuclear palisading, whirling of cells, and form Verocay bodies (compact groups of parallel spindle-shaped nuclei) (Fig. 7.18). In the Antoni type B, there is a degenerative pattern where spindle cells are haphazardly arranged within a fibromyxoid stroma [27]. Neither patterns are prognostic. Sinonasal Schwannomas differs from schwannoma at other sites by their lack of a peripheral capsule and possible ulceration of the surface epithelium [28].

Histological differential diagnosis includes neurofibroma [29], sclerotic angiofibroma [30], and other solid stromal tumors that are virtually unknown in children (solitary fibrous tumors) [31].

Immunohistological Features

Diagnostic immunohistological antibody panel should include S100, epithelial membrane antigen, calretinin, CD34, Factor XIIIa, and CD56 [6].

11. Lobular Capillary Hemangioma or the So-Called Pyogenic Granuloma

Definition

A benign vascular tumor. Rare cases in nasal cavity and inferior turbinate in young children have been reported [32]. The most common sites are the gingiva, lips, tongue, and buccal mucosa. Trigger factors proposed as the etiology are microtrauma to the skin or mucosa and in children or adolescents (accidental contusion while nose picking) [32], pregnancy (granuloma gravidarum, related to estrogen–progesterone implantation) [33]. Intranasal presentation is commonly located in the anterior portion of the nasal septum (Little's area) and on the tip of the turbinates. A case in the nasal cavity has been reported [34].

Microscopic Features

Presence of varying size capillaries in lobule arrangement. They are surrounded by a central larger caliber blood vessel. Within each lobule, capillaries may vary from the degree of packing and this affects the size of the lumen of the blood vessels. They are surrounded by pericytes and a loose stroma of spindle cells without mitotic activities. The endothelial cells have a bland cytological appearance. The surface may be ulcerated and secondary inflammation (usually mild) may be seen (Fig. 7.19).

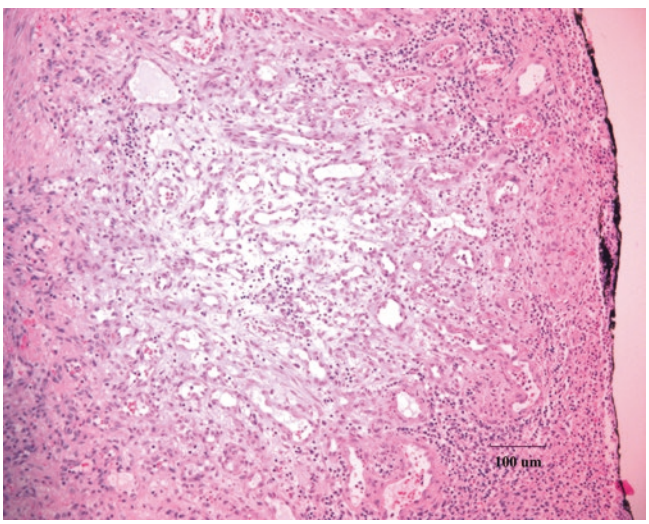

Fig. 7.19 Capillary Hemangioma. H&E. Mucosal stroma contains lobulated collections of small blood vessels and capillary tufts. A mild chronic inflammatory cellular infiltrates. Superficial ulceration causing mild acute inflammation is common

Differential histopathological diagnosis include foreign body, simple granulation tissue, and infantile/juvenile hemangioma. To distinguish infantile/juvenile hemangioma, from others, immunostain of the endothelial cells of juvenile hemangioma capillaries is positive for glucose transporter (GLUT-1) [35, 36]. In newborns or early infancy, another vascular lesion known as noninvoluting congenital hemangioma should be considered. They have irregular lobules of compact capillary growth with slit-like vascular lumen (Figs. 7.20 and 7.21). In the peripheral aspects of these capil-

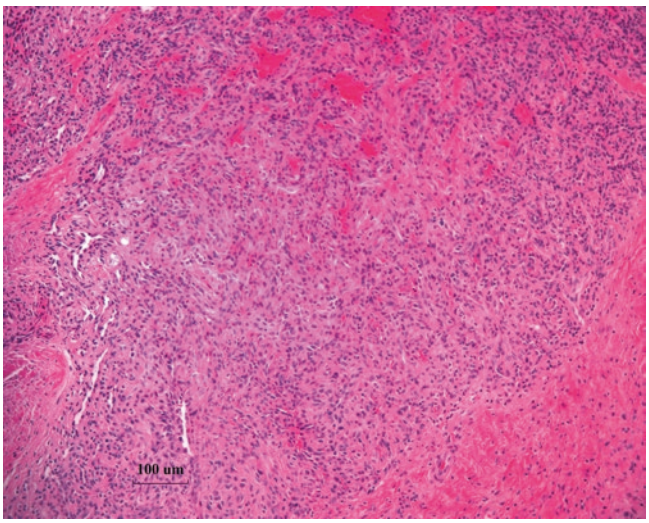

Fig. 7.20 Nasal noninvoluting congenital hemangioma (NICH). H&E. Lobules of densely packed collections of capillary size vessels are separated by wide fibrotic septae. Some forms are elongated vascular lumen that are mildly compressed

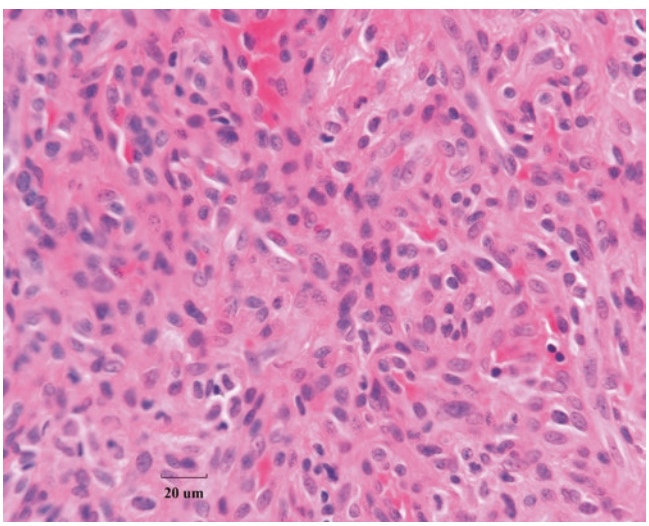

Fig. 7.21 Nasal noninvoluting congenital hemangioma (NICH). H&E. High magnification shows compacted capillaries with bland appearing endothelial cells and some pericytes

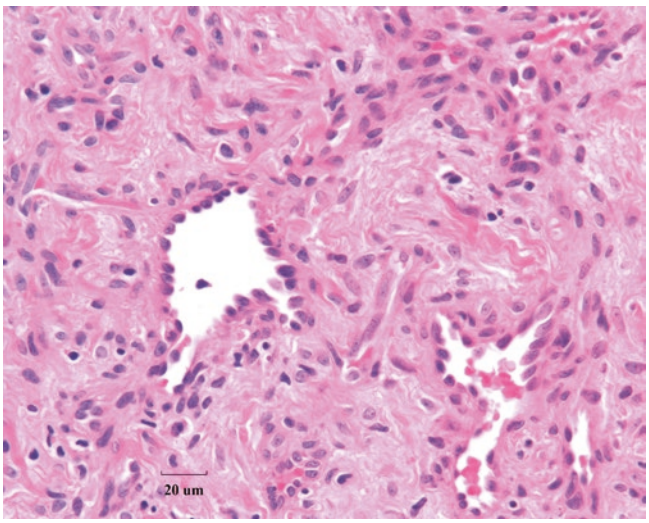

Fig. 7.22 Nasal noninvoluting congenital hemangioma (NICH). H&E. High magnification of the periphery of the vascular lobules reveal vessels with open lumina that bear the characteristic feature of endothelial cells of NICH that have a hobnail-like appearance

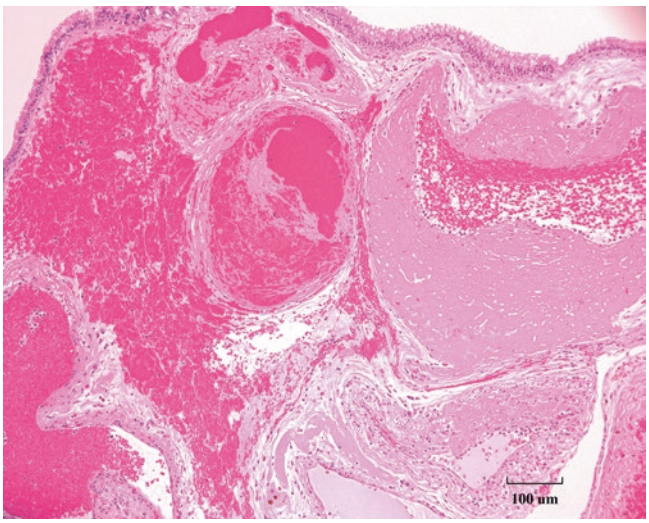

Fig. 7.23 Arterial-venous malformation. H&E. Collection of large vessels with abnormally formed wall and mural and intravascular thrombi

lary lobules, ectatic vascular lumen lined with hobnail endothelial cells are the cardinal features (Fig. 7.22).

Other histological differential diagnosis which is rare includes arteriovenous (A-V) malformation or other vascular tumors (hemangiopericytoma, angiosarcoma, or epithelioid hemangioendothelioma (uncommon at this site in children but is discussed in Chap. 31) and another rarer lesion such as an extranasopharyngeal angiofibroma of the inferior turbinate in a 9-year-old boy has also been reported [37].

12. Nasal A-V Malformation

Definition

A developmental anomaly where the intervening capillaries are absent and the arteries and veins are connected directly. At the nasal site, spontaneous and recurrent epistaxis occurs. Congenital A-V malformations of the head and neck are uncommon but its presence can present with disfigurement to cardiovascular consequences. It is considered as a high-flow lesion and hence is a high-risk lesion and despite combined treatment of embolization, surgical resection, and reconstruction, incurable situations can be a challenge [38, 39]. Of note are those multiorgan A-V malformation associated with hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant trait that presents with epistaxis around the age of 12 years due to telangiectasis in the nasal mucosa and skin [40, 41]. Genetic testing identifies pathological mutations in *ENG* (HHT1) and *ACVR1* (HHT2) in 80% and other mutations such as *GDF2* or *SMAD4* [40].

Microscopic Features

Lesional tissue exhibits collections of blood vessels with large ectatic lumen. There is abnormal muscularization within the blood vessel walls and secondary intimal thickening formed in response to aberrant flow dynamics and luminal pressure or jet stream effects. In low-flow areas, thrombi may be formed within the lumen (Fig. 7.23). Elastic tissue histochemical stain reveals abnormal elastic fibril layering or absence of elastic fibrils that is not consistent with the size of the blood vessel.

13. Nasal/Extranasopharyngeal Angiofibroma

Definition

A locally aggressive fibrovascular neoplasm of variable cellularity. It usually arise within the nasopharynx and it is prevalent in adolescent males. It can spread from the nasal cavity to the nasopharynx, paranasal sinuses, and orbital skull base with intracranial extension [42]. A review in 2012 on nasal/extranasopharyngeal angiofibroma showed that of the 11 cases, there were four pediatric/adolescent cases (ages 8, 9, 13, and 19 years old) involvement of the nasal septum, nasal cavity [43]. Two other cases were reported since and one involved the nasal septum and the inferior turbinates [44, 45]. Overall, this is a rare lesion at this location. Hypotheses of its developmental origin include an ectopic nidus of fascia basalis or turbinate-like vascular tissue [46, 47].

Microscopic Features: Same features are present as those in the nasopharynx (see Chap. 9). There is a dense fibrous stroma with spindled or stellate cells with bland cytological appearances. Thin-walled vascular spaces permeated through-

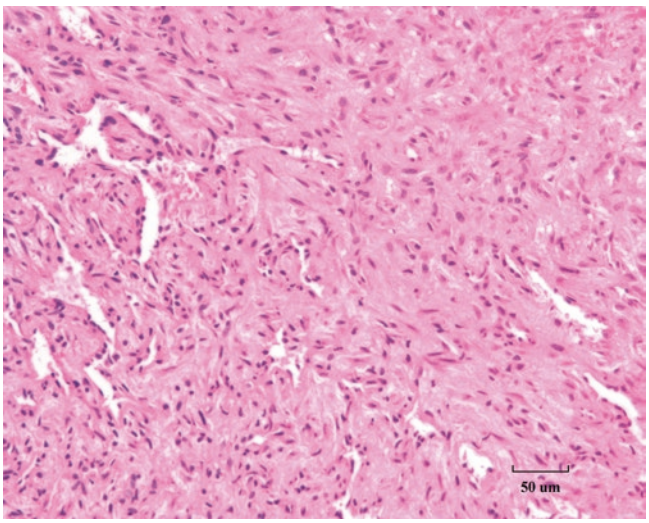

Fig. 7.24 Nasal angiofibroma. H&E. Cytologically bland endothelial cells lining vascular lumen with simplified walls that blend into a fibrotic stroma with spindle-shaped fibroblastic cells

out the stroma of the poorly demarcated lesion (Fig. 7.24). In the nasal septal angiofibromas, the vessel density, however, may be markedly reduced at this site, resembling the long-standing lesions of the nasopharyngeal angiofibromas [44].

The histological differential diagnosis includes lobular capillary hemangioma (pyogenic granuloma), antrochoanal polyp [48], angiomatous polyp, or sinonasal type hemangiopericytoma (rare in children).

Immunohistochemistry Features

Immunodiagnostic features are the same as those in the nasopharynx as described in Chap. 9. In a previous study of the pathogenic relationship between the vascular and stroma cells, an autocrine and paracrine relation is observed. Stromal cells express vascular endothelial growth factor (VEGF) while the endothelial cells express both VEGF and its receptor VEGFR [49].

14. Schneiderian Papillomas

Definition

A rare nasal, paranasal sinus, or septal neoplasm in children. Two histological types occur in children. Inverted papilloma, defined by proliferative growth of the nasal (squamous or respiratory epithelium) into the mucosal stroma and exophytic squamous papilloma where the proliferative squamous epithelium are associated with exophytic fibrovascular cores forming papillary fronds on its surface. In adults, there are other histological types such as oncocytic type. Due to the rarity, there are very few case reviews on pediatric papilloma in the literature and nearly all are inverted papilloma [50, 51] and one exophytic papilloma is noted in the Armed Force Institute of Pathology files [52]. Pediatric-inverted papilloma is noted to behave similar to adults and local recurrences prompted the necessity of comprehensive surgery. For other squamous papilloma, a laryngeal papilloma was also noted by Hefner, as well as a rare occurrence of pleomorphic adenoma in this location [52].

Microscopic Features

For inverted papilloma, the low-magnification appearance is the presence of thick convoluted ribbon of hyperplastic squamous cells that are delineated by an intact basement membrane within the nasal mucosa. These endophytic epithelium are multilayered nonkeratinizing squamous cells (5–30 cells thick) or respiratory epithelial cells. Mild intra-epithelial infiltrates of neutrophils may be present (Fig. 7.25). The cytology is bland without dyskeratosis and mitosis is infrequent and may be seen in the basal regions. Loss of mucous glands in the mucosa is seen. Malignant transformation to squamous cell carcinoma is rare but has been reported [51].

For exophytic squamous papilloma, papillary fronds that are covered by thick layers (2–20) squamous cells, respiratory type or transitional types of epithelial cells with scattered mucocytes. The squamous cells are rarely keratinized and atypical mitotic figures are present. Those in the nasal vestibule are cutaneous squamous cell papilloma and they exhibit extensive surface keratinization (Fig. 7.26).

Immunohistology and Molecular Features

Immunostain for cell cycle-related proteins and p53 in adult-inverted papilloma show strong p16, p21, p27, pRB, and cyclin D1 staining and little or no p53 expression in a majority of tumors. Tumors with dysplasia were significantly more

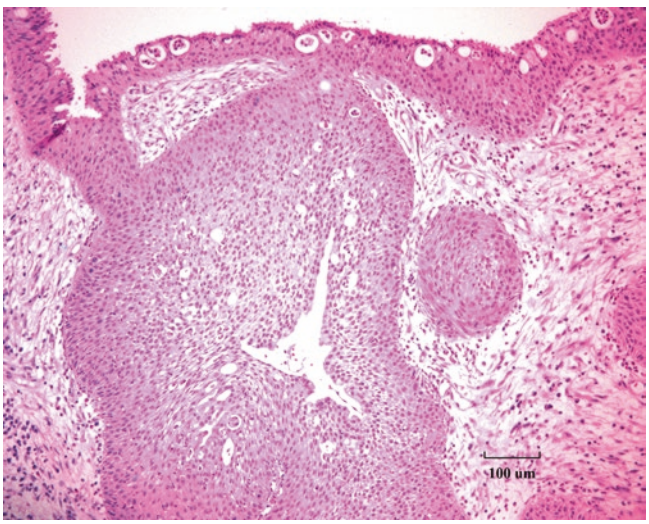

Fig. 7.25 Inverted papilloma. H&E. Endophytic Schneiderian squamous epithelium forming downward growths of thick/multilayered epithelial cells forming crypt or glandular-like differentiation. Sporadic mucous secreting cells and sporadic intra-epithelial neutrophils are commonly seen

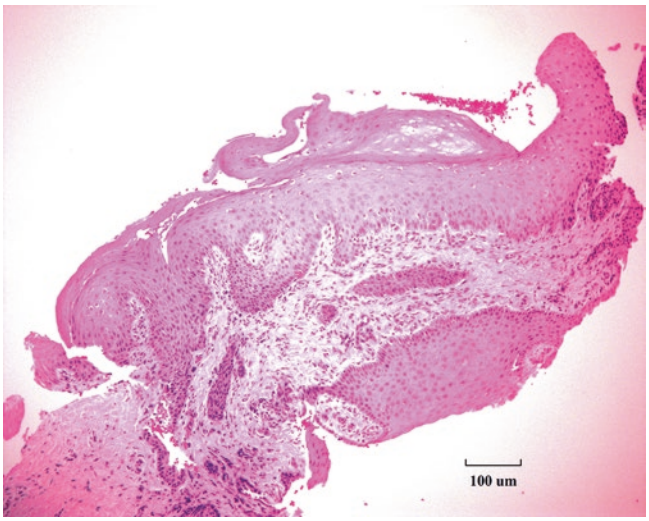

Fig. 7.26 Exophytic papilloma. H&E. Flat or verrucoid exophytic proliferation of hyperplastic, acanthotic, hyperparakeratotic, nonkeratinized squamous epithelium occurs in the mucosal lining

likely to be p53 positive and had upregulated p21 and p27 [4]. Using in situ hybridization and PCR of human papillomavirus (HPV) 11/16; 20% of adult-inverted papilloma are positive for HPV 6/11 [54], and HPV presence is correlated with p53 positivity [53].

Malignant Conditions

1. NUT Carcinoma (NUT Midline Carcinoma)

Definition

NUT carcinoma (NC) is a rare and highly aggressive subset of poorly differentiated squamous cell carcinoma not always but often arising from midline epithelial structure, harboring unique chromosomal translocation with resultant rearrangements of the gene encoding nuclear protein in testis (NUT) at 15q14. NC predominantly affects children and young adults. Most common sites of involvement are head and neck (e.g., sinonasal tract, nasopharynx, larynx, orbit, parotid gland, and tonsils) and thorax (e.g., mediastinum/thymus, trachea, and lung) [55–57].

Macroscopic Features

In most cases, the tissue samples are obtained as piecemeal materials and there have been few cases in which the NC was totally resected, thus no specific macroscopic feature has been obtained.

Microscopic Features

The tumor consists of nests or sheets of undifferentiated cells with/without focal squamous differentiation (Figs. 7.27 and 7.28). Abrupt squamoid differentiation is common. Lack of squamous differentiation does not exclude the diagnosis of

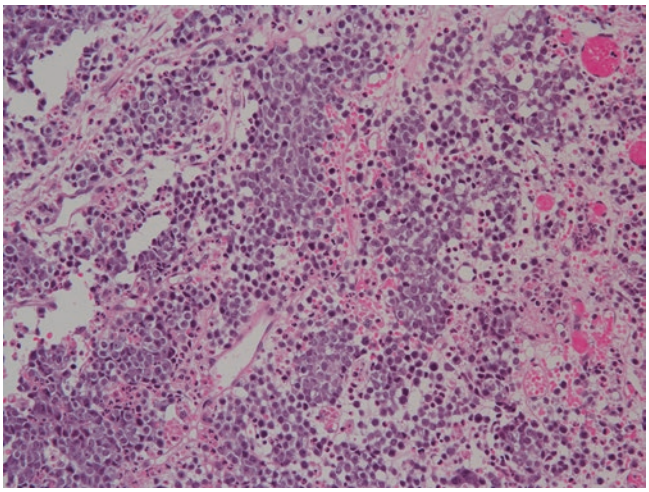

Fig. 7.27 NUT Carcinoma. H&E. Invasive diffuse growth of undifferentiated tumor cells is shown

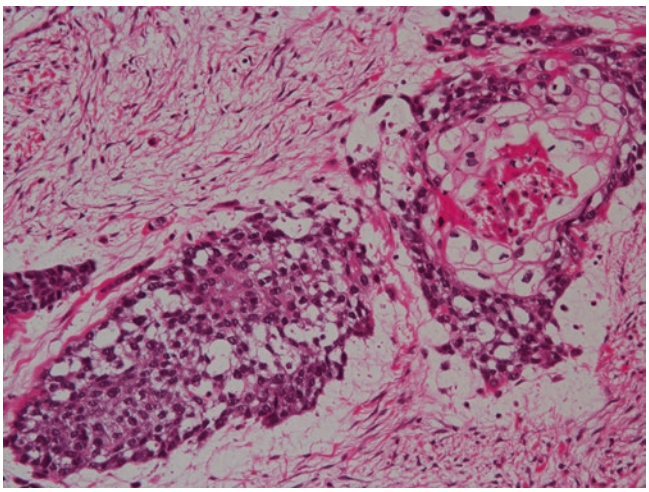

Fig. 7.28 NUT Carcinoma. H&E. Features of abrupt transition from undifferentiated cells to foci of differentiation is one of the hallmarks of this tumor

NC. The undifferentiated tumor cells included rounded, polygonal, or oval nuclei with relatively vesicular chromatin and often distinct nucleoli, and small amount of eosinophilic to amphophilic cytoplasm. Nuclear pleomorphism may be present. Mitotic feature is frequently seen and individual cell and/or large confluent necrosis may be seen. Foci of squamous differentiation are usually seen as nests of mature, well-differentiated squamous cells and often appear abruptly from the adjacent nests of undifferentiated cells (abrupt transition) (Fig. 7.28).

Immunopathological Features

Typical immunophenotypes are as follows: positive—NUT (nuclear) (Fig. 7.29), cytokeratin (e.g., pan cytokeratin, CK7, and CK8), Epithelial Membrane Antigen (EMA), p63, and p40 negative—myogenic markers, hematolymphoid mark-

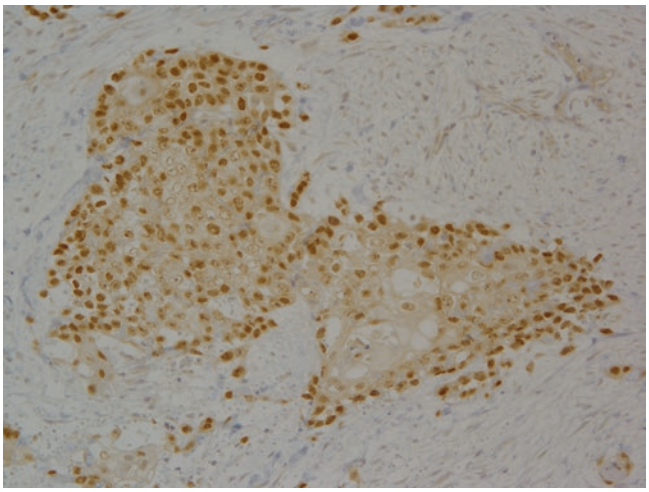

Fig. 7.29 Nut Carcinoma. Immunostain with antibody to the **NU**clear protein of **T**estis (**NUT**) marks the expression of the NUT protein within the tumor cell nuclei as a result of the gain of function type of translocation that involve the gene locus of *NUT*

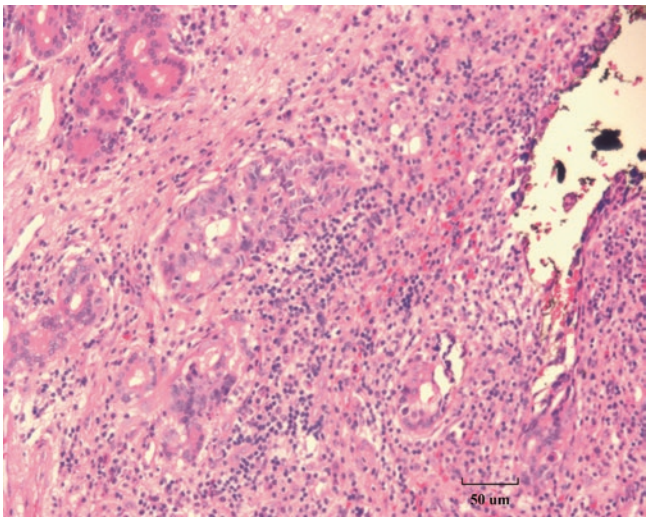

Fig. 7.30 Secondary, post-rhabdomyosarcoma poorly differentiated/nonintestinal sinonasal carcinoma. H&E. Features of in situ carcinoma in the superficial sinonasal mucous glands

ers, S-100, CD99, Alpha Feto-Protein, placental alkaline phosphatase variable—CD34 and synaptophysin.

Molecular/Cytogenetic Features

Approximately, two-thirds of NC harbor t(15;19)(q13;p13.1) and resultant *BRD4-NUT* chimeric gene. In the remaining one-third cases, the *NUT* gene fuses to other genes (NUT variants).

2. Secondary Carcinomas in Children

Definition

Extremely rare malignant glandular epithelial neoplasm in children at this site following treatment of a primary malignancy.

One patient in the pathology archive of Hospital for Sick Children who has oral rhabdomyosarcoma treated at age 5 developed a nasal mass, 6 years later with sinonasal adenocarcinoma (Figs. 7.30, 7.31, and 7.32).

A further literature search reveals that only one case had been reported, as a complication after treatment of retinoblastoma or in survivors of retinoblastoma [58]. Two other cases of neuroendocrine carcinoma were also reported in post treatment retinoblastoma patients [59].

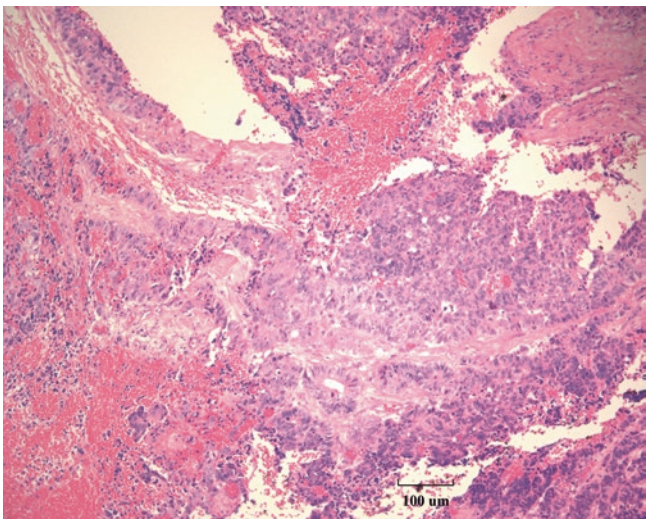

Fig. 7.31 Secondary, postrhabdomyosarcoma poorly differentiated/nonintestinal sinonasal carcinoma. H&E. Areas showing extensive and destructive invasion and the presence of poorly differentiated and hyperchromatic carcinoma cells. Left upper corner shows surface epithelium with carcinoma in situ

Microscopic Features

Histopathological features of the subtypes of salivary gland tumors in children are presented by Dr. Chami in Chap. 17.

3. Salivary Gland Tumors

Definition

Primary salivary gland tumor occurring in children and adolescents at this site is extremely rare. Survey of the literature reveals sporadic reports of various types (from adenomas to pleomorphic adenomas) at this site [60–63].

4. Olfactory Neuroblastoma (Esthesioneuroblastoma)

Definition

Olfactory neuroblastoma (ONB) or esthesioneuroblastoma is a rare type of neuroectodermal tumor that arises from progenitor cells of the olfactory epithelium [64]. ONB

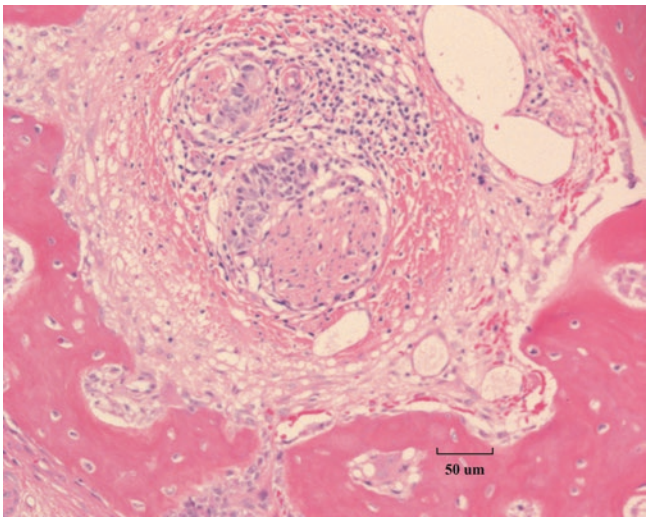

Fig. 7.32 Secondary, post-rhabdomyosarcoma poorly differentiated/nonintestinal sinonasal carcinoma. H&E. Perineural invasion is shown

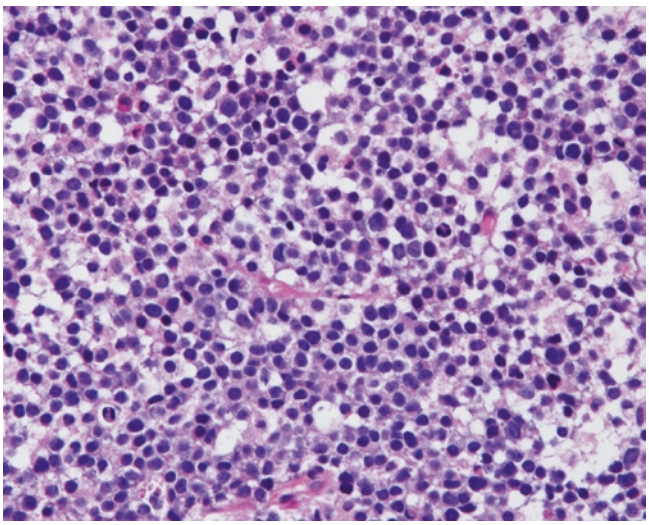

Fig. 7.33 Low-grade olfactory neuroblalstoma. H&E. Lobules consisting of small-to-medium-sized atypical round cells are seen

accounts less than 5% of malignant intranasal tumors, mostly occurs between fifth and sixth decade of age, and is seen equally in males and females. ONB is typically found in upper nasal cavity with extension mostly to ethmoid sinus, orbit, and anterior skull base. Some rare examples with ectopic occurrence have been reported [65]. ONB is a locally aggressive with a tendency to metastases to the cervical lymph nodes and less than 10% of distant metastases. ONB is rare in children but is the most common malignant tumor of the nasal cavity [66].

Macroscopic Features

The tumors are soft, glistening, reddish-gray, and hypervascular. Hemorrhage/necrosis is usually absent in low-grade tumors but is common in high-grade tumors.

Microscopic Features

Low-grade ONBs are typically composed of lobules of small-to-medium-sized atypical rounded cells with fibrillary matrix and delicate fibrovascular stroma (Fig. 7.33). Higher grade tumors display pleomorphic features, brisk mitotic activity, decreased neural matrix, and less conspicuous lobular growth. Pseudo- and true-rosette formation may be present. The variability such as poorly differentiated morphology and divergent epithelial and/or mesenchymal differentiation are also seen and may cause difficulty in diagnostic differentiation.

Immunopathological Features

The tumor cells are positive for neuronal markers such as CD56, chromogranin, neurofilament, neuron specific enolase, and synaptophysin (Fig. 7.34). S-100 positive cells are characteristically seen along periphery of neoplastic lobules. Cytokeratin may be focally positive.

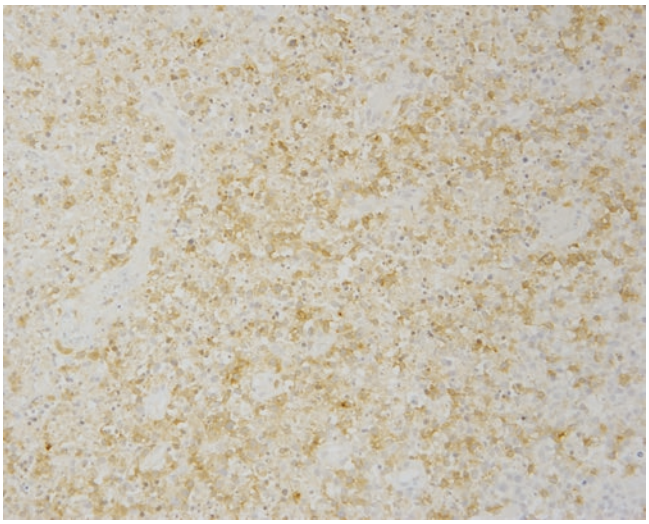

Fig. 7.34 Low-grade olfactory neuroblalstoma. Immunostain for synaptophysin. Positive cytoplasmic staining is present

Molecular/Cytogenetic Features

Some early studies referred to the association with Ewing sarcoma family of tumor, but subsequent reports have not supported the hypothesis. So far there has been no consistent pattern of molecular/cytogenetic abnormality in ONB, although a large number of chromosomal aberrations, gains, and deletions have been reported.

5. Melanotic Neuroectodermal Tumor of Infancy

Definition

Melanotic neuroectodermal tumor of infancy (MNTI) is a rare pigmented neoplasm of neural crest origin that occurs in the first year of life. The majority of cases occur in the craniofacial region, most frequently the anterior maxilla, but other sites of involvement include the skull, mandible, brain, and paratesticular region [67]. It is postulated to recapitulate the early embryonic retina [68].

Macroscopic Features

Grossly, the tumors are firm, unencapsulated masses, usually 2–4 cm in diameter but tumors up to 20 cm have been reported [69].

The cut surface varies from tan to gray-white with variable blue-black pigmentation.

Microscopic Features

MNTI is characterized by a dual population of cells: small neuroblast-like cells with hyperchromatic nuclei and scant cytoplasm, and larger polygonal epithelioid cells with vesicular nuclei and pale eosinophilic cytoplasm containing variable melanin pigment. The larger epithelioid cells are typically arranged in an alveolar to tubular architecture (Fig. 7.35) and they often surround nests of the small neuroblast-like cells (Fig. 7.36). There is surrounding dense collagenous stroma. The small neuroblastic cells may contain neurofibrillary elements (Fig. 7.37). The proportion of each cell type varies between and within tumors. Mitoses are rare or absent [68]. Metastases are rare and consist of the small neuroblastic component. There are no histologic features that are known to predict behavior.

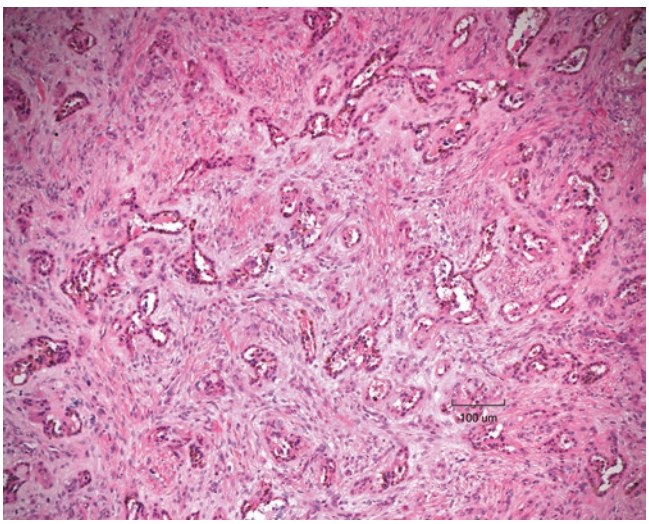

Fig. 7.35 Melanotic neuroectodermal tumor of infancy. H&E. Pigmented epithelioid cells arranged in irregular alveolar and tubular structures with in densely collagenous stroma is shown

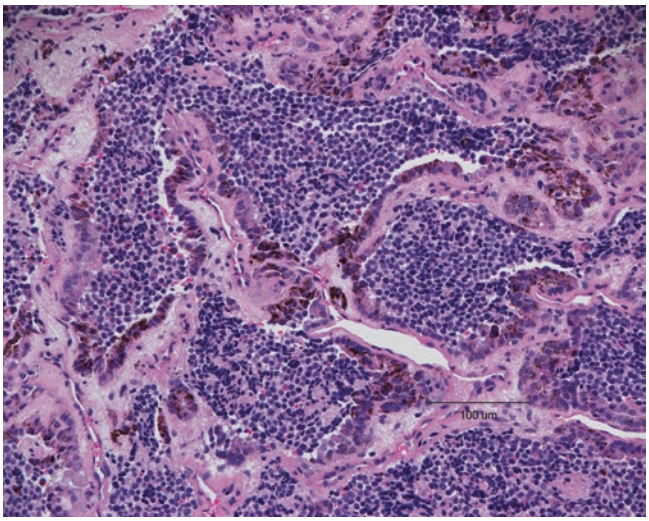

Fig. 7.36 Melanotic neuroectodermal tumor of infancy. H&E. Characteristic biphasic morphology with nests of small neuroblast-like cells surrounded by larger pigmented epithelioid cells is shown

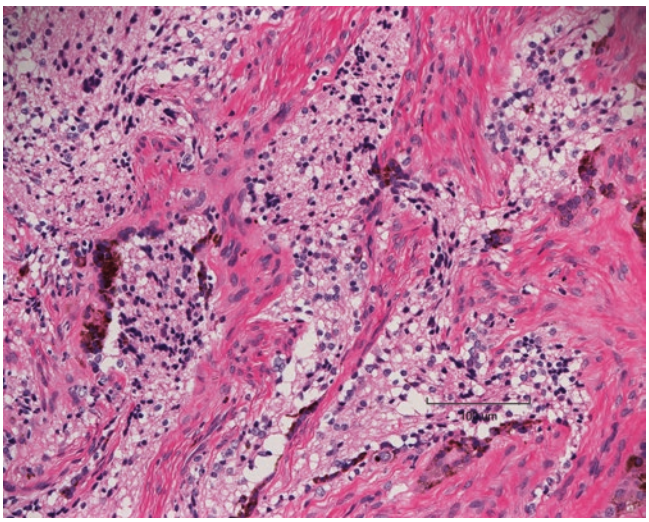

Fig. 7.37 Melanotic neuroectodermal tumor of infancy. H&E. Small neuroblastic component with neurofibrillary elements and pigmented cells at the periphery is shown

Ancillary Tests

MNTI demonstrates multiphenotypic expression of epithelial, melanocytic, and neural markers [4, 5]. The large melanin-producing epithelioid cells stain positively for cytokeratin (Fig. 7.38) and HMB45 (Fig. 7.39), but are negative for other melanoma markers, and show variable staining for EMA. The small round cells stain for CD56 with variable staining for synaptophysin (Fig. 7.40), S100, and glial fibril-

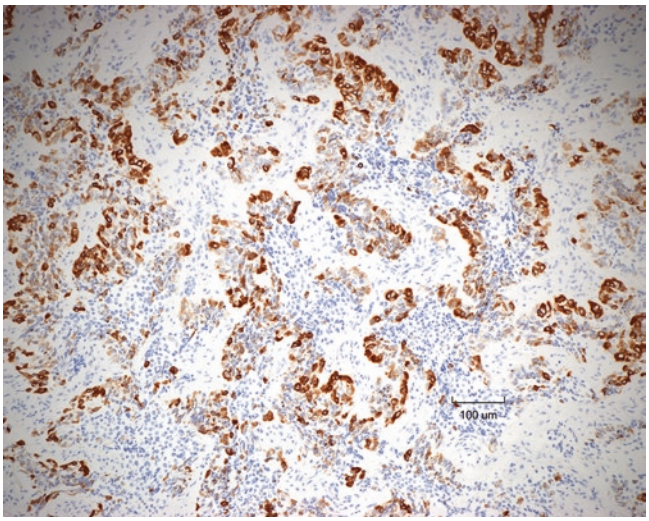

Fig. 7.38 Melanotic neuroectodermal tumor of infancy. Immunostain for pan-cytokeratin is positive

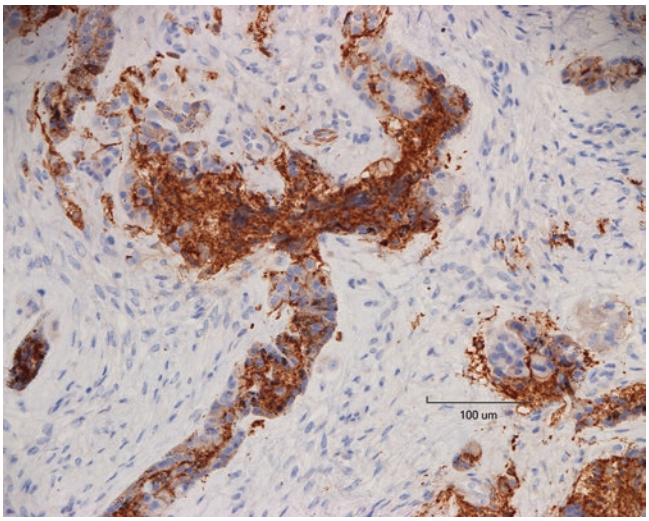

Fig. 7.40 Melanotic neuroectodermal tumor of infancy. Immunostain for synaptophysin is positive

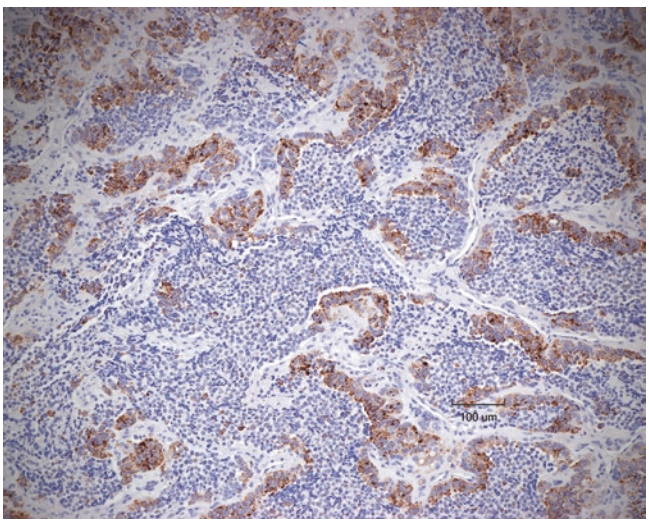

Fig. 7.39 Melanotic neuroectodermal tumor of infancy. Immunostain for HMB45 is positive

lary acidic protein (GFAP). Both cell types express neuron-specific enolase (NSE) and vimentin. Focal staining for desmin and chromogranin has been described [70]. There are inconsistent reports of NB84 expression.

Genetic Features

Flow cytometry studies have revealed both diploid and aneuploid MNTIs [2, 4].

One case harboring the *BRAFV600E* mutation has been reported [71].

Differential Diagnosis

The histology of MNTI is distinct, however, misdiagnosis may occur due to its rarity.

The differential diagnosis includes other small, round, blue cell tumors such as Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, and lymphoma. The characteristic clinical features, biphasic morphology, and immunostaining pattern of MNTI should help to distinguish it from these other entities.

6. Non-Hodgkin Lymphoma B-Cell or T-Cell Lymphomas

Burkitt Lymphoma, T-cell lymphoma, leukemia, and extranodal NK/T-cell lymphoma, nasal type

Definition

Malignant clonal proliferative lymphoid neoplasm that originate from various lymphoid lineages at various stages of their maturation and hence there are many subtypes (see Chap. 27 for details). Prevalence of certain types of lymphomas differs by age or geographic locations as well as anatomical sites. At this particular sites in children, Burkitt lymphoma is most frequent [52]. A case example is shown (Figs. 7.41 and 7.42). Burkitt lymphoma is discussed in detail in Chap. 27. The most common mature T-cell lymphoma in pediatric population is anaplastic large cell lymphoma which can manifest in extranodal sites. A case example is shown Fig. 7.43. Details of anaplastic large cell lymphoma are discussed in Chap. 27. Leukemic infiltrates can involve tissues. Shown is a case of acute megaloblastic leukemia (M7) invading the sinuses (Figs. 7.44, 7.45, and 7.46). T-cell lymphomas in general are less frequent in the western hemisphere, however, one type in particular that arises primarily in the nasal region is worth discussing here.

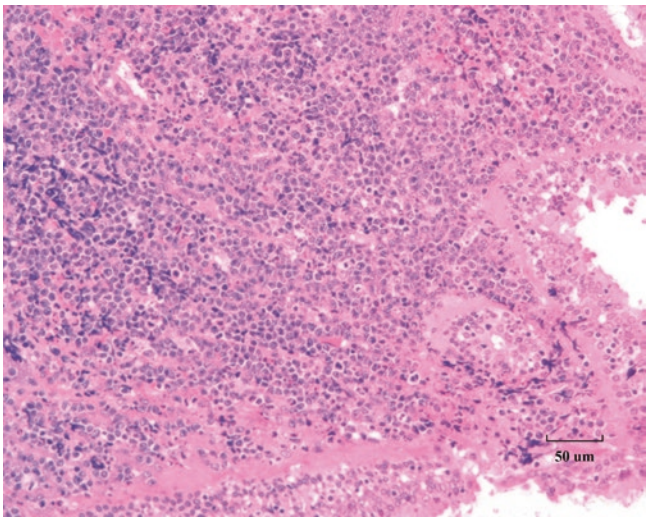

Fig. 7.41 Nasal Burkitt lymphoma. H&E. Replacement of the mucosa by a monomorphous population of small neoplastic lymphoid cells interspersed with a few reactive histiocytes in the background is shown

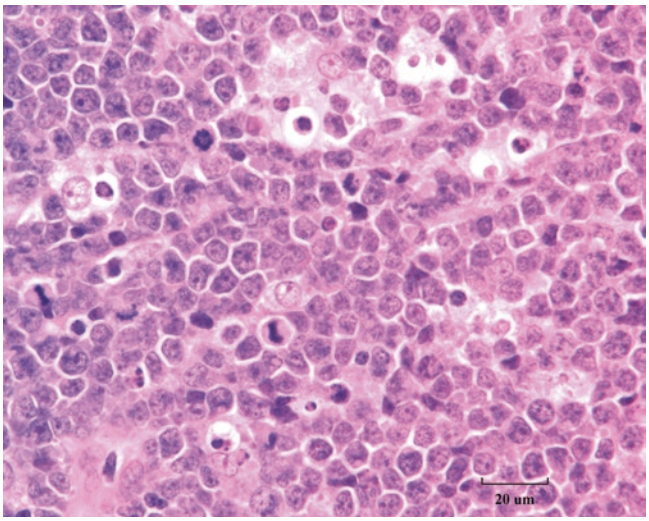

Fig. 7.42 Nasal Burkitt lymphoma. H&E. Packed small abnormal lymphoid cells with scanty cytoplasm, high nuclear-cytoplasmic ratio, square-shaped surface edges, high mitotic activity, and background phagocytotic (tangible body) macrophages (starry-sky pattern) are the usual features of this lymphoma

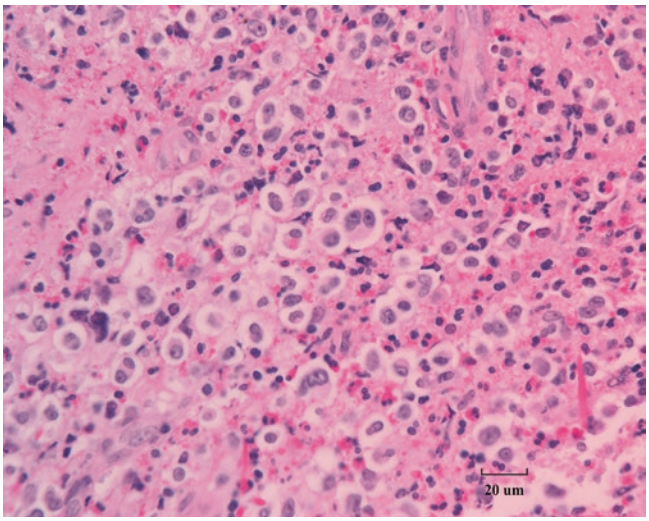

Fig. 7.43 Anaplastic large cell lymphoma. H&E. Infiltrates of monomorphic abnormal appearing large lymphoid cells, some with binucleated cells mimicking Reed Sternberg cells of Hodgkin lymphoma is shown. Immunophenotype (not shown) of this lymphoma is typically CD30+ve, ALK-1+ and exhibit aberrant loss of T-cell lineage cell surface antigens. This biopsy is Alk −ve but is clonal for T-cell receptor gene construct by molecular analyses (not shown)

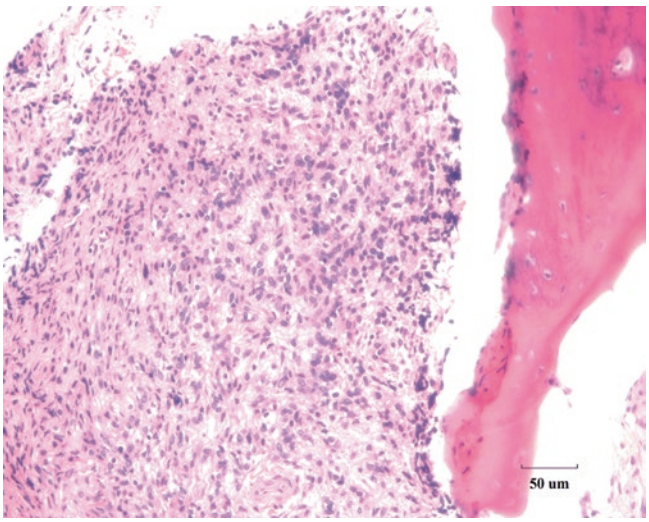

Fig. 7.44 M7 leukemic infiltrate in sinusoidal bone H&E

Extranodal NK/T-cell lymphoma, nasal type (ENKTL-N) is a neoplasm with NK cell-phenotype and, and less often, cytotoxic T-cell-phenotype [72, 73]. ENKTL-N is associated with EBV infection and is more common in Asia and Central/Latin America than in Western countries. The affected patients are broad-aged (median, fifth decade), and children are occasionally affected. The male-to-female ratio is approximately 2:1. The patients mostly present with localized disease, and 10–20% with advanced stage of disease. ENKTL-N can occur in immunosuppressed setting, such as post-transplant state.

Macroscopic Features

Macroscopic features are nonspecific. Most samples of ENKTL-N are submitted as piece-meal biopsies.

Microscopic Features

The histopathology of ENKTL-N is characterized by polymorphic neoplastic infiltrate composed of small-to-medium

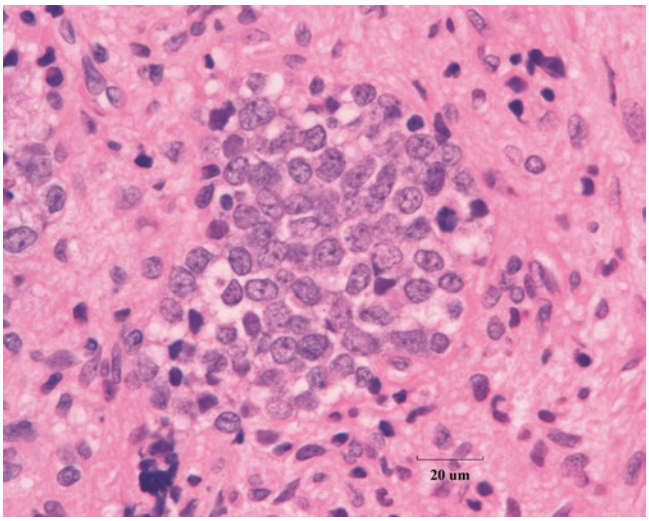

Fig. 7.45 M7 Leukemic infiltrate. H&E. Cluster of infiltrates of leukemic blasts. The cells are small with scanty cytoplasm. Nuclei are near spherical and the nuclei contain fine stippled chromatin, some contain small nucleoli

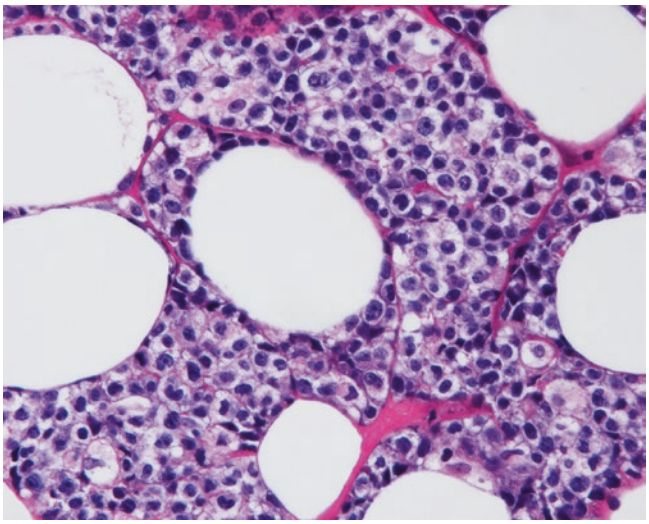

Fig. 7.47 Extranodal natural killer T-cell lymphoma, nasal type. H&E. Medium-sized, atypical rounded cells are seen admixed with lymphocytes and histiocytes

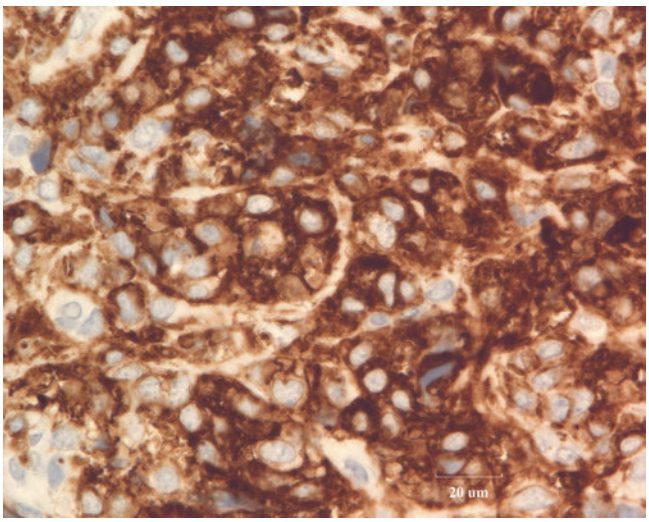

Fig. 7.46 M7 leukemic cells positive for CD61 immunostain. Other positive staining included hematolymphiod marker CD43. These cells in contrast with acute myeloid leukemias are negative for myeloperoxidase

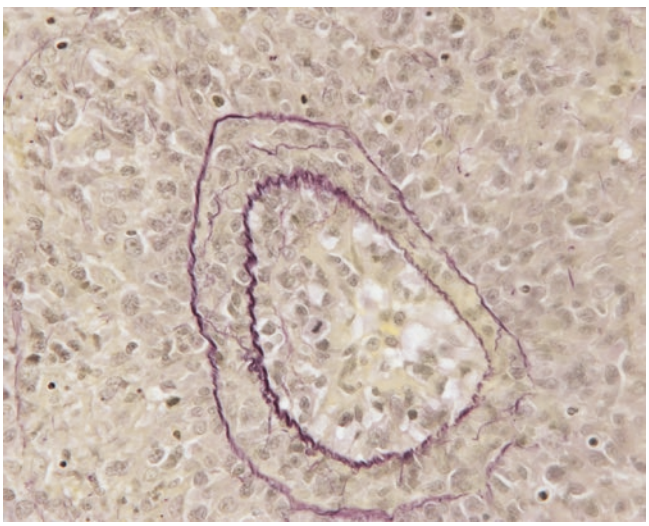

Fig. 7.48 Extranodal natural killer T-cell lymphoma, nasal type. Elastic Von Gieson Stain. Angiocentric invasion by lymphoma cells is shown

sized, occasionally large, anaplastic, lymphocytic cells, with angioinvasive and/or angiodestructive growth pattern, admixture of inflammatory cells, and extensive coagulative necrosis (Figs. 7.47 and 7.48). Because of these features, differential diagnosis often includes inflammatory diseases and autoimmune diseases such as Wegener granulomatosis. Presence of EBV in tumor cells is usually confirmed by in situ hybridization of EBV-encoded small nuclear RNA (EBER) (Fig. 7.49).

Immunopathological Features

Tumor cells of NK cell lineage are usually positive for CD2, cytoplasmic CD3, CD43, CD56 (Fig. 7.50), perforin, granzyme B, and T-cell intracellular antigen. Surface CD3, CD4, CD5, and CD8 are negative. Tumor cells of T-cell lineage may be positive for surface CD3, CD5, and CD8. CD30-expression, high labeling index of Ki-67 and MYC-expression are reported to be possibly related to aggressiveness of the tumor [74].

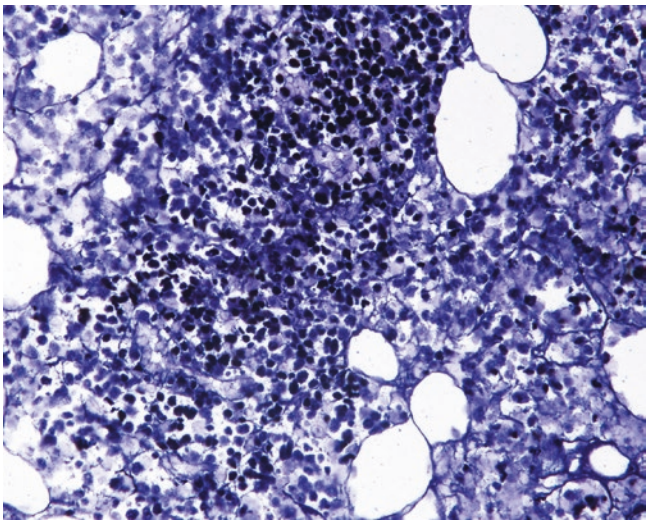

Fig. 7.49 Extranodal natural killer T-cell lymphoma, nasal type. In situ hybridization for EBV encoded RNA shows that the lymphoma cells are positive

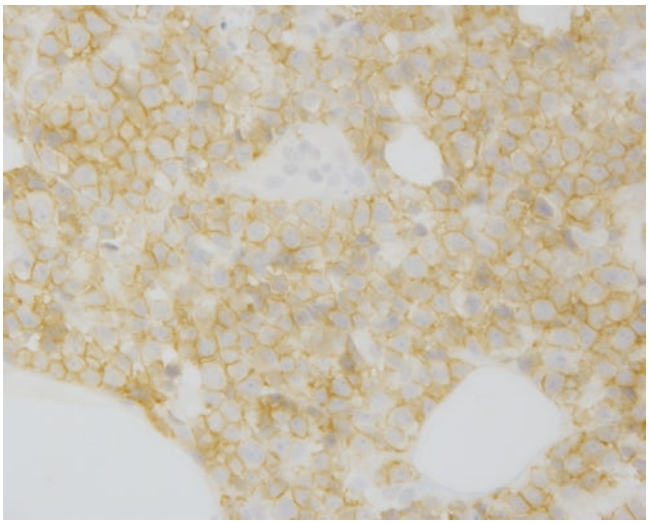

Fig. 7.50 Extranodal natural killer T-cell lymphoma, nasal type. Immunostain for CD56 is positive

Molecular/Cytogenetic Features

The EBV in tumor cells shows a clonal episomal form and type II latency pattern (EBNA-1 positive, EBNA-2 negative, and LMP1 positive). Some defect in immune surveillance due to common 30-base pair deletions of the *LMP1* gene has been suggested. T-cell receptor gene rearrangement is not present in tumors of NK cell lineage and is found in tumors of T-cell lineage. Neither specific chromosomal translocation nor relevant cytogenetic abnormality has been established.

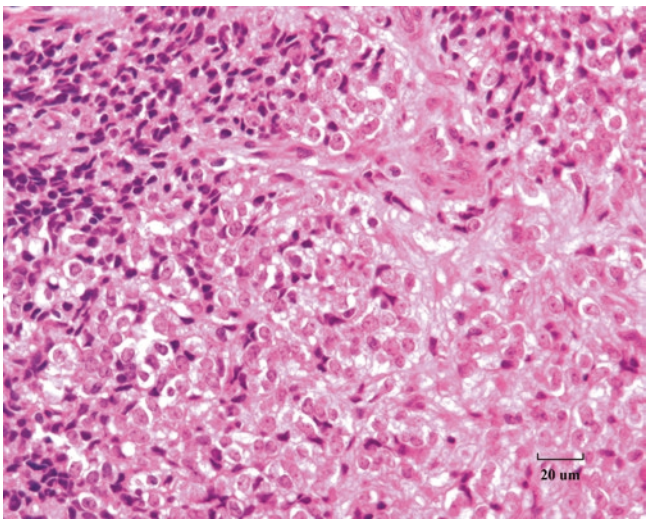

Fig. 7.51 Ewing Sarcoma. H&E. Infiltrates of small round blue cells are typical features. Some Ewing exhibit cells with two cytological appearances: those with light pale cytoplasm (glycogen containing) and others with less and nonclear cytoplasm and hyperchromatic nuclei (dark cells); seen in the left side of the figure

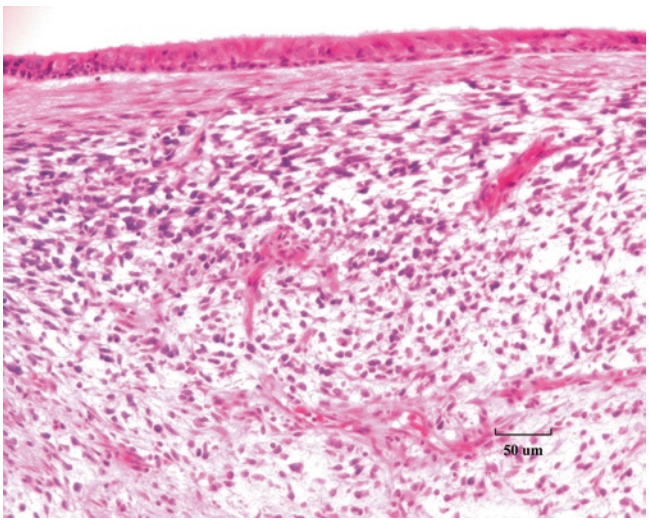

Fig. 7.52 Embryonal rhabdomyosarcoma, botryoid type. H&E. Presence of a horizontal band of condensed layer of hyperchromatic plump spindle cells in the superficial mucosa is a typical appearance of this type. In the deep part of the mucosa, the tumor cells are widely dispersed and are randomly located (scattered)

7. Pediatric Sarcoma

The pathology of specific spindle cell lesions such as fibromatosis and low-grade myofibroblastic sarcoma is discussed in Chap. 27 by Dr. Allagio. The highly malignant pediatric small round blue cell tumor group which includes Ewing sarcoma (Fig. 7.51), botryoid rhabdomyosarcoma (Fig. 7.52),

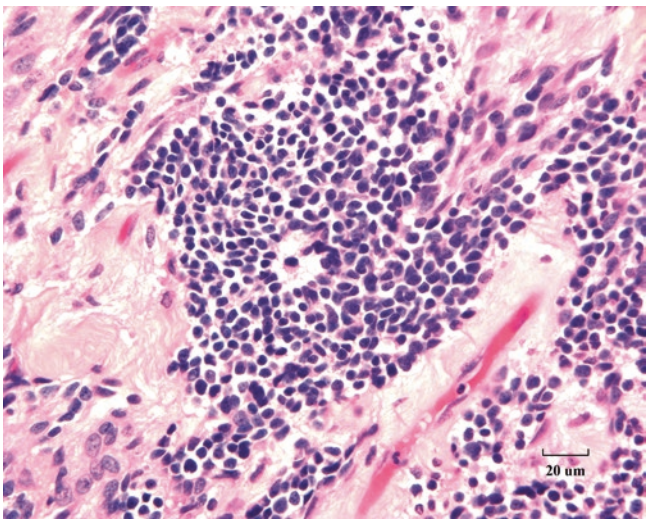

Fig. 7.53 Primitive neuroblastic component of teratocarcinosarcoma. H&E

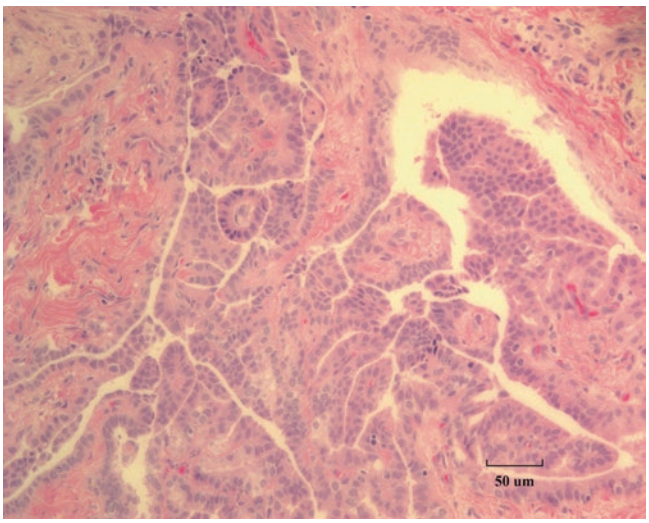

Fig. 7.54 Papillary carcinoma component of teratocarcinosarcoma. H&E

fibrosarcoma, synovial sarcoma, and pleomorphic undifferentiated tumor and its subset (with *BCOR* translocation) are discussed in Chap. 31 by Dr. Alagio.

8. Teratocarcinosarcoma

Definition

A histologic combination of malignant teratoma and carcinosarcoma with a triphasic growth pattern including epithelial, mesenchymal, and primitive neuroectoderm components [75, 76]. It is highly aggressive and has been reported to occur in the nose, paranasal sinuses, and other locations such as nasopharynx and oral cavity primarily of adults with an average age of 60 years [76]. Two pediatric cases have been reported in the literature [77, 78]. The one in our institutions (Hospital for Sick Children) involves the nasopharynx and it is associated with a cleft palate and the congenital replacement or absence of the ipsilateral Eustachian tube [78].

Microscopic Features

Malignant tissue components are present within tissue components of an otherwise teratoma. As shown in Figs. 7.53 and 7.54, patchy primitive neuroepithelial tissue and papillary epithelial tissues with malignant features present.

Other Benign Conditions

1. Nevus Sebaceous of Jadassohn

Definition

A complex congenital hamartoma located usually on face or scalp that is reported to occur in 0.3% of neonates and a case report on the side of the nose has been reported [79]. Familial cases have been reported. Histologically, it exhibits epidermal hyperplasia, immature pilosebaceous which can be reduced in infants. In young adolescents, there is enlargement of the pilosebaceous units which are placed abnormally superficial within the dermis (Figs. 7.55 and 7.56) with increased numbers of closely set lobules and malformed ducts. Although in adults, evolution to neoplasms such as trichoblastoma, syringocystadenoma papilliferum, sebaceous epithelioma, basal cell carcinoma, trichilemmoma, adnexal carcinoma, and eccrine poroma [79–81] occurs, rare case examples of transformation to these neoplasms had been reported in children [81, 82].

2. Hamartoma of the Nasal Cavity/ Chondromesenchymal Hamartoma

Definition

Nasal chondromesenchymal hamartoma is a rare benign, but locally destructive, lesion arising most commonly in the nasal cavity, paranasal sinuses, and orbit [83]. It occurs predominantly in infants under 1 year, but can be seen in older children and adults [84]. Intracranial and skull base extension can occur. Bony erosion and displacement on imaging can raise suspicion of malignancy. Histologically, it is characterized by a focal lobular arrangement of irregular islands of mature and immature hyaline cartilage set within myxoid to fibrous stroma containing bland spindle cells. The stroma shows variable cellularity but there is no nuclear atypia or atypical mitoses. The proportion of chondroid and stromal components varies. Reactive bone, blood-filled cystic spaces, and thick-walled vessels may be seen. The stromal cells are immunoreactive for smooth muscle actin and negative for

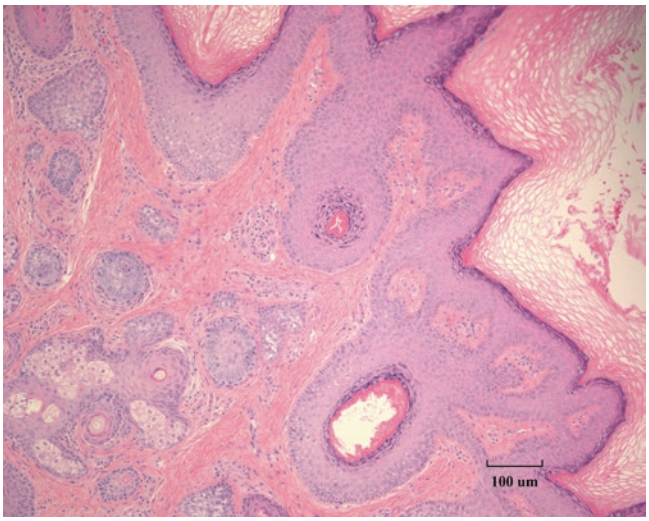

Fig. 7.55 Nasal nevus sebaceous of Jadassohn. H&E. Hyperplastic, hyperkeratotic squamous epithelium with superficially placed hair follicles and sebaceous glands

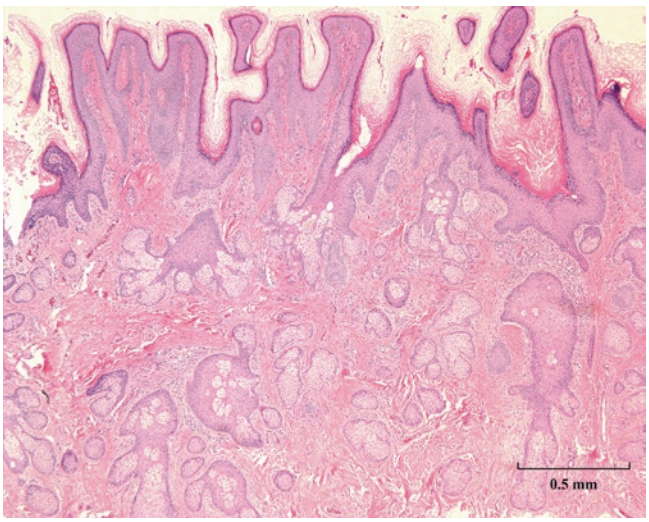

Fig. 7.56 Nasal nevus sebaceous of Jadassohn. H&E. From the neck of the same patient

cytokeratin. Chondromesenchymal hamartoma is part of the *DICER1* familial tumor susceptibility syndrome associated with pleuropulmonary blastoma [85, 86].

3. Fibrous Dysplasia

Definition

Fibrous dysplasia (FD) is a benign fibro-osseous lesion in which normal bone is replaced by spicules of disorganized bone and fibrous tissue. A single site (monostotic) or multiple (polyostotic) bones may be involved. Any bone can be affected but the most common sites are the craniofacial bones and the femur.

Macroscopic Features

The involved bone is often expanded and replaced by firm, grey-white tissue with a gritty texture.

Microscopic Features

Varying proportions of fibrous and osseous components are present. The fibrous tissue consists of bland fibroblastic cells demonstrating variable cellularity. Mitotic figures are uncommon. Irregular, curvilinear, trabeculae of woven bone characterize the osseous component [87] (Figs. 7.57 and 7.58).

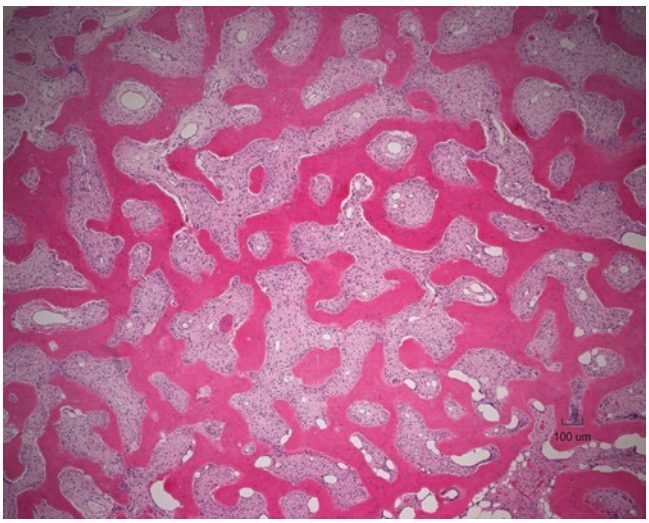

Fig. 7.57 Fibrous dysplasia. H&E. Irregular anastomosing trabeculae of woven bone and hypocellular fibrous stroma

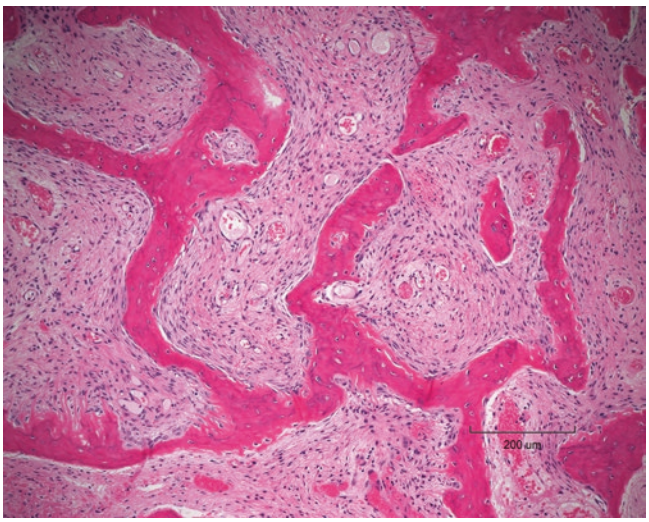

Fig. 7.58 Fibrous dysplasia. H&E. Bland fibroblastic cells characterize the fibrous component

Osteoblasts are inconspicuous. Craniofacial lesions, in particular, may show progressive maturation to lamellar bone. Islands of hyaline cartilage undergoing endochondral ossification can be seen. Spherules or globules of cementum-like material may be seen. Secondary aneurysmal bone cyst (ABC)-like changes may be present.

Genetic Features

Fibrous dysplasia is caused by postzygotic activating missense mutations in the *GNAS* gene that encodes the α-subunit of the stimulatory G-protein-α [88]. *GNAS* mutations are also present in McCune–Albright syndrome.

Differential Diagnosis

FD shares overlapping histological features with other fibro-osseous lesions, including ossifying fibroma and cemento-osseous dysplasia, and they can be distinguished by clinical and radiological features. Osteoblastomas can occur in the maxillofacial region but differ in its distinct loose fibrovascular stroma and by the presence of prominent osteoblasts. The healing phase of giant cell reparative granuloma may be devoid of giant cells and resemble FD but can be distinguished from FD by its zonal pattern of reactive bone and fibrous tissue [89].

Acknowledgments Case material illustrated in Figs. 7.20, 7.21, and 7.22 is contributed by Dr. G. Taylor (editor).

Author Contributions Topics in this chapter Nasal Xanthogranuloma, Melanotic Neuroectodermal Tumor of Infancy, Chondromesenchymal hamartoma, and Fibrous Dysplasia are contributed by Dr. C. Chung.

Topics in this chapter NUT carcinoma, olfactory neuroblastoma, and extranodal NK T-cell lymphoma are contributed by Dr. Y. Tanaka.

All other topics are contributed by Dr. B. Ngan.

References

1. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. Annu Rev Pathol. 2017;12:331–57.
2. Baba S, Kondo K, Suzukawa M, Ohta K, Yamasoba T. Distribution, subtype population, and Ig E positivity of mast cells in chronic rhinosinusitis with nasal polyps. Ann Allergy Asthma Immunol. 2017;119:120–8.
3. Kuhar HN, Tajudeen BA, Mahdavinia M, Gattuso P, Ghai R, Batra PS. Inflammatory infiltrate and mucosal remodeling in chronic rhinosinusitis with and without polyps: structured histopathologic analysis. Int Forum Allergy Rhinol. 2017;7:679–89.
4. Bent JP 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994;111:580–8.
5. Loftus PA, Wise SK. Allergic fungal rhinosinusitis: the latest in diagnosis and management. Adv Otorhinolaryngol. 2016;79:13–0.
6. Leavitt RY, Fauci AS. Less common manifestations and presentations of Wegner's granulomatosis. Curr Opin Rheumatol. 1992;4:16–22.
7. Murty GE. Wegner's granulomatosis: otolaryngological manifestations. Clin Otolaryngol. 1990;34:220–3.
8. Del Buono EA, Flint A. Diagnostic usefulness of nasal biopsy in Wegner's granulomatosis. Hum Pathol. 1991;22:107–10.
9. Zelger B, Cerio R, Orchard G, Wilson-Jones E. Juvenile and adult xanthogranuloma. A histological and immunohistochemical comparison. Am J Surg Pathol. 1994;18:126–35. PMID 8291651
10. Dehner LP. Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. Am J Surg Pathol. 2003;27:579–93. PMID 12717244
11. Janssen D, Harms D. Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the Kiel pediatric tumor registry. Am J Surg Pathol. 2005;29:21–8. PMID 15613853
12. Paradis J, Koltai PJ. Pediatric teratoma and dermoid cysts. Otolaryngol Clin N Am. 2015;48:121–36.
13. Zapata S, Kearns DB. Nasal dermoids. Curr Opin Otolaryngol Head Neck Surg. 2006;14:406–11.
14. Hartley BE, Eze N, Trozz M, Toma S, Hewitt R, Jephson C, et al. Nasal Dermoids in children: a proposal for a new classification based on 103 cases at the Great Osmond Street Hospital. Int J Pediatr Otorhinolaryngol. 2015;79:18–22.
15. Herrington H, Adil E, Moritz E, Robson C, Perez-Atayde A, Proctor M, et al. Update on current evaluation and management of pediatric nasal dermoid. Laryngoscope. 2016;126:2151–60.
16. White LJ, Shehata BM, Rajan R. Hairy polyp of the anterior nasal cavity. Otolaryngol Head Neck Surg. 2013;149:961–2.
17. Ryan MW. Diseases associated with chronic sinusitis: What is the significance? Curr Opin Otolaryngol Head Neck Surg. 2008;16:231–6.
18. Gentile VG, Issacson G. Patterns of sinusitis in cystic fibrosis. Laryngoscope. 1966;106:1005–9.
19. Tirumandas M, Sharma A, Gbenimacho I, Shoja MM, Tubbs RS, Oakes WJ, et al. Nasal encephaloceles: a review of etiology, pathophysiology, clinical presentations, diagnosis, treatment and complications. Childs Nerv Syst. 2013;29:739–44.
20. Hoving EW. Nasal encephaloceles. Childs Nerv Syst. 2000;16:702–6.
21. Penner CR, Thompson L. Nasal glial heteropia: a clinicopathologic and immunophenotypic analysis of 10 cases with a review of the literature. Ann Diagn Pathol. 2003;7:354–9.
22. Verocay J. Multiple Geschwulste als Systemerkrangkung am nervosen Apparate. Wein & Leipzig: Festschrift fur Chiari; 1908. p. p378.
23. Berlucchi M, Piazza C, Blanzuoli L, Battaglia G, Nicolai P. Schwannoma of the nasal septum: a case report with review of the literature. Eur Arch Otorhinolaryngol. 2000;257:402–5.
24. Gupta SC, Sachin J, Savyasachi S, Ritesh J, Neha G, Singh HP. Solitary nasal schwannoma clinically presenting as an angiofibroma of the nasopharynx. Ear Nose Throat J. 2010;89:E28–30.
25. Ashrafi SK, Suhail Z, Khambaty Y, Ahmed A. Schwannoma of nasal inferior turbinate in Young male: a rare occurrence. J Coll Physicians Surg Pak. 2015;25:460–1.
26. Chou MS, Chung HK, Tsou YA, Chen JJ, Tsai MH, Jan CI. Endoscopic management of paediatric sinonasal schwannoma: case report. B-ENT. 2014;10:299–302.
27. Antoni NRE. Ruckenmarkstumoren und Neurofibrome. Munchen: Bergmann Verlag; 1920. p. 413–23.
28. Buob D, Wacrenier A, Chevalier D, Aubert S, Quinchon J-F, Gosselin B, et al. Schwannoma of the sinonasal tract. A clinicopathologic and immunohistochemical study of 5 cases. Arch Pathol Lab Med. 2003;127:1196–9.
29. Min HJ, Kim KS. Differential diagnosis between nasal septal schwannoma and nasal septal neurofibroma. J Craniofac Surg. 2017;28:1780–3.

30. Dogan S, Yazci H, Baygit MM, Soy FK. Extranasopharyngeal angiofibroma of the nasal septum: a rare clinical entity. J Craniofasc Surg. 2013;24:e390–3.
31. Alobid I, Alos L, Blanch JL, Benitez P, Bernal-Sprekelsen M, Mullol J. Solitary fibrous tumor of the nasal cavity and paranasal sinuses. Acta Otolaryngol. 2003;123:71–4.
32. Marino-Sanchez F, Lopez-Chacon M, Jou C, Haag O. Pediatric intranasal lobular capillary hemangioma: report of two new cases and review of the literature. Respir Med Case Rep. 2016;18:31–4.
33. Delbrouck C, Chamiec M, Hassid S, Ghanooni R. Lobular capillary haemangioma of the nasal cavity during pregnancy. Laryngo Otol. 2011;125:973–7.
34. Ifeacho SN. Caulfield HM. A rare case of paediatric epitaxis: lobular capillary hemagioma of the nasal cavity. BMJ Case Rep. 2011;2011: bcr 0720103199 Feb 23 https://doi.org/10.1136/bcr.07.2010.3199.
35. Gaines SA, Blum C, Chiu ES. Nasal tip infantile hemangioma, a case of mistaken identity. J La State Med Soc. 2013;65:269–72.
36. Patino-Seijas B, Lorenzo-Franco F, Rey-Sanjurjo JL, Gonzalez-Cuesta M, Lopez-Cedrun Cembranos JL. Vascular lesions: Glut-1 expression as a diagnostic tool to discriminate tumors from malformations. J Oral Maxillofac Surg. 2012;70:2332–42.
37. Gaffney R, Hui Y, Vojovdich S, Forte V. Extranasopharyngeal angiofibroma of the turbinate. Int J Pediatr Otorhinolaryngol. 1997;40:177–80.
38. Eivazi B, Werner JA. Extracranial vascular anomalies (hemangiomas and vascular malforamtions) in children and adolescents-diagnosis, clinic and therapy. Laryngorhinootologie. 2014;93(Suppl 1):S185–202.
39. Almesberger D, Manna F, Guarneri GF, Marchesi A, Parodi PC. Arterio-venous malformations of the nose: combined approach for a successful strategy. J Craniofac Surg. 2016;27:1524–6.
40. McDonald J, Pyeritz RE. Hereditary hemorrhagic telangiectasia. In: Adam MP, Ardinger HH, Pargon RA, Wallace SE, LJH B, Mefford HC, et al., editors. Gene reviews [internet]. Seattle, WA: University of Washington, Seattle 1993-2017; 2000. [updated 2017 Feb 2].
41. Khalid SK, Pershbacher J, Makan M, Barzilai B, Goodenberger D. Worsening of nose bleed heralds high cardiac output state in hereditary hemorrhagic telangiectasis. Am J Med. 2009;122:779.e1–779.e19.
42. Coutinho-Camillo CM, Bretani MM, Nagal MA. Genetic alterations in junvenile nasopharyngeal angifibromas. Head Neck. 2008;30:390–400.
43. Garcia-Rodriguez L, Rudman K, Cogbill CH, Loehrl T, Poetker DM. Nasal septal angiofibroma, a subclass of extranasopaharyngeal angiofibroma. Am J Ototlayngo-Head Neck Med and Surg. 2012;33:473–6.
44. Dogan S, Yazici H, Baygit Y, Metin M, Soy FK. Extranasopharyngeal angiofibroma of the nasal septum: a rare clinical entity. J Craniofac Surg. 2013;24:e390–2.
45. Nazar R, Naser A, Rubio F, Ortega G. Extranasophrayngeal angiofibroma of the left lower turbinate: a case report. Acta Otorinolaryngol Esp. 2015;66:56–8.
46. Madana J, Yolmo D, Gopalakrishnan S, Saxena S. Extranasopharyngeal angiofibroma of the cartilage nasal septum possible origin from ectopic tissue trapped during septal development. Internet J Otorhinolaryngol. 2012;14(1):105580/2a8e.
47. Handa KK, Kumar A, Singh MK, Chhabra AH. Extranasopharyngeal angiofibroma arising from the nasal septum. Int J Pediatr Otorhinolaryngol. 2001;58:163–6.
48. Chen JM, Schloss MD, Azouz ME. Antro-choanal plyp: a 10 year retrospective study in the pediatric population with a review of the literature. J Otolaryngol. 1989;18:168–72.
49. Ngan BY, Forte V, Campisi P. Molecular angiogenic signaling in angiofibromas after embolization: implications for therapy. Arch Otolaryngol Head Neck Surg. 2008;134:1170–6.
50. Limaye AP, Mirani N, Kwartler J, Raz S. Inverted Schneiderian papilloma of the sinonasal tract in children. Pediatr Pathol. 1989;9:583–90.
51. Eavey RD. Inverted papilloma of the nose and paranasal sinuses in children and adolescence. Laryngoscope. 1985;95:17–23.
52. Heffner DK. Problems in pediatric otorhinolaryngic pathology. IV. Epithelial and lymphoid tumors of the sinonasal tract and nasopharynx. Int J Pediatr Otorhinolaryngol. 1983;6:219–37.
53. Altavilla G, Staffieri A, Busatto G, Canesso A, Giacomelli L, Marioni G. Expression of p53, p16INK4A, pRB, p21WAF1/CIP1, p27KIP1, cyclin D1, Ki-67 and HPV DNA in sinonasal endophytic Schneiderian (inverted) papilloma. Acta Otolaryngol. 2009;129:1242–9.
54. McLachlin CM, Kandel RA, Colgan TJ, Swanson DB, Witterick IJ, Ngan BY. Prevalence of human papillomavirus in sinonasal papillomas: a study using polymerase chain reaction and in situ hybridization. Mod Pathol. 1992;5:406–9.
55. Ziai J, French CA, Zambrano E. NUT gene rearrangement in a poorly-differentiated carcinoma of the submandibular gland. Head Neck Pathol. 2010;4:163–8.
56. Bishop JA, Westra WH. NUT midline carcinomas of the sinonasal tract. Am J Surg Pathol. 2011;36:1216–21.
57. Hellquist H, French CA, Bishop JA, Coca-Pelaz PEJ, Paiva Correia A, et al. NUT midline carcinoma of the larynx: an international series and review of the literature. Histopathology. 2017;70:861–8.
58. Bhagia P, Colanta AB, Abramson DH, Carlson DL, Kleinerman RA, Kraus D, et al. Sinonasal adenocarcinoma: a rare second malignancy in long term retinoblastoma survivors. Pediatr Blood Cancer. 2011;57:693–5.
59. Franchi A, Sardi I, Cetica V, Buccoliero A, Giordano F, Mussa F, et al. Pediatric sinonasal neuroendocrine carcinoma after treatment of retinoblastoma. Hum Pathol. 2009;40:750–5.
60. Vranic S, Caughron SK, Djuricic S, Bilaovic N, Zaman S, Suljevic I, et al. Hamartomas, teratomas and teratocarcinomas of the head and neck: report of 3 new cases with clinic-pathological correlation, cytogenetic analysis and review of the literature. BMC Ear Nose Throat Disord. 2008;8:8.
61. Agaimy A, Ihrler S, Markl B, Lell M, Zenk J, Hartman A, et al. Lipomatous salivary gland tumors: a series of 31 cases spanning their morphologic spectrum with emphasis on sialolipoma and oncocytic lipoadenoma. Am J Surg Pathol. 2013;37:128–37.
62. Vaze P, Aterman K, Hutton C, Idikio HA. Monomorphic adenoma of the nasal septum in newborn (case report and ultrastructural findings). J Laryngol Otol. 1983;97:251–9.
63. Chang KT, Chadha NK, Leung R, Shago M, Philips MJ, Thorner PS. Lymphoadenoma: case report of a rare salivary gland tumor in childhood. Pediatr Dev Pathol. 2010;13:331–7.
64. Bell D, Franchi A, Gillison M, et al. Olfactory neuroblastoma. In: WHO classification of head and neck tumours. Lyon: International Agency for Research on Cancer; 2017. p. 57–9.
65. Wormald R, Lennon P, O'Dwyer TP. Ectopic olfactory neuroblastoma: report of four cases and a review of the literature. Eur Arch Otorhinolaryngol. 2011;268:555–60.
66. Venkatramani R, Pan H, Furman WL, et al. Multimodality treatment of pediatric esthesioneuroblastoma. Pediatr Blood Cancer. 2016;63:465–70.
67. Fabien-Dupuis C, Niver B, Shillingford N, Wang L, Kokorowski PJ, Zhou S. Melanotic neuroectodermal tumor of infancy presenting with fast growing scrotal swelling: a case report and literature review. Pediatr Dev Pathol. 2017;20:411–5. PMID 26669807
68. Pettinato G, Manival JC, d'Amore ES, Jaszcz W, Gorlin RJ. Melanotic neuroectodermal tumor of infancy. A re-examination

of a histogenetic problem based on immunohistochemical, flow cytometric and ultrastructural study of 10 cases. Am J Surg Pathol. 1991;15:233–45. PMID: 1847607
69. Rachidi S, Sood A, Patel KG, Nguyen SA, Hamilton H, Neville BW, et al. Melanotic neuroectodermal tumor of infancy: a systematic review. J Oral Maxillofac Surg. 2015;73:1946–19556. PMID 25936939
70. Kapadia SB, Frisman DM, Hitchcock CL, Ellis GL, Popek EJ. Melanotic neuroectodermal tumor of infancy. Clinicopathological, immunohistochemical and flowcytometric study. Am J Surg Pathol. 1993;17:566–73. PMID: 8392815
71. Barrett AW, Morgan M, Ramsay AD, Farthing PM, Newman L, Speight PM. A clinicopathological and immunohistochemical analysis of melanotic neuroectodermal tumor of infancy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93:688–98. PMID12142876
72. Chan JKC, Quintanilla-Martinez L, Ferry JA, et al. Extranodal NK/T-cell lymphoma, nasal type. In: WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer; 2008. p. 85–8.
73. Li S, Feng X, Li T, et al. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. Am J Surg Pathol. 2013;37:14–23.
74. Yu JB, Zuo Z, Zhang WY, et al. Identification of immunophenotypic subtypes with different prognoses in extranodal natural killer/T-cell lymphoma, nasal type. Hum Pathol. 2014;45:2255–62.
75. Fernández PL, Cardesa A, Alós L, Pinto J, Traserra J. Sinonasal teratocarcinosarcoma: an unusual neoplasm. Pathol Res Pract. 1995;191:166–71.
76. Vranic S, Caughron SK, Djuricic S, Bilalovic N, Zaman S, Suljevic I, et al. Hamartomas, teratomas and teratocarcinosarcomas of the head and neck: report of 3 new cases with clinico-pathologic correlation, cytogenetic analysis, and review of the literature. BMC Ear Nose Throat Disord. 2008;8:8.
77. Martínez Redondo R, Rey López A, Reguerra Parra V, Bolaòos Rodríguez C. Sinusal teratocarcinosarcoma. Acta Otorrinolaringol Esp. 1991;42:363–7.
78. Rotenberg B, El-Harkim H, Lohda A, MacCormick A, Ngan BY, Forte V. Nasopharyngeal teratocarcinoma. Int J Pediatr Otorhinolaryngol. 2002;62:159–64.
79. Bronsnick T, Kirkorian AY, Cha J. Teen with lesion on nasal sidewall. JAMA Pediatr. 2013;16:1167–8.
80. Depeyre A, Barthelemy I, Dechelotte P, Dang NP. A case of basaloid degeneration of Nevus Sebaceous during childhood: should Nevus Sebaceous be excised or followed up? Facial Plast Surg. 2016;32:576–7.
81. Jaqueti G, Requena L, Sanchez Yus E. Trichoblastoma is the most common neoplasm developed in nevus sebaceous of Jadassohn: a clincopathologic study of a series of 155 cases. Am J Dermatopathol. 2000;22:108–18.
82. Zeller KA, Billmire DF. Trichoblastoma: management of a rate skin lesion. J Pediatr Surg. 2012;47:250–2.
83. McDermott MB, Ponder TB, Dehner LP. Nasal chondromesenchymal hamartoma: an upper respiratory tract analogue of the chest wall mesenchymal hamartoma. Am J Surg Pathol. 1998;22:425–33.
84. Ozolek JA, Carrau R, Barnes EL, Hunt JL. Nasal chondromesenchymal hamartoma in older children and adults: series and immunohistochemical analysis. Arch Pathol Lab Med. 2005;129:1444–50.
85. Priest JR, Williams GM, Mize WA, Dehner LP, McDermott MB. Nasal chondromesenchymal hamartoma in children with pleuropulmonary blastoma-A report from the International Pleuropulmonary Blastoma Registry. Int J Pediatr Otorhinolaryngol. 2010;74:1240–4.
86. Stewart DR, Messinger Y, Williams GM, Yang J, Field A, Schultz KA, Harney LA, Doros LA, Dehner LP, Hill DA. Nasal chondromesenchymal hamartomas arise secondary to germline and somatic mutations of DICER1 in the pleuropulmonary blastoma tumor predisposition disorder. Hum Genet. 2014;133:1443–50.
87. Alawi F. Benign fibro-osseous diseases of the maxillofacial bones. A review and differential diagnosis. Am J Clin Pathol. 2002;118(Suppl):S50–70. PMID 14569813
88. Shenker A, Chanson P, Weinstein LS, Chi P, Spiegel AM, Lomri A, et al. Osteoblastic cells derived from isolated lesions of fibrous dysplasia contain activating somatic mutations of the Gs alpha gene. Hum Mol Genet. 1995;4:1675–6. PMID8541861
89. McCarthy EF. Fibro-osseous lesions of the maxillofacial bones. Head Neck Pathol. 2013;7:5–10. PMID 23459840