

Core Messages

- › The most common polyps found in the nose and paranasal sinuses are those associated with chronic rhinosinusitis (CRS).
- › Histologic subclassification of CRS polyps is mainly descriptive and is not specific for any particular entity.
- › The presence of eosinophilic mucin should not be ignored, since this places the disease in the EMCRS/AFS category.
- › Unilateral or unusual appearance necessitates the need to biopsy a polyp to exclude other possible lesions.
- › Other lesions that present as polypoid masses include Schneiderian papillomas and mesenchymal neoplasms.

sinuses is diverse, ranging from inflammatory nasal polyps to benign and malignant epithelial, mesenchymal, and hematolymphoid neoplasms (Table 3.1). In the context of chronic rhinosinusitis (CRS), “polyp” refers to benign nongranulomatous inflammatory tissue projection with an epithelial lining within the sinonasal cavity. There are several histopathological features that differentiate CRS nasal polyps from other types of polypoid lesions occurring in the nose and paranasal sinuses. Furthermore, nasal polyps may have some unique characteristics that are distinguishable from the surrounding nonpolypoid CRS mucosa.

3.2 Normal Sinonasal Histology

The normal sinonasal histology is characterized by structural components including the epithelium, basement membrane, and submucosal tissue, and nonstructural components including resident and nonresident cells from the lymphoid and myeloid lineage.

3.1 Introduction

The term polyp refers to the macroscopic appearance of a pedicled tissue arising from a mucosal surface and projecting into a lumen or cavity. The histopathology of polypoid tissue affecting the nose and paranasal

3.2.1 Structural Component

Epithelium and basement membrane: The anterior 2 cm of the nasal cavity is lined by skin, composed of an epidermis with keratinizing stratified squamous epithelium, a fibrocollagenous dermis, and adnexal glands. The rest of the nasal cavity is lined by respiratory-type mucosa that is derived from ectoderm, also known as the Schneiderian membrane. Normal sinonasal mucosa is depicted in Fig. 3.1. The respiratory epithelium consists of four major cell types: ciliated columnar or cuboidal cells interspersed with goblet cells, nonciliated columnar cells with microvilli, and basal cells. The ratio of

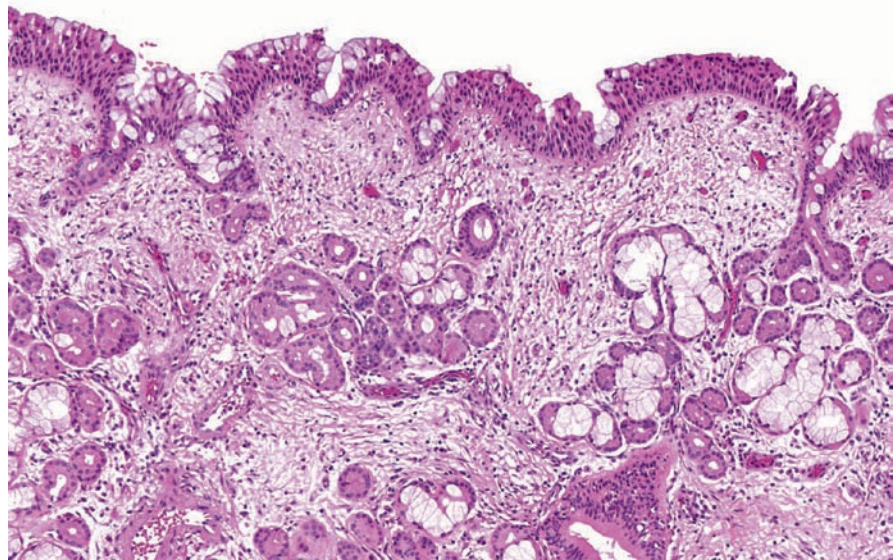
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Table 3.1 Mesenchymal lesions that may mimic sinonasal polyps

Differential diagnostic consideration	Distinguishing clinical features and morphology	Immunophenotype
Nasopharyngeal angiofibroma	Size, cellular stroma with thick muscular arteries, young adolescent males	Beta-catenin +, androgen receptor +
Solitary fibrous tumor	Size, cellular with dense “ropey” collagen and “staghorn” pericytomatous vasculature	CD34 +, bcl-2 +, CD99 +
Inflammatory myofibroblastic tumor	Size, cellular myxoid stroma arranged in fascicles with inflammatory background	Smooth muscle actin +, anaplastic lymphoma kinase (ALK) ±
Neuroglial heterotopia	Fibrillary matrix, ± ganglion cells	Glial fibrillary acidic protein +, synaptophysin +, neurofilament ±

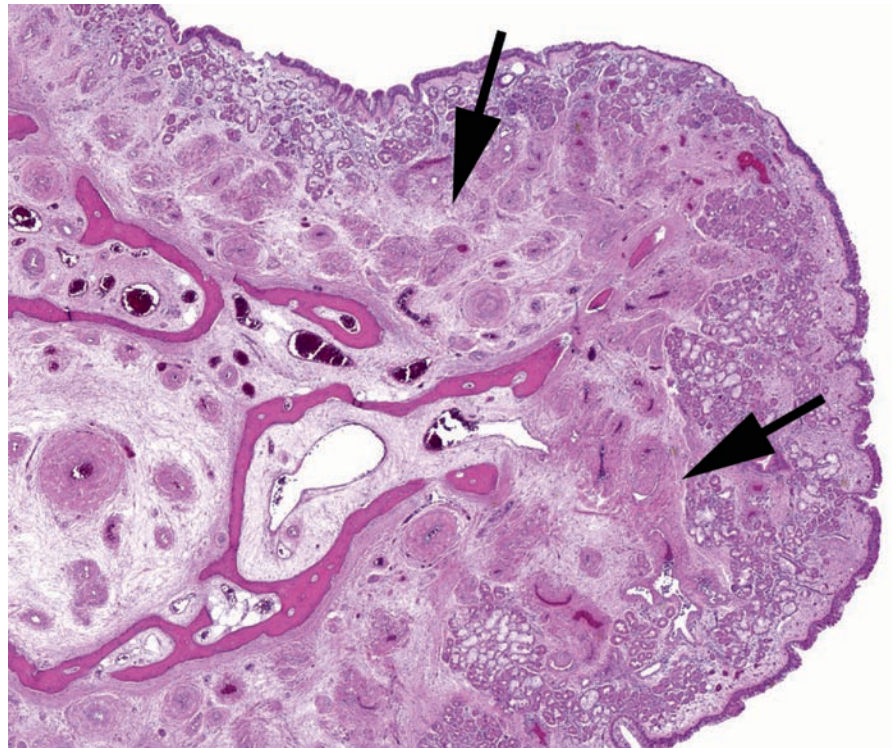
Fig. 3.1 Normal sinonasal mucosa (H&E, 100×). The surface is lined by ciliated pseudostratified columnar epithelium with goblet cells resting on a delicate basement membrane. The submucosa consists of delicate connective tissue with lobules of mucoserous glands and sparse lymphocytes representing NALT



columnar cells to goblet cells is approximately 5:1 and this ratio may vary depending on the site [21]. The normal respiratory-type epithelium often shows scattered areas of metaplastic squamous or cuboidal epithelium, and this is especially seen in the inferior turbinates [3]. The cells contain tight junctions and rest on a basement membrane composed principally of collagen fibers (types I, III, IV, V, VI, and VII) and other constituents that include heparan sulfate proteoglycan, laminin, and nidogen [1]. The basement membrane is delicate; however, in the inferior turbinate, a thick basement membrane may be seen. Compared with the nasal cavity, the paranasal sinuses have a thinner, less specialized surface epithelium and lamina propria [22]. These differences in the structural and cellular components between the sinus and nasal mucosa may reflect their different embryological origins and functional differences [2, 17].

The superior turbinate, superior nasal septum, roof of the nasal cavity and superior and medial portion of the middle turbinate are lined by olfactory epithelium also known as neuroepithelium [16]. This is also a ciliated pseudostratified columnar epithelium, which consists of a basal cells, bipolar ciliated olfactory cells, microvillar cells, and supporting or “sustentacular” cells. The central axonal process of olfactory cells passes through the cribriform plate to synapse with neurons present in the olfactory bulbs. With increased age, and following injury and infections, olfactory epithelium shows patchy loss and subsequent replacement with respiratory epithelium. The epithelial surface is covered by mucus produced by goblet cells, submucous glands, and ciliated cells. Mucus is actively propelled by the cilia toward the openings of the sinuses, enabling its drainage into the nasal cavity.

Fig. 3.2 Normal turbinate (H&E, 20×). Similar to other regions the surface is lined by respiratory-type mucosa with underlying mucoserous glands. Unique features of turbinate, however, are the thick prominent muscular arteries (*arrows*) seen below the mucoserous glands and between bony trabeculae



Submucosa: Beneath the basement membrane, the submucosa overlying the cartilage and bony sinonasal framework contains loose fibrovascular connective tissue, stromal cells including numerous seromucinous and minor salivary glands, blood vessels, nerves, and myeloid and lymphoid cells. Multiple seromucinous glands are present in superficial and deep layers and are separated by large venous sinusoids. The lobular units of the glands have a peripheral clustering of serous (~10%) and mucous (~90%) acini that secrete mucins, immunoglobulins, and enzymes that drain sequentially into the intercalated, striated, excretory, and ultimately, the main ducts. The main duct communicates with the epithelial surface. Over the age of 60, these mucoserous glands may show oncocytic change, a senescent phenomenon characterized by the abnormal accumulation of mitochondria in the cytoplasm imparting a granular densely eosinophilic appearance by light microscopy. The underlying vasculature consists of subepithelial capillaries, periglandular microvessels, and numerous arterial and venous anastomoses. The capillaries have specialized fenestrations that facilitate transport of fluid and high-molecular weight compounds. These networks communicate with venous

erectile vessels that are irregularly shaped with multiple smooth muscle layers and are most prominent in the submucosa of the nasal turbinates (Fig. 3.2). Here, the prominence and irregularity of these veins may simulate an arteriovenous malformation or cavernous hemangioma to those who are unfamiliar with the regional histology. Glands are usually more abundant in the normal middle turbinate, whereas veins are more prominent in normal inferior turbinate [8].

3.2.2 Nonstructural Components

The lymphoid compartment in the sinonasal mucosa is comprised of single lymphocytes scattered among the epithelial cells and lamina propria, and the nasal-associated lymphoid tissue (NALT) [13]. The NALT are discrete unencapsulated aggregates of lymphoid cells, akin to that in the mucosa-associated lymphoid tissue in the gut (Peyer's patches). However, NALT are not as well formed in the sinonasal mucosa, but may become more pronounced in chronic inflammation. The lymphocyte population is composed of T cells, B cells and

plasma cells, natural killer (NK) cells, and natural killer T (NKT) cells, and the myeloid cells include monocytes, macrophages, dendritic cells, granulocytes (including neutrophils and eosinophils), and mast cells. These cells form an integral component in the adaptive and innate mucosal immune responses.

3.3 Nasal Polyp Histopathology

3.3.1 Chronic Rhinosinusitis with Nasal Polyps

Approximately 20% of CRS patients have nasal polyps [9]. Presence of polyps may signify a distinct type of CRS with recalcitrant disease. Clinical conditions often associated with nasal polyps include asthma, asthma and aspirin sensitivity (Samter's triad), eosinophilic mucus chronic rhinosinusitis (EMCRS, including allergic fungal sinusitis), cystic fibrosis, Churg–Strauss disease, Kartagener's syndrome, and Young's syndrome. Histologically, polyps have been classified into several groups, based on the proposed etiology, predominant inflammatory cell infiltrate, and stromal appearance. This classification is purely descriptive and not specific to an underlying associated disorder or pathology.

3.3.1.1 Macroscopic Pathology

Macroscopically, most polyps have an edematous, smooth and shiny appearance with a soft consistency compared with the surrounding nonpolypoid mucosa. The cut surface is usually pale, edematous with a translucent appearance (Fig. 3.3). Biopsies from long-standing disease may be firm and solid white suggesting extensive fibrosis. Polyps are generally mobile and often attached via a stalk to the underlying mucosa. The surrounding CRS mucosa and middle turbinate is generally more erythematous and is firm to palpation. The CRS mucosa, depending on the degree of edema, may appear polypoid, but does not have a discrete stalk. Polyps commonly arise from the middle meatus and the sphenoethmoidal recess and are often bilateral. However, unilateral polyps are not uncommon. Polyps vary in size, and in severe cases, may completely fill the nasal cavity. In long-standing polyps, the sinonasal bones may remodel and cause broadening of the nasal dorsum.

The mucosa of the middle turbinate, inferior turbinate, uncinat process, and septum may also have broad-based polyps. A large polyp originating from the inferior turbinate is unusual [4]. Polypoid mucosa in the posterior portion of the inferior turbinate is not uncommon, referred to as a “mulberry” turbinate [10], and is usually not associated with CRS. Contrary

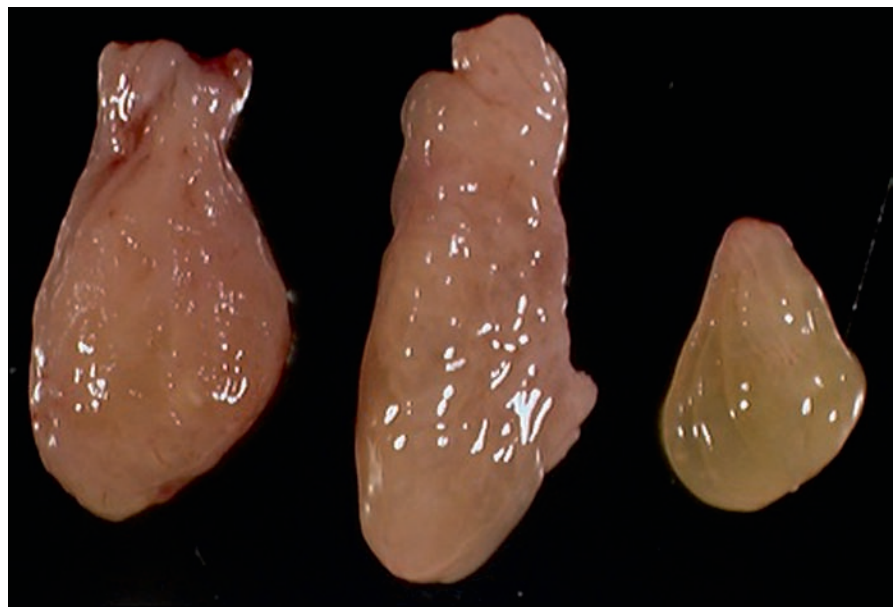


Fig. 3.3 Macroscopic appearance of a serially sectioned edematous polyp showing a delicate glistening yellow cut surface

to the middle and superior turbinates, the anterior portion of the inferior turbinate is rarely polypoid and this may be due to the presence of squamous epithelium and the aerodynamics in the region. A polyp arising from the maxillary sinus and into the nasal cavity is characteristic of antrochoanal polyp and is generally unilateral [25]. Nasal polyps associated with CRS do not usually have macroscopic surface ulceration, and the presence of such may indicate other pathologies. A more lobulated or “bunch of grapes” may signify other pathologies such as a sinonasal papilloma; however, based on the appearance alone, the underlying pathology is not always possible to determine. Therefore, all polyps, especially unilateral ones, need a histopathological examination at some point.

A proportion of CRS with nasal polyps also has characteristic thick, dark, and tenacious mucus, termed eosinophilic mucus. This mucus is typically seen in allergic fungal sinusitis but is also present in patients with severe and recalcitrant polypoid CRS including cystic fibrosis and Sampter’s triad and in the lungs of allergic bronchopulmonary aspergillosis. In many cases, the pathology of allergic fungal sinusitis may have been missed because the mucus was not examined for fungal elements.

3.3.1.2 Microscopic Pathology

The major histological characteristics of nasal polyps and CRS mucosa compared with normal mucosa include (1) structural changes involving the epithelium, submucosa, and sometimes underlying bone; and (2) the nature and degree of inflammatory cell infiltrate. Nasal polyps are typically lined by respiratory epithelium and have a basement membrane with variable thickness and an underlying stroma with a range of structural changes and inflammatory cells. Polyps have historically been classified based on their histological structural appearance and the nature of predominant inflammatory cell population into (1) edematous, eosinophilic, or “allergic” polyps, (2) chronic inflammatory polyps, and (3) seromucinous, glandular polyps. The description eosinophilic vs. noneosinophilic polyps is often used in the literature. But this classification is not specific to any associated or underlying pathology.

Edematous and eosinophilic polyps are the most common type and are also known as “allergic” nasal polyps. However, only a small proportion of CRS with NP have coexisting allergy and the controversy involving an allergic etiology is discussed elsewhere. These polyps are lined with respiratory epithelium with a range of mucosal alterations that include ulceration, granulation tissue, acute mucositis, epithelial and goblet cell hyperplasia, and squamous metaplasia. The basement membrane is often thickened, and there is abundant submucosal edema (Fig. 3.4). Mucus retention cysts are common and varying amounts of mixed inflammatory cell infiltrates contain mostly eosinophils, plasma cells, and scattered lymphocytes. The mucoserous glands are often incorporated within the edematous polyps. The edematous and eosinophilic polyps are seen in the whole spectrum of associated disorders including, EMCRS, allergic fungal sinusitis, Sampter’s triad, cystic fibrosis, and Churg–Strauss syndrome. Classically, nasal polyps associated with cystic fibrosis have delicate rather than thickened basement membranes and less stromal eosinophilia, and more neutrophils, hence termed neutrophilic polyps. Also characteristic is the presence of dense, deeply eosinophilic inspissated mucus secretions.

Chronic inflammatory polyp, also known as fibroinflammatory polyp, is less common, forming less than 10% of inflammatory nasal polyps [14]. These may represent a spectrum of edematous polyps, where occasionally, when a polyp is traumatized, the stroma may undergo secondary inflammatory change resulting in a myofibroblastic proliferation that may mimic a soft tissue neoplasm. The main histological features are the presence of submucosal fibrosis and an often prominent mixed inflammatory infiltrate with a lymphoid predominance often with germinal centers. Similar to other sinonasal polyps, mucoserous glands are still present within the polyp, unlike true mesenchymal lesions that tend to displace mucoserous glands. The surface epithelium is likely to show squamous metaplasia as a marker of chronicity (Fig. 3.5). Polyps with hyperplasia of seromucinous glands are less common. Lesions in this category are relatively new and somewhat controversial as to their relationship with true epithelial neoplasms, and include respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma [23, 24].

Fig. 3.4 Edematous polyp (H&E, 20×). This polyp shows slightly thickened basement membranes (*arrows*) and marked submucosal edema resulting in extensive clear space between submucosal connective tissue fibers. Inset (H&E, 400×) – scattered throughout are mixed inflammatory infiltrates including eosinophils and plasma cells

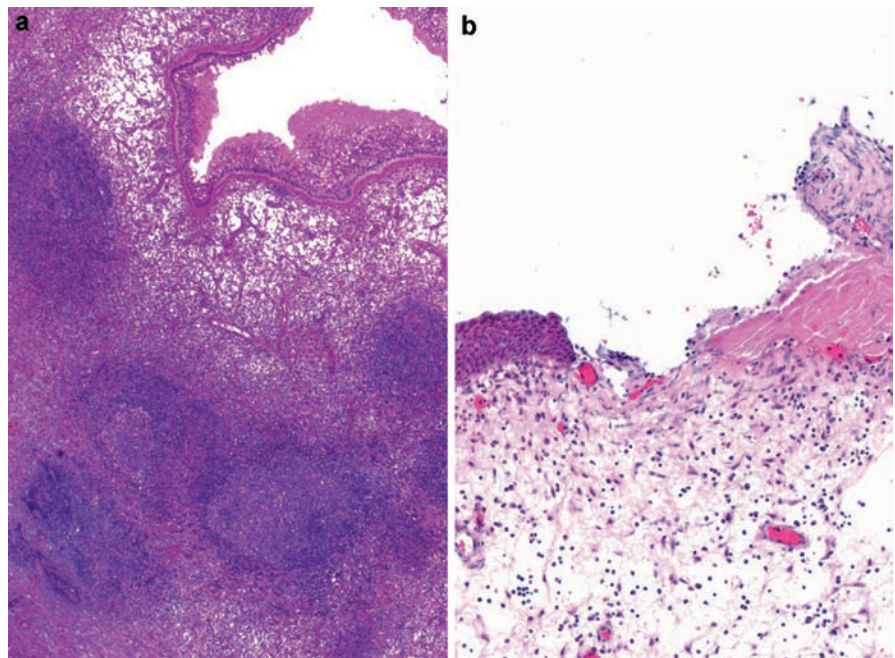
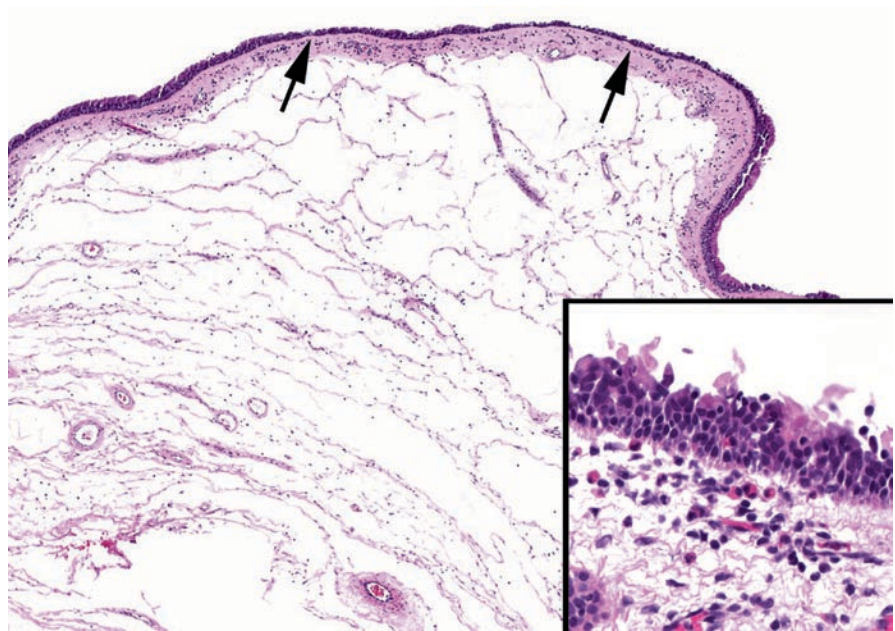


Fig. 3.5 Chronic inflammatory changes in polyps. (a) (H&E, 20×). This polyp shows an exuberant lymphoid hyperplasia with reactive germinal centers. (b) (H&E, 100×). This polyp shows mucosal ulceration (*right*) and squamous metaplasia (*left*)

3.3.2 Bone Changes

Underlying bone may show remodeling particularly in fibroinflammatory polyps.

3.3.3 Mucus Histopathology, Including “Eosinophilic Mucus”

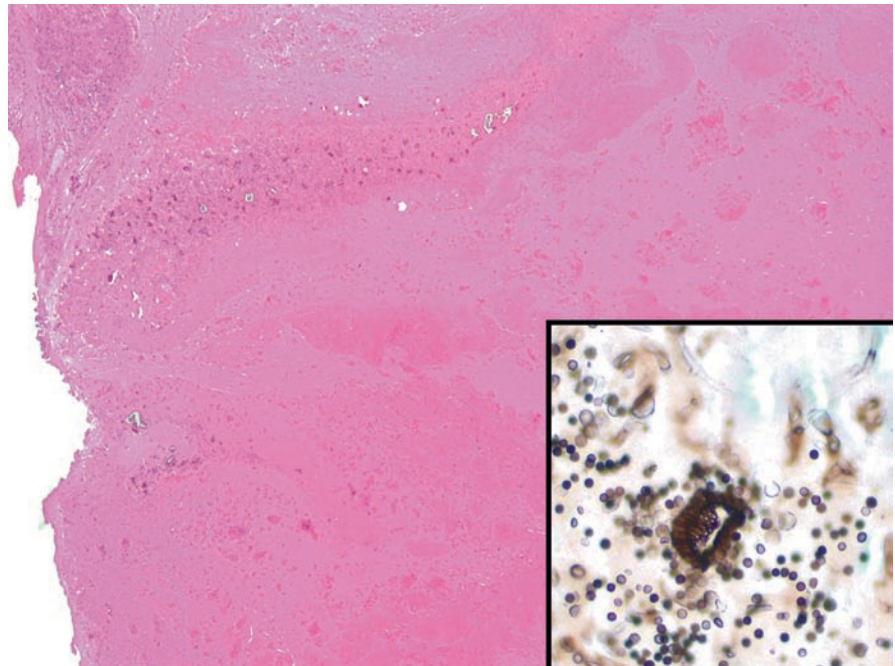
The secretions associated with CRS with and without polyps have a range of consistencies and contain numerous inflammatory cells that reflect the infiltrate found in the mucosa and polyps. Secretions from CRS with polyps generally contain more eosinophils than those without polyps, regardless of consistency of the mucus. In the clinical group, EMCRS, the secretions are typically thick, almost solid. Formalin-fixed H&E stained sections of this mucus typically show clusters of eosinophils, eosinophil breakdown products (Charcot–Leyden crystals), and other inflammatory and epithelial cells (Fig. 3.6). Fungal elements can be detected in up to 100% of these samples, (silver stains). This mucus, termed eosinophilic mucus, is the diagnostic criteria for EMCRS and allergic fungal sinusitis.

3.3.4 Antrochoanal Polyps

Antrochoanal polyps are the most common type of choanal polyp (most common source). Other sites of origin may be sphenoid, ethmoid, rarely septum, and inferior turbinate. These are all histologically similar. Antrochoanal polyps represent 4–6% of all polyps, and in the pediatric population, up to 33% (REF). As suggested by their designation, they have an antral and choanal component. These typically arise from the posterior wall of maxillary antrum and often have a thin “neck” that passes through the maxillary sinus ostium (or accessory ostium) [5]. They are often unilateral, but may be bilateral on rare occasions. Macroscopically, these range from erythematous to cystic with the latter often seen in the antral portion. The nasal and choanal portions are usually solid.

Microscopically, these polyps are lined by ciliated pseudostratified epithelium that is usually intact, with a thin basement membrane. Stroma may exhibit myxoid change and stromal giant cells, but usually lacks a significant inflammatory component. Rarely, degenerative changes including cholesterol granulomas and angiomatous change may be found [8, 20].

Fig. 3.6 Allergic or “eosinophilic” mucus (H&E, 40×). This consists of granular intensely eosinophilic mucus imparting a *bright pink* appearance. Inset (Grocott stain, 600×). A careful search will almost always yield fungal organisms. In this particular case, in addition to hyphae, conidiophores with conidia were seen compatible with *Aspergillus niger* and confirmed by fungal culture



3.3.5 Noninflammatory Polypoid Lesions

Polyps may occasionally resemble neoplasms, both epithelial and mesenchymal. The main epithelial differential diagnostic considerations are the Schneiderian papillomas. These consist of three types, exophytic, inverted, and oncocytic (rare). Nasal polyps with extensive squamous metaplasia or basal cell hyperplasia are the most likely mimics of Schneiderian papillomas. Grossly, these are distinguished from nasal polyps by their relative opacity. Exophytic Schneiderian papillomas arise invariably on the nasal septum and have a lower propensity for local aggressiveness and malignant transformation than inverted papillomas that typically occur on the lateral nasal wall. Histologically, all Schneiderian papillomas consist of a more complex epithelial proliferation, with the inverted type showing endophytic growth of epithelial nests (Fig. 3.7). Exophytic and inverted Schneiderian papillomas are lined by a mixture of squamous, respiratory, and “transitional” epithelium that is several layers thick. Unlike nasal polyps, the basement membranes in Schneiderian papillomas are characteristically delicate. The epithelium shows scattered mucus cells and “transmigration” neutrophils. Oncocytic papillomas are lined by oncocytic columnar epithelium with numerous epithelial microabscesses. It is important to note that both nasal

polyps and Schneiderian papillomas often coexist in patients, and thus, familiarity with the distinguishing characteristics is important [6].

Nasal polyps may mimic a variety of stromal neoplasms as well. This occurs when there is fibrous change or prominent vascularization of a polyp. Basically, any mesenchymal neoplasm of the sinonasal tract may present as a “nasal polyp.” However, a few lesions may also show histologic overlap with nasal polyps. Hemangiomas may mimic a vascularized nasal polyp. They are most commonly located in the anterior nasal septum and turbinates. In the nasal cavity they are either of the capillary or cavernous type. These are distinguished from vascular nasal polyps by their lobular arrangement. On the other hand, lesions such as solitary fibrous tumor, nasopharyngeal angiofibroma, and inflammatory myofibroblastic tumor may mimic a fibrous nasal polyp. Clinically, these true neoplasms tend to be larger than inflammatory nasal polyps. While nasopharyngeal angiofibromas may present in the nasal cavity, they typically arise from the nasopharynx and are invariably found in young to adolescent males. Additionally, these tend to show androgen receptor positivity and beta catenin nuclear reactivity [11, 18]. Solitary fibrous tumors and inflammatory myofibroblastic tumors have a characteristic morphology, and immunophenotype [15, 16] (see Table 3.1).

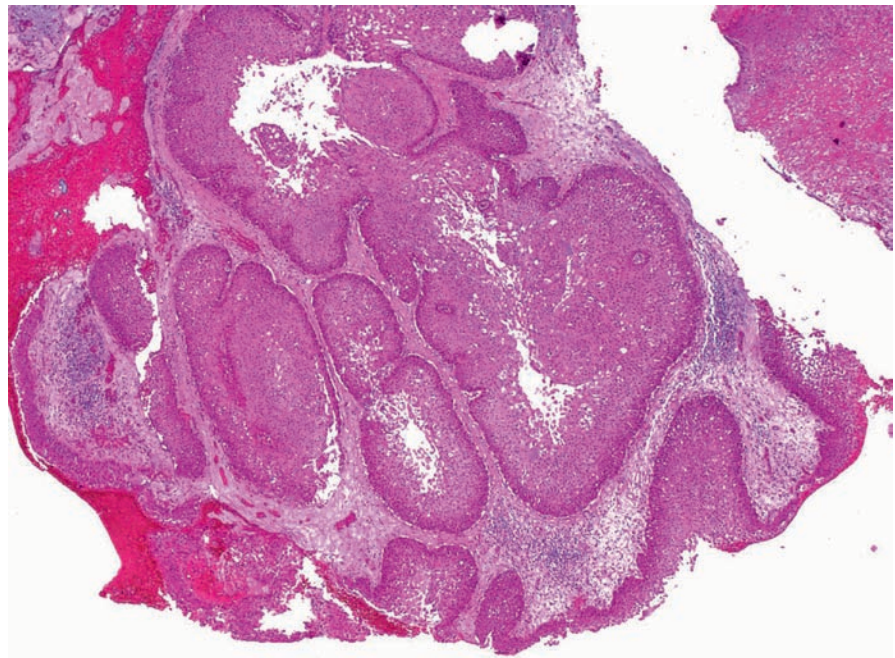


Fig. 3.7 Schneiderian papilloma, inverted type (H&E, 40×). This is a complex nested proliferation of transitional type epithelium with an endophytic growth. The nests are surrounded by delicate basement membrane

Both have a more prominent proliferation of stromal cells. In contrast, fibrous change in a sinonasal polyp is localized and not very prominent. Finally, very rarely neuroglial heterotopias may present as nasal polyps. The fibrillary glial tissue may be subtle and blend in with surrounding soft tissue edema. Immunostains directed toward synaptophysin, neurofilament, and/or glial fibrillary acidic protein may be useful to make this distinction [19].

3.4 Conclusions

Polyps associated with CRS are the most common cause of polypoid sinonasal lesions. The histological features of CRS with nasal polyps are similar among most associated disorders, and therefore cannot reliably discriminate pathologies. Pathologic evaluation is important to differentiate from other polypoid sinonasal lesions, especially in unilateral cases to differentiate from benign tumors. The presence of mucin should be reported and evaluated as polyps with this belonging to the clinicopathologic spectrum of EMCRS/AFS.

Take Home Pearls

- ▶ The most sinonasal polyps are associated with chronic rhinosinusitis (CRS) and have a broad histopathologic spectrum.
- ▶ Sinonasal polyps may be seen in the setting of EMCRS/AFS and may then be associated with eosinophilic mucin.
- ▶ Schneiderian papillomas and mesenchymal neoplasms may present as polypoid masses, and thus, unilateral or unusual appearing polyps should be biopsied.

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