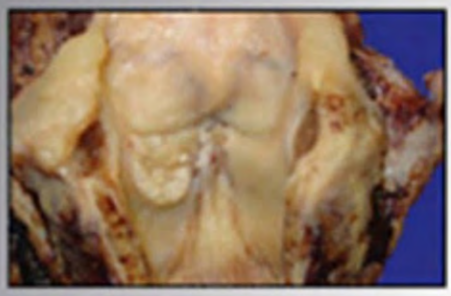
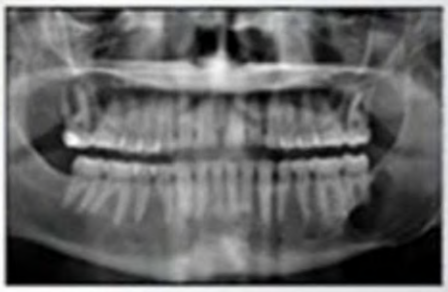
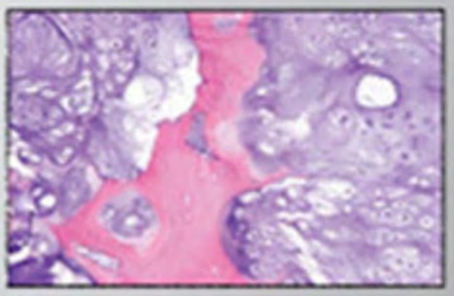
Lester D. R. Thompson
Justin A. Bishop

Head and Neck Pathology

THIRD EDITION

a volume in the series
FOUNDATIONS IN DIAGNOSTIC PATHOLOGY

series editor
John R. Goldblum

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Head and Neck Pathology

THIRD EDITION

A Volume in the Series Foundations in Diagnostic Pathology

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FOREWORD

The study and practice of anatomic pathology are both exciting and somewhat overwhelming, as surgical pathology (and cytopathology) have become increasingly complex and sophisticated. It is simply not possible for any individual to master all of the skills and knowledge required to perform the daily tasks at the highest level. Simply being able to make a correct diagnosis is challenging enough, but the standard of care has far surpassed merely providing an accurate diagnosis. Pathologists are now asked to provide huge amounts of ancillary information, both diagnostic and prognostic, often on small amounts of tissue, a task that can be daunting even to the most experienced surgical pathologists.

Although large general surgical pathology textbooks remain useful resources, by necessity they cannot possibly cover many of the aspects that diagnostic pathologists need to know and include in their daily surgical pathology reports. As such, the concept behind *Foundations in Diagnostic Pathology* was born. This series is designated to cover the major areas of surgical pathology, and each volume is focused on one major topic. The goal of every book in this series is to provide the essential information that any pathologist, whether general or subspecialized, in training or in practice, would find useful in the evaluation of virtually any type of specimen encountered.

Dr. Lester Thompson and Dr. Justin Bishop, both renowned and highly prolific head and neck pathologists, have edited an outstanding state-of-the-art book on the essentials of head and neck pathology. In fact, this area is one of the most common topics encountered by any surgical pathologist, but very few pathologists actually have formal training in this area. As such, a comprehensive reference such as this has great practical value in the day-to-day practice of any surgical pathologist. The list of contributors, as usual, includes some of the most renowned pathologists in this area, all of whom have significant expertise as practicing pathologists, researchers, and renowned educators on this topic. Each chapter is organized in an easy-to-follow manner, the writing is concise, tables are practical, and the photomicrographs are of high quality. There are thorough discussions pertaining to the handling of biopsy and resection specimens as well as frozen sections, which can be notoriously challenging in this field.

The book is organized into 29 chapters, including separate chapters that provide thorough overviews of non-neoplastic, benign, and malignant neoplasms of the larynx, hypopharynx, trachea, nasal cavity, nasopharynx, paranasal sinuses, oral cavity, oropharynx, salivary glands, ear and temporal bone, gnathic bones, and neck. Similarly, chapters describing the non-neoplastic, benign, and malignant neoplasms of the thyroid gland, parathyroid gland, and paraganglia system are included.

I am truly grateful to Dr. Thompson and Dr. Bishop as well as to all of the contributors who put forth tremendous effort to allow this book to come to fruition. It is yet another outstanding edition in the *Foundations in Diagnostic Pathology* series, and I sincerely hope you enjoy this comprehensive textbook and find it useful in your everyday practice of head and neck pathology.

John R. Goldblum, MD

PREFACE

There is an axiom in computing called Moore's law that states the computing speed of processors doubles every 2 years while the cost halves. However, if you actually read the fine print, it is the number of transistors in an average computer that would double every 2 years—a corollary if you will. Thus, the average CPU in a computer now has 904 million transistors, which clearly contributes to the overall speed, even though perhaps the "law" has slowed down.

How does this apply to pathology and medicine? Well, it seems that there is a tremendous increase in the number of discoveries, new entities being carved out of old ones, new diagnostic tools to achieve even greater precision in diagnostic terms and clinical prognostication. Even with this staggering volume of data, it must always be harnessed by a mind willing to synthesize all of the data points into a meaningful and actionable diagnosis that a clinician and patient alike can use to treat the disease and achieve the best outcome for the patient.

It is the aim of this edition to highlight several of the new diagnostic entities within the anatomic confines of the larynx, sinonasal tract, ear and temporal bone, salivary gland, oral, oropharynx, nasopharynx, gnathic, and neck regions. Clearly, the unlimited nature of the internet with countless webpages of information cannot be contained within a single book without requiring a forklift to move it around. Thus, the reader is encouraged to use this book as a starting point to make a meaningful diagnosis of the most common and frequent diagnoses that may beset a busy surgical pathologist in daily practice, while using the references and other materials to lead to greater understanding. Use the pertinent clinical, imaging, laboratory, macroscopic, microscopic, histochemical, immunohistochemical, ultrastructural, and molecular results presented herein to reach a meaningful, useful, and actionable diagnosis.

Lester D.R. Thompson, MD, and Justin A. Bishop, MD

ACKNOWLEDGMENTS

With the passage of time, transition and change are inevitable. As such, death seems to become more a part of life than the inherent meaning that the word suggests. And so it seems that many of those who influence you the most reach death's doorstep ahead of you, creating a vacuum and space in your heart that is never refilled. The guidance provided by a parent, especially in the early years, is an example of this type of powerful influence.

From as early as I can remember, my mother, Frances Avril Dawn Ansley Thompson (can you tell where I got all of my names!), provided love, support, and encouragement. She so wanted me to be happy, healthy, and wise. With each success or failure, triumph or rejection, I was always able to count on my mother to say the right thing—or say nothing at all, but just hold me, whether physically or emotionally. Last year as we were chatting about my projects, books, lectures, and work, she very quietly said: "It's great that you have a written legacy, but remember to work on your spiritual, social, and emotional legacy with the same devotion and vigor."

Those words rang loud and clear at my 25th wedding anniversary celebration the following weekend, a party she would have loved to attend, but couldn't as she had died of complications of a ruptured thoracic aortic aneurysm. Taking her final words to heart, I find myself drawn to other pursuits, attempting to keep work in an ever shrinking box, including the time devoted to philanthropic endeavors with my wife, Pam, whose role in my life continues to grow and expand with each passing year.

Although patently obvious, the responsibility for any errors, omissions, or deviation from current orthodoxy is mine alone!

Lester D.R. Thompson, MD

I dedicate my work on this book to my wonderful wife, Ashley, and our beautiful children, Riley and Avery. I am very grateful for their willingness to sacrifice so much of our time together for this and other projects. I thank my parents, Debbie and Fred, my sister, Kristen, and my brother, Martin, for their unwavering support. I am also appreciative of Dr. William Westra, my mentor at The Johns Hopkins Hospital who took a chance on me and taught me much of what I know. Finally, I thank Dr. Lester Thompson for generously inviting me to co-edit the newest edition of this book. I have enjoyed working with him immensely and look forward to our many future collaborations.

Justin A. Bishop, MD

1

Non-Neoplastic Lesions of the Nasal Cavity, Paranasal Sinuses, and Nasopharynx

■ **Austin McCuiston** ■ **Justin A. Bishop**

■ RHINOSINUSITIS

Rhinosinusitis is defined simply as inflammation of the nasal cavity (rhinitis), paranasal sinuses (sinusitis), or both (rhinosinusitis).

Clinical Features

Rhinosinusitis is a common condition that can be caused by myriad etiologies, including allergies (most common), infections, aspirin intolerance, exposures to toxins or medications, pregnancy, systemic diseases, among others. Rhinosinusitis can also be idiopathic, with no known cause. Regardless of etiology, patients share the symptoms of nasal obstruction and discharge.

Acute rhinosinusitis is typically infectious, either viral (e.g., rhinovirus, adenovirus, respiratory syncytial virus, among others) or bacterial (*Streptococcus pneumoniae*, *Haemophilus influenzae*, among others). Viral rhinosinusitis results in a watery nasal discharge, whereas bacterial disease results in a mucopurulent discharge, headache, and fever. Bacterial rhinosinusitis can occasionally be superimposed on viral disease.

Chronic rhinosinusitis (i.e., symptoms lasting longer than 12 weeks) is most often allergic in etiology as a result of an IgE-mediated reaction. Patients with allergic rhinosinusitis complain of a clear nasal discharge, sneezing, and itching after exposure to the offending allergen. Clinical examination reveals sinonasal mucosa that is edematous, pale, and sometimes bluish in color. Inflammatory polyps, as described later, are often seen in this setting.

By imaging, inflamed sinuses demonstrate opacification and mucosal thickening (Fig. 1.1A). Air-fluid levels are classically identified in acute disease (see Fig. 1.1B).

Pathologic Features

Gross Findings

In general, the gross findings consist of fragments of soft tissue and bone with no specific changes. Inflammatory polyps (as described later) may be encountered.

RHINOSINUSITIS—DISEASE FACT SHEET

Definition
- Inflammation of the nasal passages, most commonly as the result of allergies or infection

Incidence
- Common
- Nasal cavity and paranasal sinuses, often bilateral

Morbidity and Mortality
- Usually minimal, although rarely untreated bacterial sinusitis can extend to the orbit or meninges

Sex and Age Distribution
- Any age, no sex predilection

Clinical Features
- Nasal discharge, watery in allergic and viral, mucopurulent in bacterial
- Allergic disease accompanied by itching and sneezing

Treatment and Prognosis
- Allergic rhinosinusitis treated with antihistamines, nasal steroids, allergic desensitization
- Bacterial rhinosinusitis requires antibiotics, while viral infection is treated supportively
- Surgery is reserved for refractory, chronic disease

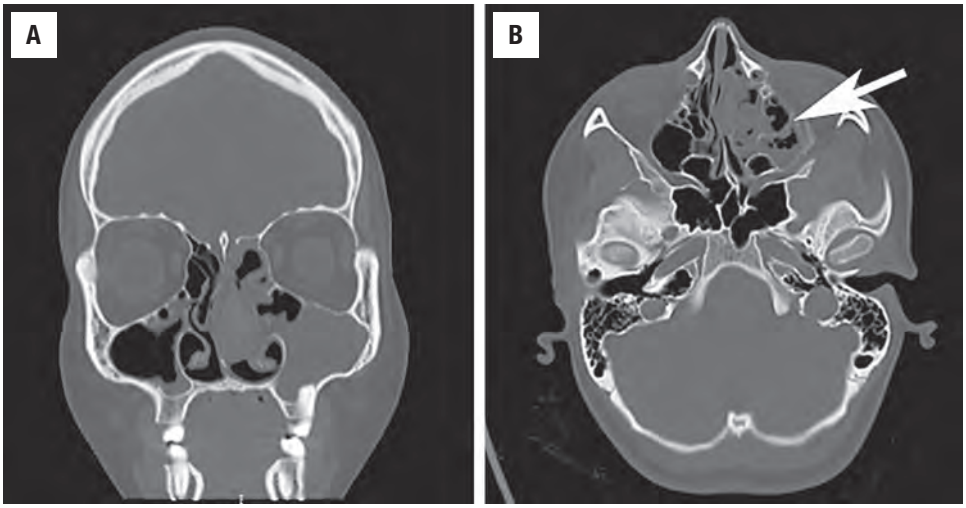

FIGURE 1.1

This computed tomography scan demonstrates radiographic features of both acute and chronic sinusitis. The left maxillary sinus demonstrates near complete opacification (**A**), and air-fluid levels are noted (*arrow*) in the left ethmoid sinus (**B**).

Microscopic Findings

Rhinosinusitis exhibits sinonasal mucosa with a submucosal inflammatory infiltrate. The inflammatory cells are generally composed of lymphocytes, plasma cells, macrophages, and eosinophils, which predominate in allergic disease (Fig. 1.2). Acute rhinosinusitis is characterized by increased neutrophils, especially when associated with a bacterial etiology. There is often a component of stromal edema, which leads to the development of inflammatory polyps (described in detail in the next topic). The surface epithelium may also demonstrate changes, including inflammation, squamous metaplasia (Fig. 1.3A), or reactive papillary hyperplasia (so-called *papillary sinusitis*) (see Fig. 1.3B).

RHINOSINUSITIS—PATHOLOGIC FEATURES

Gross Findings
- Nonspecific

Microscopic Findings
- Submucosal infiltrate of lymphocytes, plasma cells, neutrophils, eosinophils, often with edema
- Surface epithelium may demonstrate squamous metaplasia, inflammation, or reactive papillary hyperplasia

Pathologic Differential Diagnosis
- Inflammatory polyps, sinonasal papilloma, adenocarcinoma

Differential Diagnosis

The diagnosis of rhinosinusitis is usually not difficult. Many of the changes overlap with sinonasal inflammatory polyps, and the distinction between the two entities is not important. In cases with squamous metaplasia and/or reactive papillary hyperplasia of the surface epithelium, sinonasal papilloma can enter the differential diagnosis. Sinonasal papillomas have squamous or squamoid epithelium that is also thickened, proliferative with endophytic and/or exophytic growth, and infiltrated by neutrophils with microabscesses. Rarely, adenocarcinoma may enter the differential diagnosis when there is a reactive proliferation of seromucinous glands.

Prognosis and Therapy

Acute viral rhinosinusitis is treated symptomatically, whereas bacterial disease requires antimicrobials. Chronic allergic sinusitis is treated with antihistamines, intranasal corticosteroids, and/or allergic desensitization. Patients with chronic rhinosinusitis refractory to medical therapy may require endoscopic surgery. Rhinosinusitis is generally not life-threatening, with the rare exception of untreated bacterial infection that can lead to infection of the orbit or meninges.

SINONASAL INFLAMMATORY POLYPS

Sinonasal inflammatory polyps are common non-neoplastic masses of sinonasal tissue that essentially result from edema within the submucosa.

Clinical Features

Inflammatory polyps are associated with many conditions. They are most often seen in the setting of allergic rhinosinusitis but may also be seen in the setting of infections,

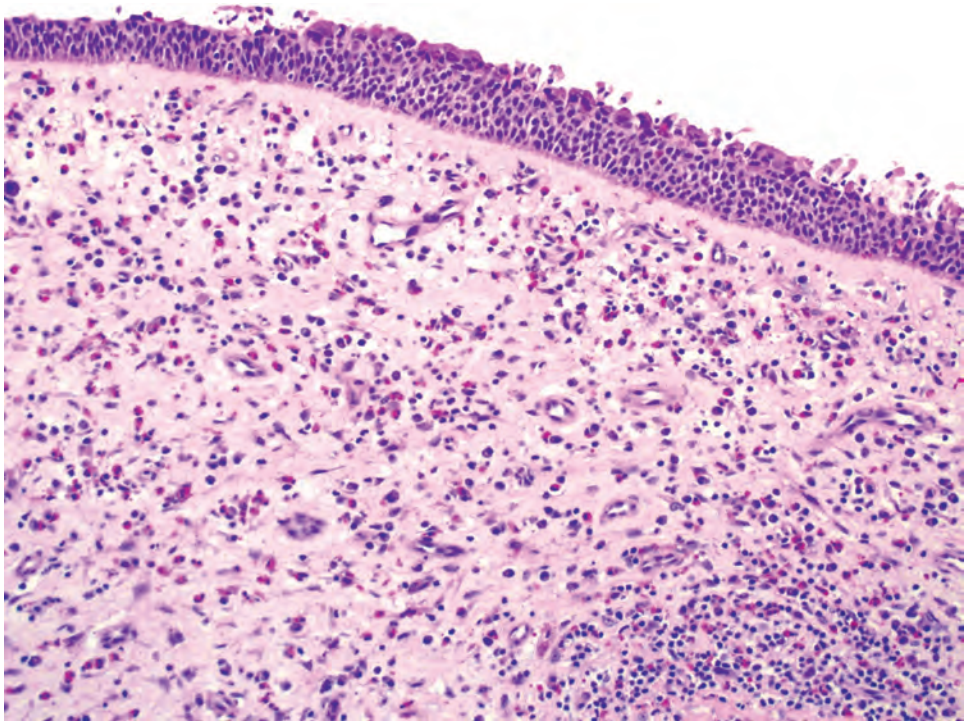

FIGURE 1.2

Chronic sinusitis is histologically characterized by a submucosal infiltrate of chronic inflammatory cells including lymphocytes, plasma cells, and eosinophils, which tend to predominate in allergic sinusitis.

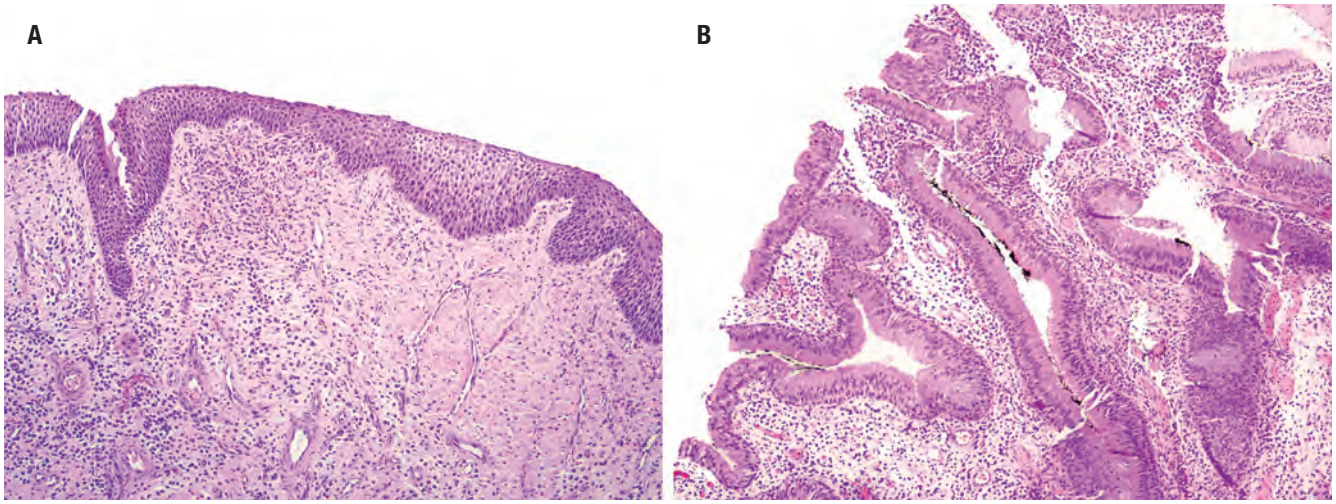

FIGURE 1.3

Some cases of chronic sinusitis can demonstrate foci of surface epithelial squamous metaplasia (**A**). In addition, chronic sinusitis occasionally exhibits papillary surface epithelial hyperplasia as a reactive change. When prominent, this finding can be confused with other lesions such as respiratory epithelial adenomatoid hyperplasia or sinonasal papilloma (**B**).

asthma, aspirin intolerance, cystic fibrosis, diabetes mellitus, and other conditions. Inflammatory polyps are typically seen in adults (except for cystic fibrosis-associated polyps), with no sex predilection. They involve the nasal cavity (especially the lateral wall) and maxillary and ethmoid sinuses and are usually bilateral (Fig. 1.4A). In addition to the symptoms of the underlying condition (e.g., allergies), sinonasal inflammatory polyps may cause nasal obstruction and pain. A subtype of inflammatory polyp known as antrochoanal polyp arises from the maxillary antrum and extends through the sinus ostia into the nasal cavity, nasopharynx, or oral cavity (see Fig. 1.4B). Antrochoanal polyps are usually seen in younger patients (teenagers and young adults), usually males, and are typically unilateral.

Pathologic Features

Gross Findings

Inflammatory polyps are typically translucent and mucoid in appearance (see Fig. 1.4A). Antrochoanal polyps tend to be elongated with a stalk and fibrotic.

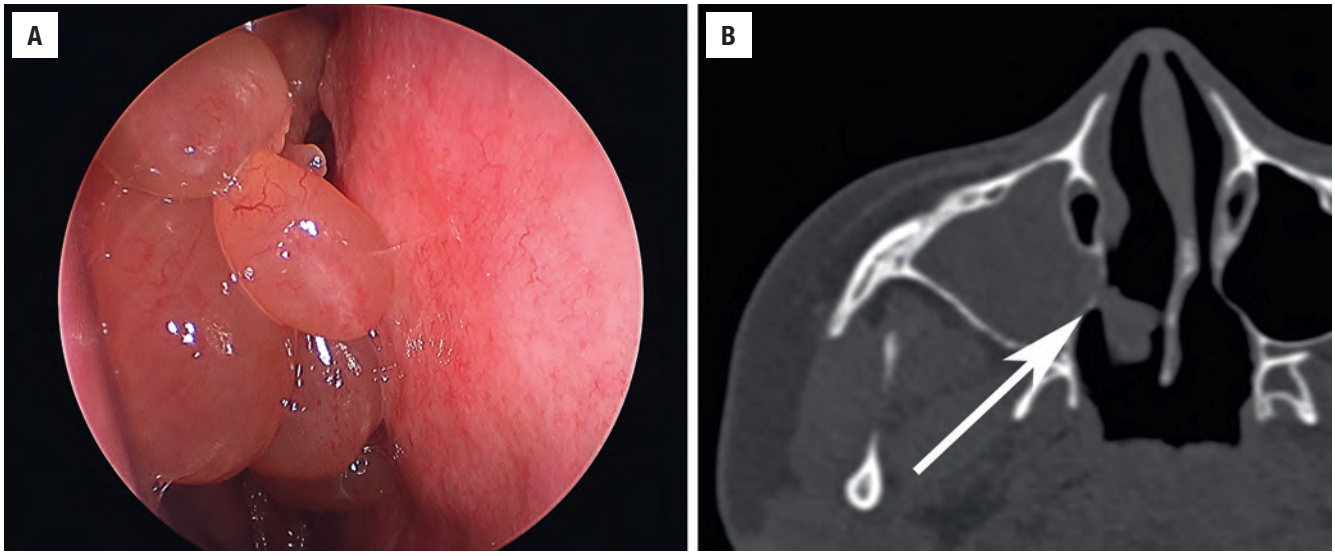

FIGURE 1.4

The typical clinical appearance of inflammatory polyps is that of bilateral, multiple mucoid polypoid masses with a translucent appearance involving the nasal cavity (**A**). The antrochoanal polyp is a subtype of inflammatory polyp arising from the maxillary antrum and protruding into the nasal cavity via a stalk (*arrow*) through the nasal choana (**B**). (***A,*** *Courtesy of Dr. Douglas Reh.)*

SINONASAL INFLAMMATORY POLYPS—DISEASE FACT SHEET

Definition
- Polypoid growths of sinonasal mucosa that result primarily from submucosal edema
- An allergic etiology is most common

Incidence
- Common
- Nasal cavity and paranasal sinuses, often bilateral
- Antrochoanal polyp is a subtype that arises from the maxillary antrum and protrudes through the sinus ostium, usually unilateral

Morbidity and Mortality
- Usually minimal, although rarely may lead to bone erosion or remodeling

Sex and Age Distribution
- Typically adults (except antrochoanal polyps in teenagers/young adults and cystic fibrosis polyps in children)

Clinical Features
- Symptoms of underlying disease (e.g., rhinorrhea, nasal stuffiness, headaches in allergic polyps)
- Nasal obstruction and epistaxis

Treatment and Prognosis
- Endoscopic removal
- Treatment of underlying disease (e.g., nasal steroids for allergic polyps)

SINONASAL POLYPS—PATHOLOGIC FEATURES

Gross Findings
- Translucent, glistening, and mucoid
- Antrochoanal polyps have a long stalk and are fibrotic

Microscopic Findings
- Polypoid fragments of sinonasal mucosa with abundant stromal edema
- Chronic inflammatory cell infiltrate with numerous eosinophils
- Epithelial basement membrane is usually hyalinized
- Secondary changes including infarction, hemorrhage, and fibrin deposition can be seen.
- Antrochoanal polyps are less edematous, more fibrotic, fewer eosinophils, and minimal basement membrane hyalinization.

Pathologic Differential Diagnosis
- Amyloidosis, hemangioma, lymphangioma, infections, respiratory epithelial adenomatoid hamartoma, nasopharyngeal angiofibroma, sinonasal papilloma, embryonal rhabdomyosarcoma

Microscopic Findings

The most prominent feature of a sinonasal inflammatory polyp is submucosal edema beneath an intact respiratory epithelium (Fig. 1.5A). The subepithelial basement membrane is typically hyalinized (see Fig. 1.5B). There is usually a mild to moderate infiltrate of chronic inflammatory cells with a predominance of eosinophils (see Fig. 1.5B). Scattered stellate or spindled fibroblasts are seen, some of which may exhibit enlarged, hyperchromatic nuclei (see Fig. 1.5C). Larger inflammatory polyps may demonstrate prominent submucosal hemorrhage with fibrin

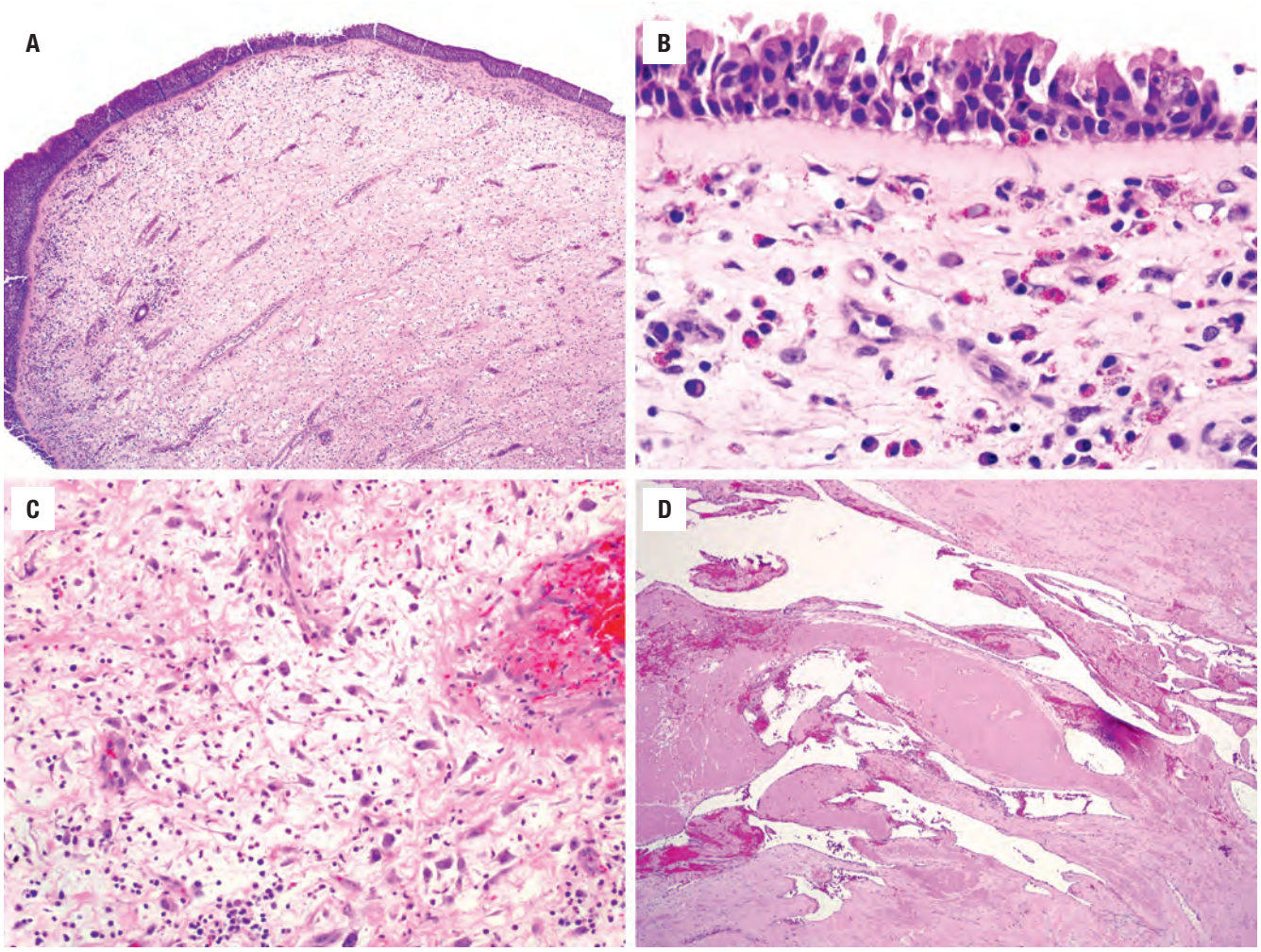

FIGURE 1.5

A sinonasal inflammatory polyp consists of a rounded proliferation of sinonasal mucosa with submucosal inflammation and edema (**A**). An inflammatory polyp often has a hyalinized subepithelial basement membrane and an infiltrate of chronic inflammatory cells, especially eosinophils (**B**). Inflammatory sinonasal polyps commonly demonstrate scattered atypical stromal myofibroblasts. When prominent, a mesenchymal neoplasm is a diagnostic consideration (**C**). In the angiectatic or angiomatous variant of inflammatory polyp, there is abundant fibrin deposition (which can be mistaken for amyloid) as well as recanalizing vessels (which can be mistaken for a vascular tumor) (**D**).

deposition or infarction, a pattern that has been referred to as "angiomatous" or "angiectatic" (see Fig. 1.5D).

Antrochoanal polyps have a similar appearance but tend to be more fibrotic and less edematous (Fig. 1.6A), have fewer eosinophils, and lack a hyalinized basement membrane (see Fig. 1.6B). Bizarre stromal cells are more common in antrochoanal polyps than in inflammatory polyps.

Differential Diagnosis

The diagnosis of sinonasal inflammatory polyp is usually straightforward. When there is prominent fibrin deposition, amyloidosis is a consideration. True amyloid is positive with Congo red showing apple-green birefringence, in contrast to fibrin. In angiomatous polyps in which recanalizing vessels are prominent, a vascular or lymphatic neoplasm could be considered. Recognizing the context of the vessels (i.e., with organizing fibrin within a sinonasal polyp) is useful in avoiding this pitfall. The fibrous stroma and occasional nasopharyngeal location of antrochoanal polyps are somewhat reminiscent of nasopharyngeal angiofibroma. In addition, both tumors, typically as unilateral masses, arise in younger men. Recognizing the dilated, "staghorn" appearance of the vessels is important for diagnosing angiofibroma; the vessels of antrochoanal polyp are typically small and inconspicuous. In difficult cases, immunohistochemistry for beta-catenin and androgen receptor may be used: the stromal cells of angiofibroma are positive for both, whereas antrochoanal polyps are negative. The atypical stromal cells of sinonasal inflammatory polyps can, in some cases, be alarming and raise the possibility of a sarcoma such as embryonal rhabdomyosarcoma.

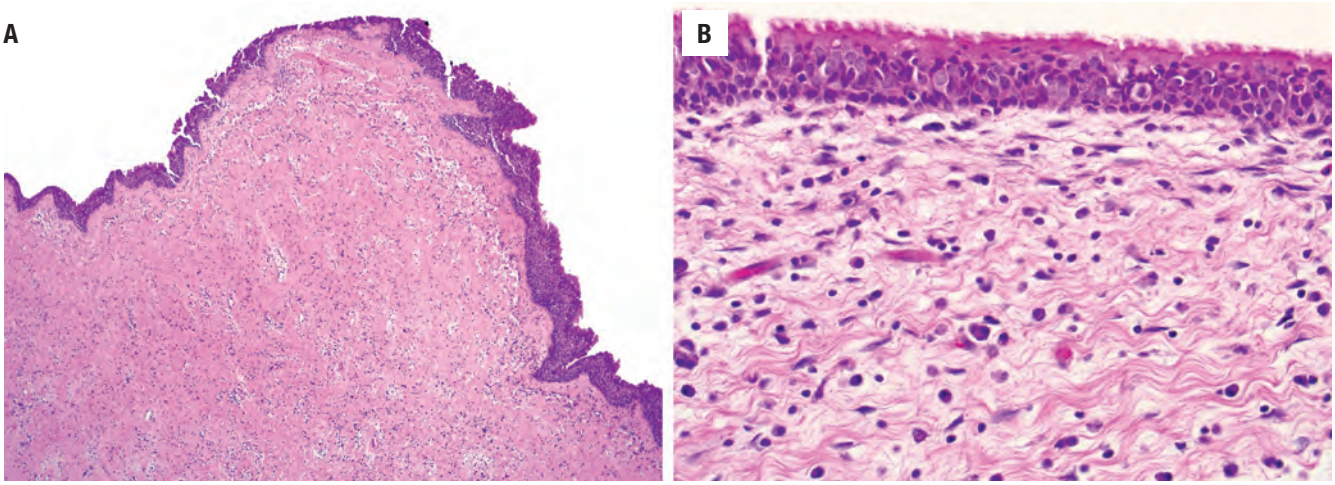

FIGURE 1.6

Antrochoanal polyp is a variant of inflammatory polyp that typically exhibits more prominent subepithelial fibrosis at low power (**A**). In contrast to the usual inflammatory polyp, antrochoanal polyps have fewer eosinophils and lack a hyalinized basement membrane (**B**).

However, the atypical stromal cells of benign polyps are singly and randomly distributed, do not aggregate (e.g., no "cambium" layer characteristic of embryonal rhabdomyosarcoma), are not mitotically active, and are negative for desmin and myogenin. Respiratory epithelial adenomatoid hamartoma (REAH) tends to show widely spaced glands, surrounded by a thick, eosinophilic basement membrane, showing connections of the invaginations to the surface. Finally, one must be sure to exclude the presence of another sinonasal neoplasm such as sinonasal papilloma that are often seen in association with inflammatory polyps.

Prognosis and Therapy

These are benign lesions. Treatment includes endoscopic surgery in addition to treatment of the underlying medical cause (e.g., nasal steroids for allergic polyps).

PARANASAL SINUS MUCOCELE

Mucoceles of the paranasal sinus result from obstruction of the sinus outflow tract with subsequent expansion of the sinus with mucin.

Clinical Features

Sinus mucoceles can occur in any age or sex. They result from any disease that obstructs the sinus outflow tract (ostium or duct), most commonly chronic sinusitis, but also occasionally trauma, neoplasms, or other causes. The obstruction leads to expansion of the involved sinus, usually frontal or ethmoid (Fig. 1.7A). Mucoceles can produce alarming clinical and radiographic features, including facial deformity, headaches, visual disturbances, proptosis, bone erosion and sclerosis, and rarely, invasion

PARANASAL SINUS MUCOCELE—DISEASE FACT SHEET

Definition
- Expansion of the paranasal sinus by mucin resulting from obstruction of the outflow tract

Incidence
- Uncommon
- Frontal and ethmoid sinuses most commonly affected

Morbidity and Mortality
- Can result in facial deformity, brain or orbit involvement if untreated

Sex and Age Distribution
- Any age or sex

Clinical Features
- Nasal obstruction, headaches, visual disturbances, proptosis
- Radiographs show expanded sinus with bone erosion and sclerosis and rarely invasion of the orbit or cranial cavity

Treatment and Prognosis
- Surgical excision
- Treatment of underlying cause (usually chronic sinusitis)

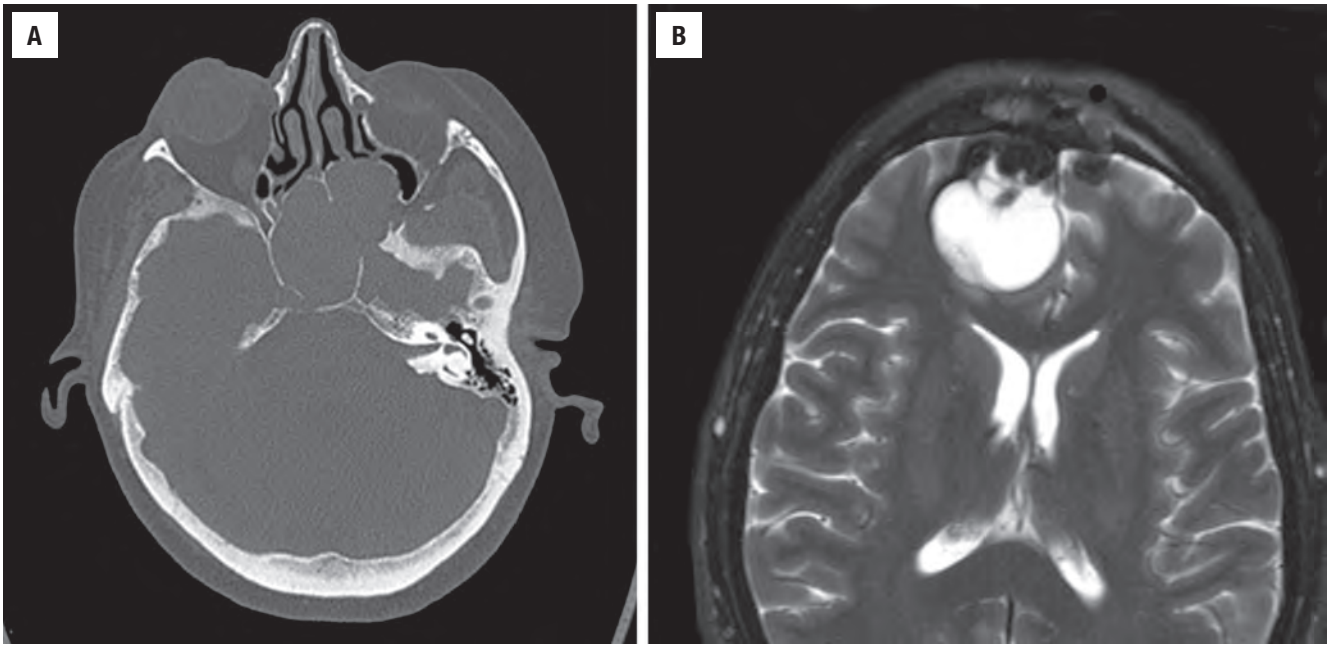

FIGURE 1.7

This computed tomography scan demonstrates a sphenoid sinus mucocele, with expansion of the sinus with secretions and thinning and remodeling of the surrounding bones (**A**). This T2-weighted magnetic resonance imaging scan shows a fluid-filled mucocele involving the brain (**B**).

PARANASAL SINUS MUCOCELE—PATHOLOGIC FEATURES

Gross Findings

- Abundant mucin, otherwise nonspecific

Microscopic Findings

- Very nonspecific
- Sinonasal mucosa with inflammation, sometimes attenuation, squamous metaplasia, scarring, reactive bone, or cholesterol granulomas

Pathologic Differential Diagnosis

- Normal sinonasal mucosa, inflammatory polyps, unsampled neoplasm leading to obstruction

of the orbit or cranial cavity (see Fig. 1.7B). Given these dramatic symptoms and radiographic features, a neoplastic process is often suspected clinically.

Pathologic Features

Gross Findings

Abundant mucin is generally apparent grossly or reported intraoperatively (if suction has removed all of the contents).

Microscopic Findings

The microscopic features of mucoceles are typically underwhelming (particularly in the setting that is suspicious for malignancy) and closely mimic normal sinonasal tissue. The sinonasal tissue sometimes has an attenuated appearance resembling a cyst lining (Fig. 1.8A and B). Epithelial squamous metaplasia, fibrosis, a rim of reactive bone, or cholesterol granuloma formation can also be seen. Because of their nonspecific nature, a definitive diagnosis cannot be made on histologic grounds without clinical or radiographic input.

Differential Diagnosis

The main diagnostic consideration is normal sinonasal tissue. Clinical and radiographic correlation is needed to make the distinction. Sinonasal polyps or a salivary gland mucocele may also be in the differential. An unsampled neoplasm may be the cause of the obstruction leading to a mucocele.

Prognosis and Therapy

Sinus mucoceles are treated by surgical excision. The underlying cause of the obstruction (e.g., chronic sinusitis) should also be addressed. The prognosis is excellent.

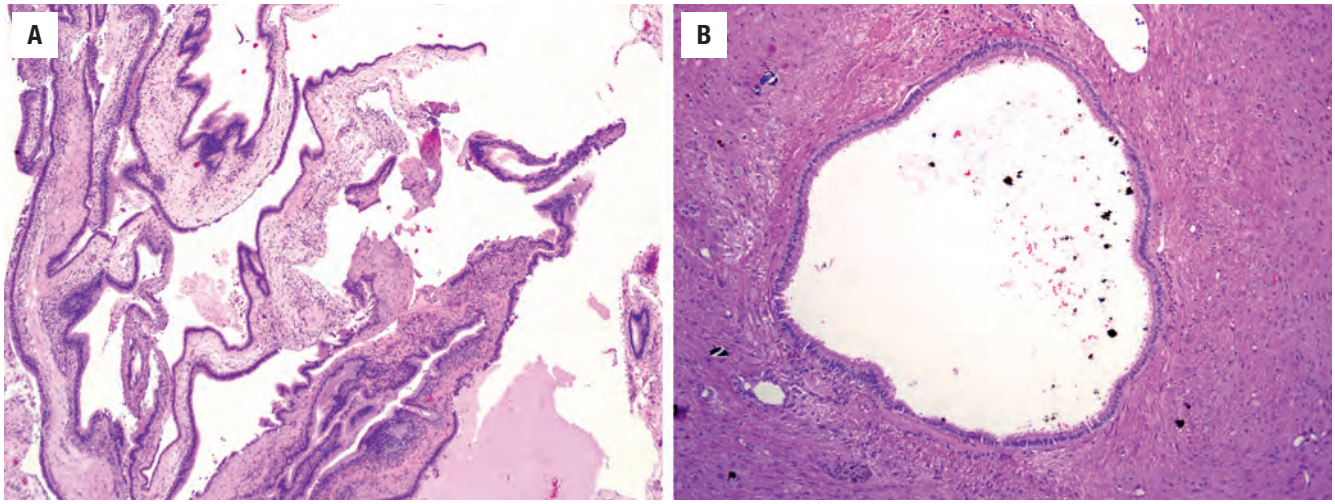

FIGURE 1.8

Histologically, paranasal sinus mucoceles have a nonspecific appearance, consisting of attenuated strips of relatively normal appearing sinonasal mucosa. Radiographic correlation is needed to make the diagnosis of mucocele (**A**). In this example of an aggressive mucocele, normal-appearing sinonasal epithelium is seen in brain tissue (**B**).

ALLERGIC FUNGAL SINUSITIS

Allergic fungal sinusitis (AFS) is a relatively common condition believed to represent an allergic reaction to antigens from fungi (most commonly *Aspergillus* species) that have colonized the sinonasal tract.

Clinical Features

AFS most often affects children and young adults, with no sex predilection. Affected patients present with nasal discharge along with allergic-type symptoms such as nasal stuffiness, facial pressure, and fullness. Patients are often observed to have firm, viscous, foul-smelling mucin within their affected sinuses. In addition, patients typically exhibit peripheral eosinophilia and elevated serum IgE levels. In severe cases, patients uncommonly may exhibit facial asymmetry with bone destruction.

Pathologic Features

Gross Findings

Grossly, the secretions of AFS are firm, thick, and rubbery and have the quality of putty or peanut butter.

Microscopic Findings

The microscopic hallmark of AFS is so-called *allergic mucin*: inspissated mucin that is admixed with eosinophils, neutrophils, Charcot-Leyden crystals, fibrin, and desquamated epithelial cells (Figs. 1.9 and 1.10). The various components of allergic mucin are typically arranged in a laminated fashion, creating a striated or "tigroid" appearance (see Fig. 1.9). Fungal elements are usually not apparent on routine histology. The background

ALLERGIC FUNGAL SINUSITIS—DISEASE FACT SHEET

Definition
- A noninvasive form of fungal sinusitis resulting from an allergic reaction to colonizing fungal antigens

Incidence and Location
- More common in warmer climates such as southern and southwestern United States

Morbidity and Mortality
- Typically minimal, although rarely patients may demonstrate facial asymmetry and bone destruction

Sex and Age Distribution
- Typically children or young adults, no sex predilection

Clinical Features
- Nasal discharge, allergic-type symptoms
- Elevated serum IgE levels and peripheral eosinophilia
- Sinus contents with firm, rubbery, foul-smelling mucus

Treatment and Prognosis
- Evacuation of tenacious mucus
- Intranasal steroids
- Some patients benefit from fungal allergic desensitization
- Long-term therapy may be needed to control relapses

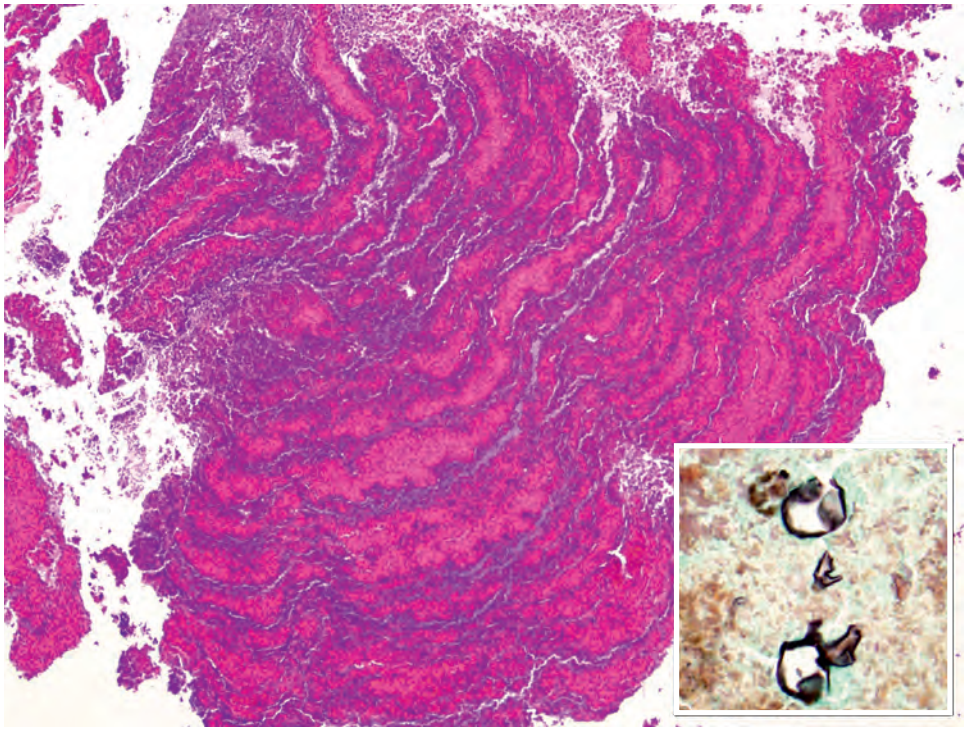

FIGURE 1.9

The diagnostic histologic finding is allergic mucin, which is composed of inflammatory cells (particularly eosinophils), Charcot-Leyden crystals, desquamated epithelial cells, and other debris. A lamellated ("tigroid") appearance is classic for allergic mucin. Stains for fungi (in this case, Gomori methenamine silver) highlight fungal hyphae in a subset of allergic fungal sinusitis cases. The hyphae are often degenerated and distorted, as seen here (*inset*).

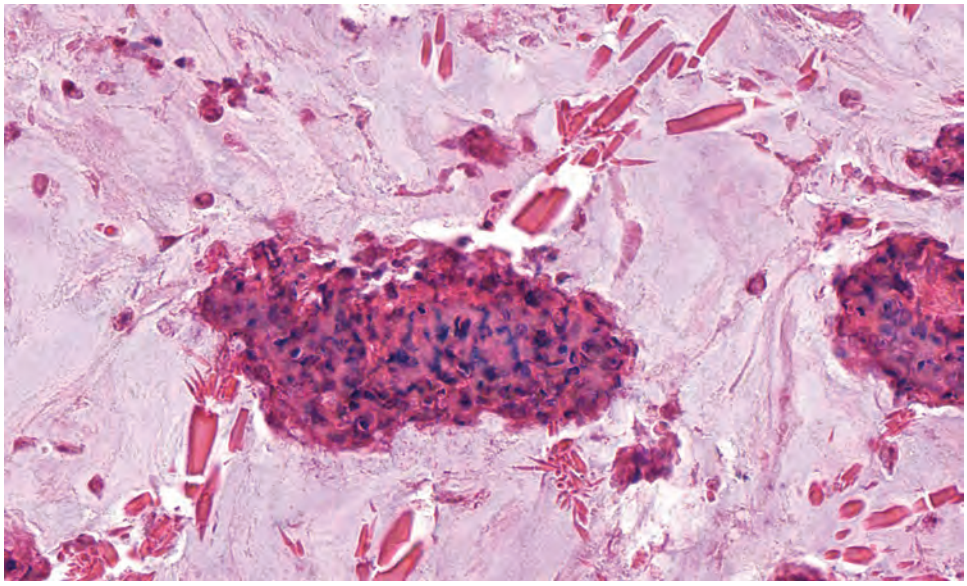

FIGURE 1.10

Charcot-Leyden crystals are seen as long needlelike and bipyramidal-shaped crystals in this case of allergic fungal sinusitis.

sinonasal mucosa exhibits edema and chronic inflammation with frequent eosinophils.

Ancillary Studies

Special stains for fungi (Gomori methenamine silver [GMS] and periodic acid–Schiff [PAS]) reveal scattered fungal hyphae within the allergic mucin in about half of cases. These fungal elements are often scarce and may have an unusual, degenerated appearance (see Fig. 1.9, inset).

Differential Diagnosis

The histologic appearance of AFS may resemble nonspecific rhinosinusitis or sinonasal polyps, but the characteristic presence of allergic mucin is diagnostic for AFS. The allergic mucin of AFS may be confused with another form of noninvasive fungal sinusitis known as mycetoma or fungus ball. However, in mycetoma the debris is composed entirely of matted fungal hyphae in far greater numbers than what is seen in AFS. Mycetomas may calcify or show conidia (fungal fruiting bodies)

(Fig. 1.11A). Finally, AFS must be distinguished from acute or chronic forms of invasive fungal sinusitis, in which fungal elements invade stroma with frequent involvement of vessels (see Fig. 1.11B).

Prognosis and Therapy

Treatment includes removal of the mucus as a means to restore mucociliary function. Intranasal steroids are frequently used. Fungal desensitization may also be used as a treatment option. There does not appear to be a role for antifungal agents. Prognosis is good, although long-term therapy may be needed to control relapses in some patients.

ALLERGIC FUNGAL SINUSITIS—PATHOLOGIC FEATURES

Gross Findings
- Thick, viscous mucin that may resemble putty or peanut butter

Microscopic Findings
- Allergic mucin: a striated mixture of mucin, inflammatory cells, Charcot-Leyden crystals, and other debris
- Fungal hyphae seen in approximately half of cases with special stains
- Fungi often scarce and have a degenerated appearance

Pathologic Differential Diagnosis
- Nonspecific rhinosinusitis, sinonasal polyp, mycetoma (fungus ball), invasive fungal sinusitis (acute or chronic)

NASAL GLIAL HETEROTOPIA

Nasal glial heterotopia is a benign condition resulting from the failure of the developing frontal lobe to completely retract into the cranial cavity during fetal development. Because it is not a neoplasm, the historical term "nasal glioma" should not be used.

Clinical Features

Nasal glial heterotopia usually affects infants, although it can occasionally be encountered in older patients. There is no predilection for either sex. Glial heterotopia presents as a firm nodule that can be extranasal (60%) on the bridge or side of the nose, intranasal within the nasal cavity (30%), or both intranasal and extranasal (10%). Patients often have nasal obstruction and infants may show difficulty feeding as a result of the mass. By radiology, there is no connection to the intracranial cavity, a crucial feature that distinguishes glial heterotopia from an encephalocele (Fig. 1.12A and B).

Pathologic Features

Gross Findings

Well-circumscribed nodule of firm soft tissue, 1 to 3 cm in size, with a glistening cut surface.

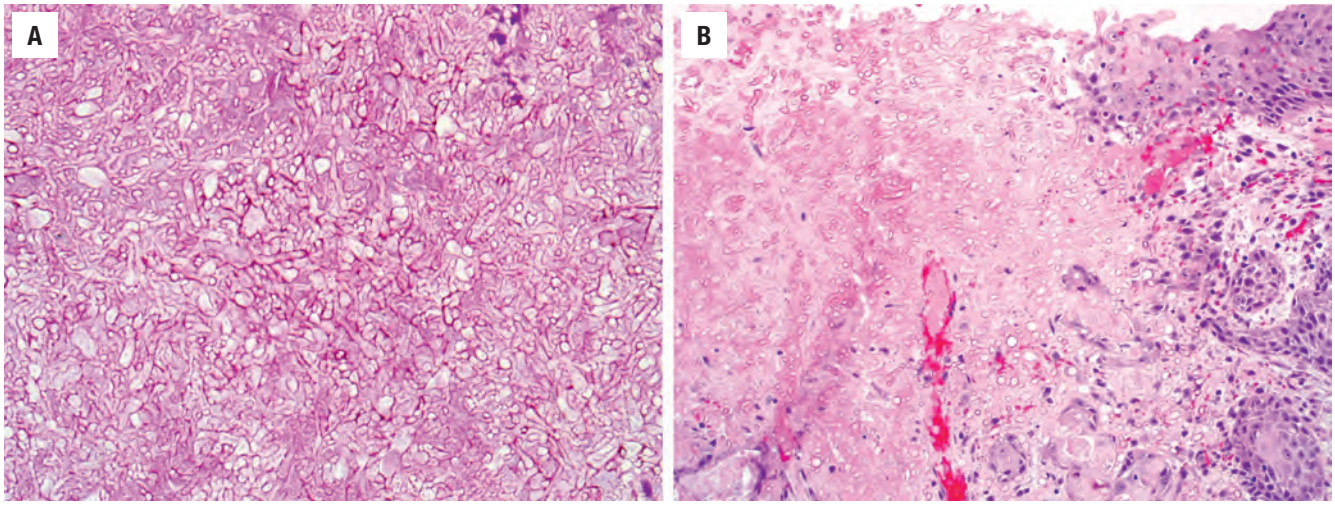

FIGURE 1.11

Mycetoma (fungus ball) is a form of noninvasive fungal sinusitis consisting of a matted collection of degenerating fungal hyphae growing within the sinus, with no tissue invasion (**A**). In contrast, fulminant invasive fungal sinusitis is characterized by invasion of tissues with necrosis and a limited inflammatory reaction (**B**).

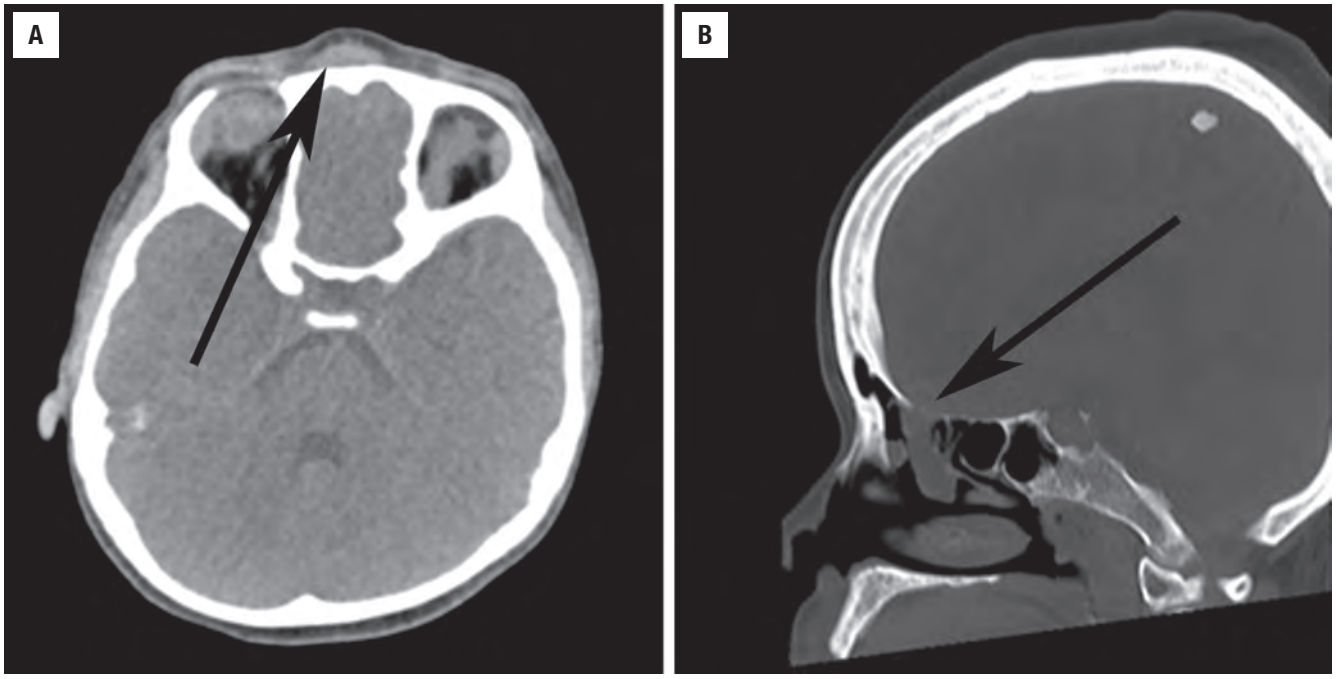

FIGURE 1.12

Computed tomography scan of extranasal glial heterotopia (*arrow*) without a connection to the cranial cavity (**A**). In contrast, this encephalocele involving the nasal cavity has a clear connection to the cranial cavity (*arrow*) (**B**).

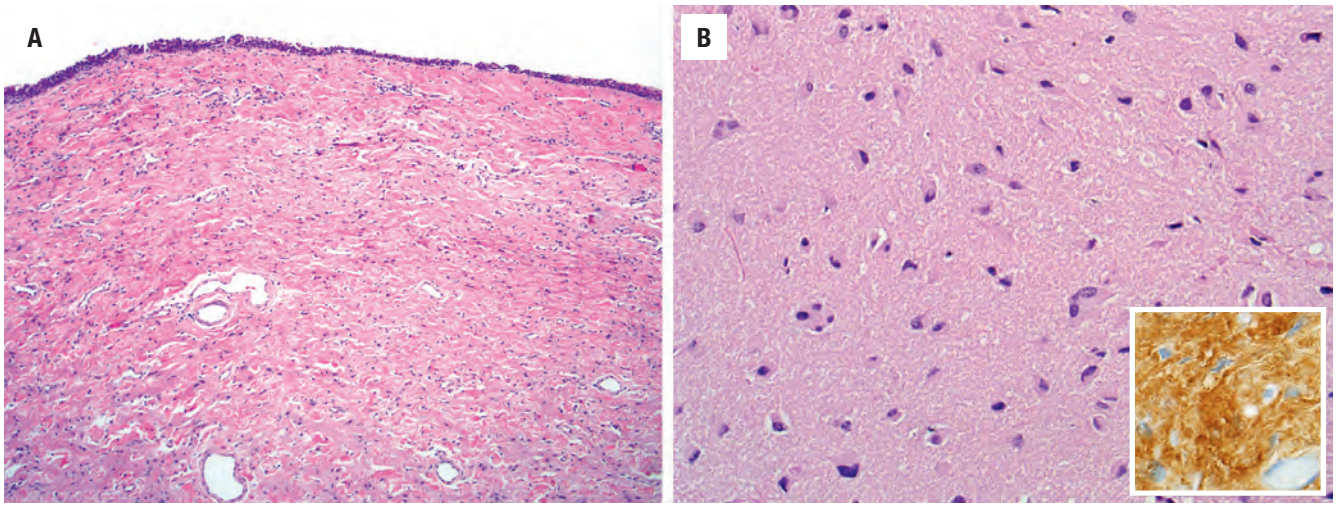

FIGURE 1.13

Nasal glial heterotopia manifests as fibrotic glial tissue in the sinonasal submucosa (**A**). At high power the glial tissue consists of scattered astrocytes in a pink, fibrillary background (**B**). Immunostaining for glial fibrillary acidic protein confirms the glial nature of the tissue (*inset*).

Microscopic Findings

Heterotopic glial tissue resembles gliotic brain tissue, with astrocytes admixed with eosinophilic fibrillary glial tissue underlying skin or sinonasal mucosa (Fig. 1.13A and B). Neurons are only rarely seen, whereas dura and meninges are not present. The glial tissue may be obscured by fibrosis, necessitating immunohistochemical confirmation.

Ancillary Studies

Nasal glial heterotopia can be confirmed immunohistochemically by positivity for the glial markers glial fibrillary acidic protein (GFAP) (see Fig. 1.13B), S100 protein, and the newly introduced nuclear marker OLIG2.

NASAL GLIAL HETEROTOPIA—DISEASE FACT SHEET

Definition
- Developmentally displaced glial tissue in the sinonasal tract *without* a connection to the cranial cavity

Incidence
- Uncommon
- Extranasal (bridge or side of nose) in 60%, intranasal in 30%, and mixed in 10%

Morbidity and Mortality
- Minimal, although can result in difficulty feeding for some infants

Sex and Age Distribution
- Usually infants
- No sex predilection

Clinical Features
- Nasal mass, often resulting in obstruction

Treatment and Prognosis
- Surgical excision
- Excellent prognosis after complete excision

NASAL GLIAL HETEROTOPIA—PATHOLOGIC FEATURES

Gross Findings
- Small circumscribed firm nodule with a glistening cut surface

Microscopic Findings
- Astrocytes in a glial fibrillary matrix
- Neurons only rarely present, leptomeninges are absent
- May be fibrotic, obscuring the glial nature of the lesion

Ancillary Studies
- Glial tissue positive for GFAP, S100 protein, OLIG2

Pathologic Differential Diagnosis
- Nonspecific fibrosis in sinonasal polyp, encephalocele

Differential Diagnosis

Heterotopic glial tissue can be misdiagnosed as nonspecific fibrosis in a sinonasal polyp, a distinction that can be easily addressed by immunohistochemistry for glial markers. Another diagnostic consideration is encephalocele. The distinction is not trivial, because an encephalocele, by definition, means that there is a patent connection with the cranial cavity, which puts the patient at risk for meningitis. The presence of dura/leptomeninges or well-organized glial tissue with neurons favors an encephalocele, but these features are often lost, especially in long-standing lesions. Ultimately, the distinction requires clinical and radiographic input (see Fig. 1.12B).

Prognosis and Therapy

Glial heterotopia is treated with simple excision. The prognosis is excellent following complete removal of the glial tissue.

RHINOSCLEROMA

Rhinoscleroma is a rare, chronic infectious disease caused by *Klebsiella rhinoscleromatis*, a gram-negative coccobacillus bacterium, that affects the nasal cavity and nasopharynx.

Clinical Features

Rhinoscleroma most often affects young adults in their second and third decades. There is a slight female predominance. It is endemic to certain parts of South America, Central America, Africa, India, and Indonesia, but is rare in North America. Rhinoscleroma affects the nasal cavity and nasopharynx, and there are three distinct clinical stages. The rhinitic or exudative stage is characterized by a foul-smelling mucopurulent nasal discharge with nasal obstruction and erythema. With progression of the disease after months or years without treatment, the florid or proliferative stage is marked by mucosal thickening by numerous small masses and subsequent nasal obstruction (Fig. 1.14). Finally, long-term rhinoscleroma is known as the fibrotic or cicatrical stage and is characterized by marked scarring and nasal stenosis. Rhinoscleroma can result in marked facial deformities, particularly in the latter stages of the disease.

Pathologic Features

Gross Findings

The gross pathologic appearance varies based on the clinical disease stage. The rhinitic/exudative stage has a nonspecific appearance, whereas the florid/proliferative stage produces friable nasal polyps. Finally, the fibrotic/cicatrical stage is characterized by densely fibrotic tissues.

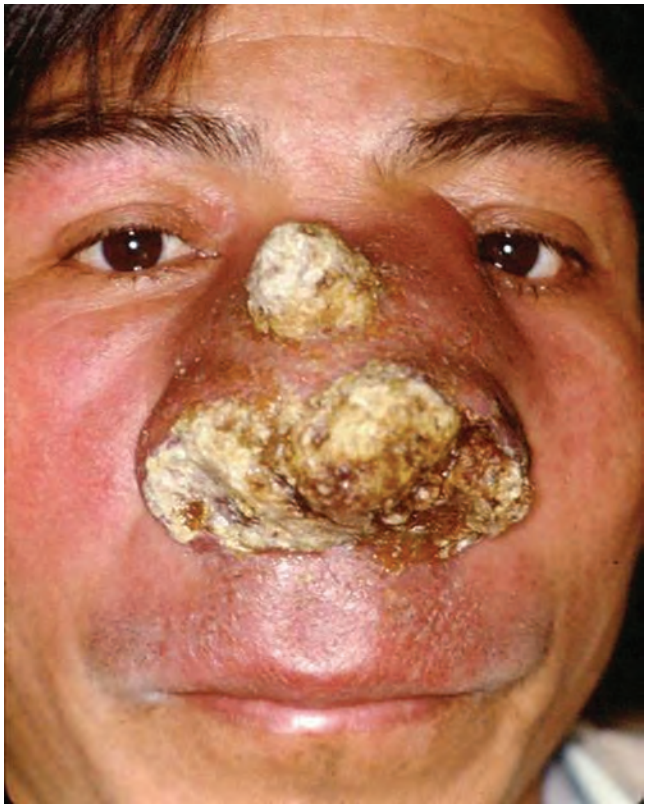

FIGURE 1.14

A clinical photograph of a 42-year-old man with rhinoscleroma presenting as several years of progressive nasal ulceration, along with palatal perforation, yielding marked nasal and mid-facial distortion. *(Courtesy of Dr. R. Carlos.)*

RHINOSCLEROMA—DISEASE FACT SHEET

Definition
- Infectious disease caused by *Klebsiella rhinoscleromatis*, a gram-negative coccobacillus bacterium

Incidence and Location
- Rare
- Endemic in parts of South America, Central America, Africa, India, and Indonesia

Morbidity and Mortality
- Can cause marked facial deformity and nasal stenosis

Sex and Age Distribution
- Second and third decades
- Slight female predilection

Clinical Features
- Three clinical stages: rhinitic (exudative) with abundant foul-smelling mucopurulent secretions; florid (proliferative) with numerous small friable nodules causing obstruction and deformity; and fibrotic (cicatrical) with marked scarring and stenosis

Treatment and Prognosis
- Long-term antibiotics and possibly surgical débridement
- High relapse rates necessitate long-term follow-up

Microscopic Findings

Rhinoscleroma is most often biopsied in the florid stage, where the submucosa is expanded by an inflammatory infiltrate including lymphocytes, plasma cells, neutrophils, and histiocytes. As in any disease with abundant plasma cells, Russell bodies—large cytoplasmic inclusions composed of immunoglobulin—are frequent. The diagnostic microscopic finding is the presence of "Mikulicz cells"—large histiocytes with abundant, clear, vacuolated cytoplasm (Fig. 1.15). As rhinoscleroma progresses, lesions become increasingly fibrotic and less inflammatory.

RHINOSCLEROMA—PATHOLOGIC FEATURES

Gross Findings
- Nonspecific, or friable polyps, or dense sclerosis

Microscopic Findings
- Marked chronic inflammation with lymphocytes, plasma cells, neutrophils, and histiocytes in the sinonasal submucosa
- The diagnostic finding is the "Mikulicz cell"—large histiocytes with clear, vacuolated cytoplasm

Ancillary Studies
- Warthin-Starry stain highlights the rod-shaped organisms within the Mikulicz cells

Pathologic Differential Diagnosis
- Rosai-Dorfman disease, infections (atypical mycobacteria, leprosy, syphilis), granulomatosis with polyangiitis, clear cell epithelial neoplasms

Ancillary Studies

A Warthin-Starry stain highlights rod-shaped *Klebsiella* organisms within the Mikulicz cells (see Fig. 1.15).

Differential Diagnosis

Rhinoscleroma can mimic Rosai-Dorfman disease; however, in rhinoscleroma emperipolesis is not observed (Fig. 1.16). Moreover, although Mikulicz cells are positive for CD68, they are negative for S100 protein. In some cases of rhinoscleroma, the Mikulicz cells can be so prominent that the lesion may be mistaken as a clear cell epithelial neoplasm such as mucoepidermoid

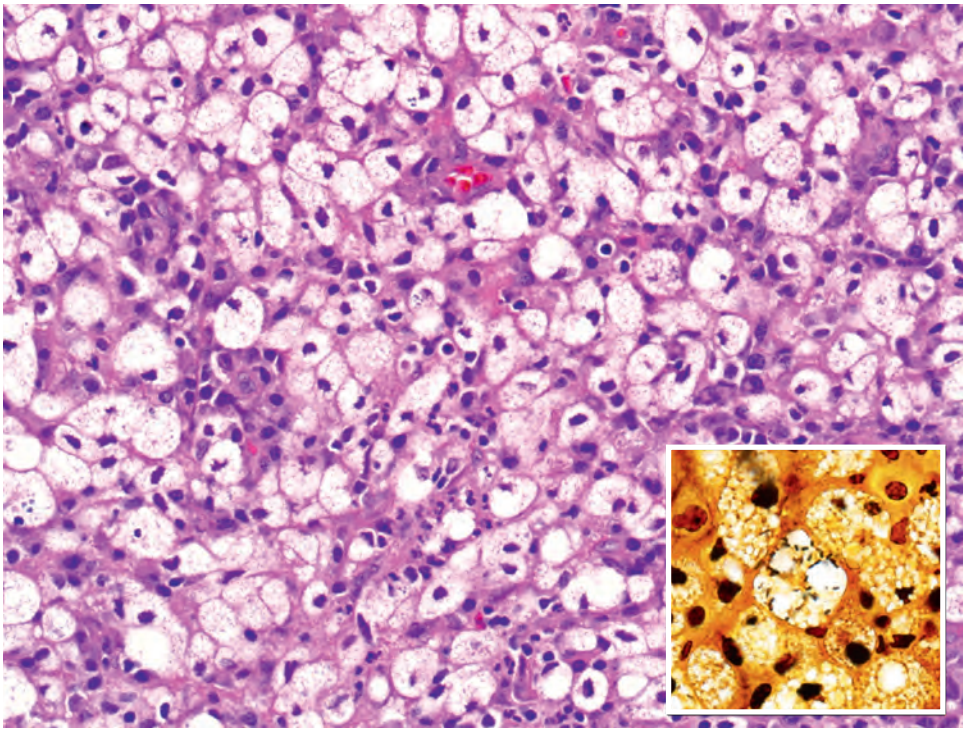

FIGURE 1.15

In the florid phase of rhinoscleroma, there are numerous "Mikulicz cells"—large histiocytes with abundant, clear, vacuolated cytoplasm. These cells are positive for rod-shaped bacteria on Warthin-Starry staining (*inset*).

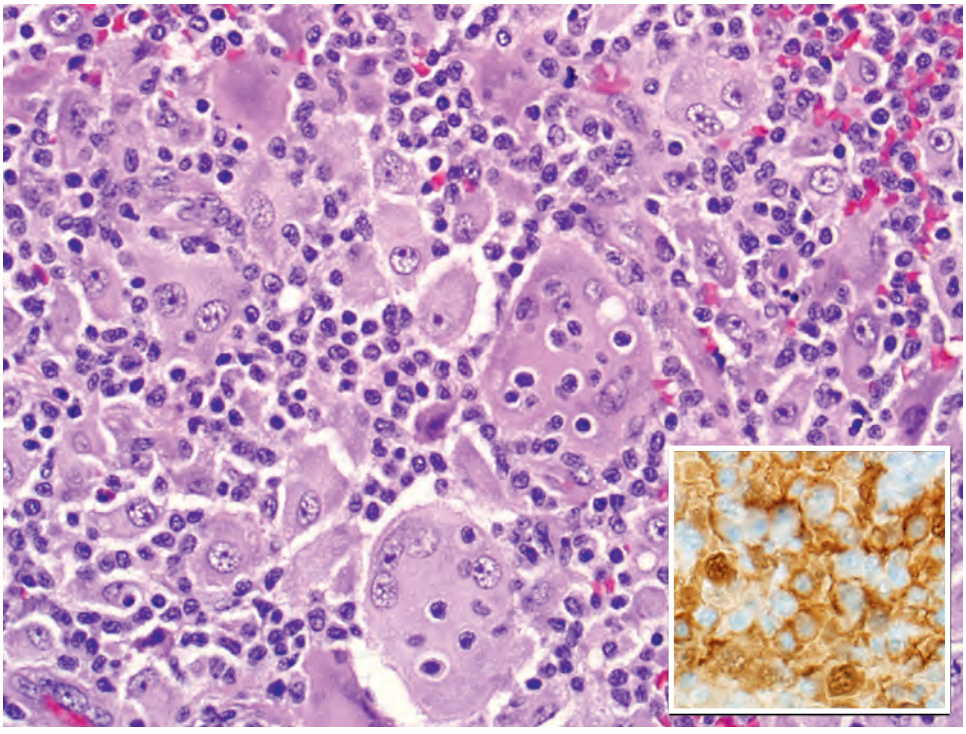

FIGURE 1.16

Rosai-Dorfman disease may affect the sinonasal tract and can mimic rhinoscleroma. The diagnostic feature of Rosai-Dorfman disease is emperipolesis—large histiocytes with intracytoplasmic lymphocytes. These histiocytes are positive for S100 protein by immunohistochemistry (*inset*).

carcinoma or myoepithelioma. This can be resolved by immunohistochemistry for CD68 (positive in rhinoscleroma) and cytokeratin (negative), as well as positive Warthin-Starry staining. Other infections (atypical mycobacteria, leprosy, and syphilis) may result in granulomata. Giant cells and granulomas may be seen in granulomatosis with polyangiitis (GPA) (Wegener), but vasculitis is not seen in rhinoscleroma.

Prognosis and Therapy

Long-term systemic antibiotics are indicated for rhinoscleroma. Surgical débridement may be needed to correct stenotic nasal passages. Rhinoscleroma generally shows a good response to antibiotics, but high relapse rates necessitate long-term follow-up.

RHINOSPORIDIOSIS

Rhinosporidiosis is a chronic zoonotic infection caused by the eukaryotic organism *Rhinosporidium seeberi.*

Clinical Features

Rhinosporidiosis is typically localized to the sinonasal tract and conjunctiva but is rarely encountered in other anatomic sites like larynx, trachea, esophagus, genital tract, and others. It is rare in North America, but it is endemic in parts of India and Sri Lanka. Patients of any age can be affected, but it is most commonly encountered in patients in their third and fourth decades. There is a slight male predominance in patients with nasal disease. Patients with sinonasal disease complain of nasal obstruction, rhinorrhea, and nosebleeds.

Pathologic Features

Gross Findings

Rhinosporidiosis typically manifests as friable nasal polyps or masses, classically described as *strawberry-like* in appearance.

Microscopic Findings

Rhinosporidiosis microscopically appears as polypoid fragments of edematous sinonasal mucosa with chronic inflammation, similar to nonspecific inflammatory polyps. The diagnostic finding is the presence of numerous cysts (sporangia) of variable sizes (Fig. 1.17). Larger cysts (up to 300 μm) contain numerous endospores (see Fig. 1.17). The cysts are present in the stroma but may uncommonly also involve the epithelium. On occasion, rupture of cysts can induce an acute stromal inflammatory infiltrate.

RHINOSPORIDIOSIS—DISEASE FACT SHEET

Definition
- Zoonotic infection caused by the eukaryotic organism *Rhinosporidium seeberi*

Incidence and Location
- Rare in North America but endemic in parts of India and Sri Lanka
- Affects the mucous membranes of the sinonasal tract and less commonly conjunctiva, upper airway, genital tract, and other sites

Morbidity and Mortality
- Typically minimal

Sex and Age Distribution
- Slight male predominance
- Any age, most common in third and fourth decades

Clinical Features
- Nonspecific: rhinorrhea, nosebleeds, obstruction

Treatment and Prognosis
- Surgical
- Excellent prognosis

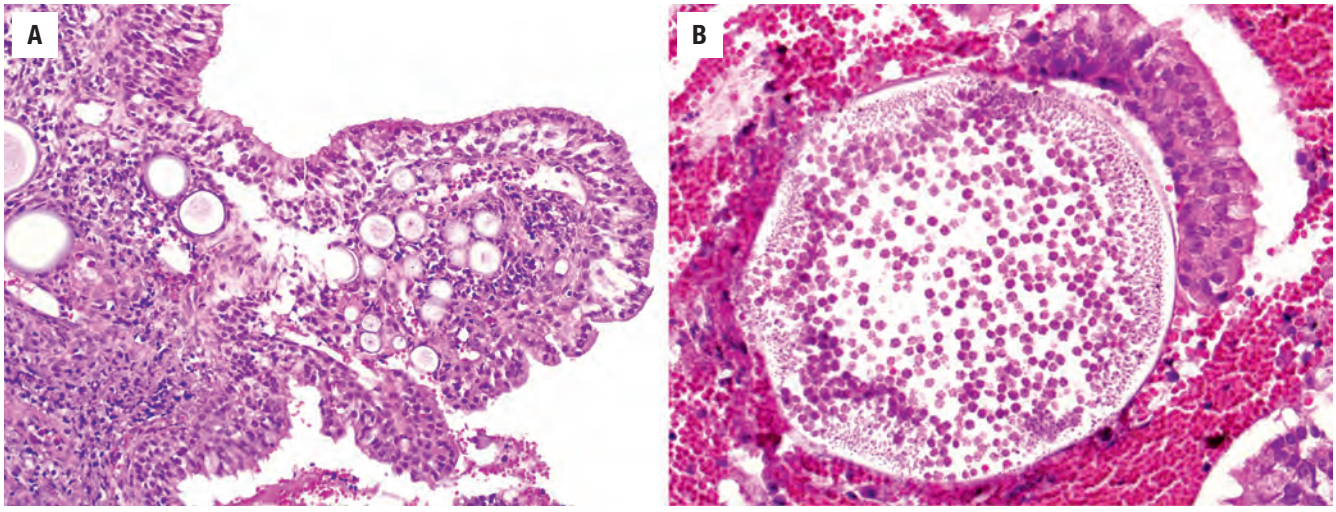

FIGURE 1.17
Rhinosporidiosis is an infection that exhibits presence of numerous scattered cysts (sporangia) of variable sizes (**A**). Larger cysts (up to 300 μm) contain numerous endospores (**B**).

RHINOSPORIDIOSIS—PATHOLOGIC FEATURES

Gross Findings
- Friable polyps or masses

Microscopic Findings
- Variably sized cysts up to 300 µm, predominantly subepithelial
- The largest cysts contain small endospores
- Background nonspecific chronic inflammation and edema, acute inflammation if cysts rupture

Ancillary Studies
- GMS and PAS highlight organisms, though usually not needed for diagnosis

Pathologic Differential Diagnosis
- Oncocytic sinonasal papilloma, coccidiomycosis

GMS, Gomori methenamine silver; *PAS*, periodic acid–Schiff.

Ancillary Studies

Special studies are not generally needed as the cysts are typically numerous and visible on routine stains, but microorganisms can be highlighted with PAS and GMS stains.

Differential Diagnosis

The oncocytic type of sinonasal papilloma exhibits numerous intraepithelial microcysts that can be confused with the cysts of rhinosporidiosis. However, in oncocytic sinonasal papilloma the microcysts are confined to the epithelium. The cysts of rhinosporidiosis can be confused with the spherules of *Coccidioides immitis*, but these spherules are much smaller (up to 60 µm) and accompanied by a granulomatous inflammatory infiltrate.

Prognosis and Therapy

Rhinosporidiosis is treated by complete surgical excision. Antibiotics are not effective. The prognosis is excellent, with only occasional recurrences. The disease is not infectious to other individuals.

GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis (GPA) is a systemic immune complex vasculitis of unknown etiology that often affects the sinonasal tract. Although the synonymous term Wegener granulomatosis is still widely used, many organizations (e.g., American College of Rheumatology, the European League against Rheumatism, and the American Society of Nephrology) recommend avoiding it due to a trend against eponyms.

Clinical Features

GPA tends to affect middle-aged adults, with a slight male predominance. GPA classically affects the head and neck (especially sinonasal tract), lung, and kidney, but it can be localized to only one or two of these areas. Affected patients complain of nasal discharge, nasal obstruction, nosebleeds, and pain. On clinical examination, patients have a nasal septum ulcer with crusting, which can sometimes progress to perforation and collapse of the nasal cartilages (Fig. 1.18A). Respiratory disease manifests as hemoptysis, lung infiltrates, or cavitary masses, whereas renal disease results in glomerulonephritis.

Pathologic Features

Gross Findings

The gross appearance is often a nonspecific appearing ulcer.

Microscopic Features

The histologic triad of GPA is biocollagenolytic (necrobiotic) necrosis, granulomatous inflammation, and vasculitis. "Biocollagenolytic" or "necrobiotic" necrosis refers to zones of geographic basophilic necrosis with granular, cellular debris (see Fig. 1.18B). The granulomatous inflammation of GPA is typically poorly formed, sometimes simply consisting of scattered giant cells (see Fig. 1.18C). Vasculitis of small to medium-sized vessels is the most specific finding but is often focal or absent. Unfortunately, most patients with GPA have biopsies that show nonspecific acute and chronic inflammation with eosinophils and sometimes neutrophilic microabscesses, and multiple biopsies may be required to establish a pathologic diagnosis.

Ancillary Studies

Elastic stains may be helpful by highlighting vessels that are involved by vasculitis (see Fig. 1.18D). Special stains for microorganisms are negative. Patients with GPA have positive serum cytoplasmic antineurtrophil cytoplasmic antibodies (c-ANCA) and proteinase 3 (PR3) antibodies in approximately 80% of cases (Fig. 1.19).

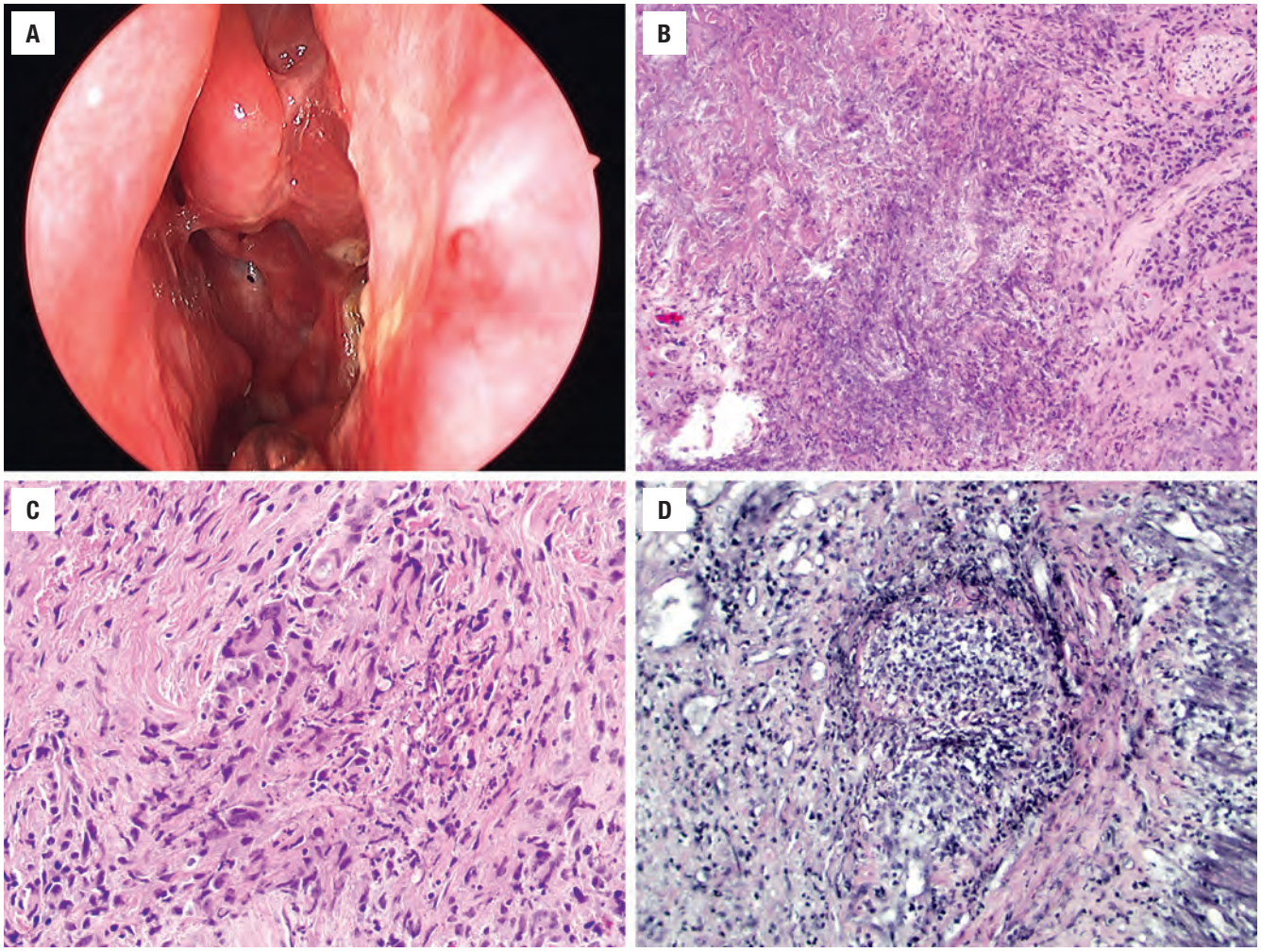

FIGURE 1.18

Granulomatosis with polyangiitis clinically presents as nasal erythema, crusting, ulcer, and perforation (**A**). Histologically a classic feature of granulomatosis with polyangiitis is "biocollagenolytic necrosis" (or "necrobiosis"), which is basophilic necrosis with nuclear debris (**B**). The granulomas of granulomatosis with polyangiitis are typically not well formed and may consist simply of giant cells (**C**). An elastic stain can highlight foci of vasculitis (**D**). (***A,*** *Courtesy of Dr. Douglas Reh.)*

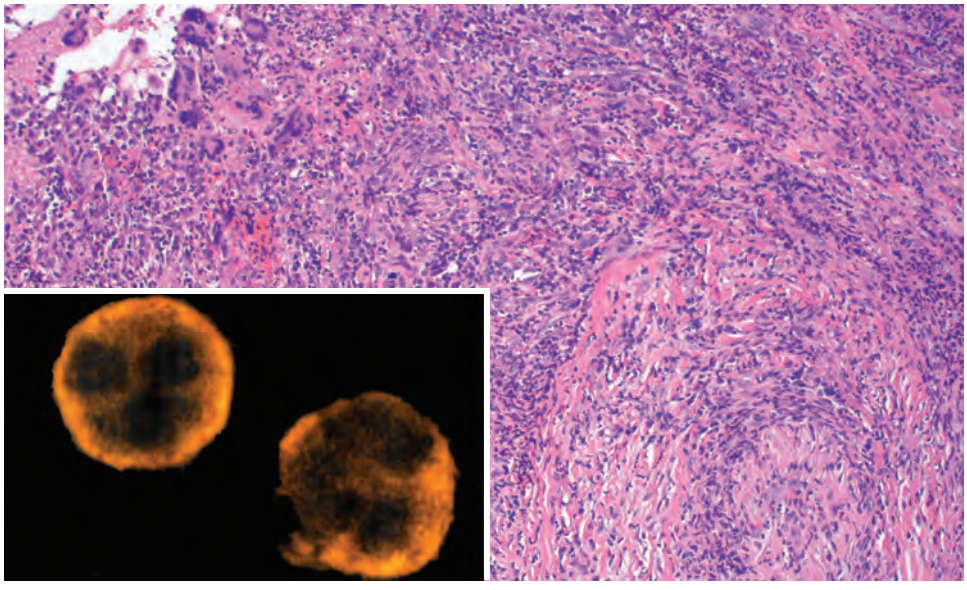

FIGURE 1.19

In granulomatosis with polyangiitis, giant cells may be present (*upper left*), but well-formed granulomas are absent. Note the vessel wall in the lower right, with destruction by the inflammatory process in an example of vasculitis. Inset: A c-ANCA shows a granular cytoplasmic pattern in a case of granulomatosis with polyangiitis.

GRANULOMATOSIS WITH POLYANGIITIS—DISEASE FACT SHEET

Definition
- Immune complex–mediated small vessel vasculitis of unknown etiology

Incidence
- Uncommon
- Affects the head and neck (especially sinonasal tract), respiratory tract, and/or kidneys

Morbidity and Mortality
- Sinonasal disease can result in significant facial deformities
- Renal and pulmonary disease can be life-threatening

Sex and Age Distribution
- Middle-aged adults, with a slight male predominance

Clinical Features
- Nasal disease results in nasal obstruction, pain, epistaxis, septal ulcer, and possibly perforation and deformity

Treatment and Prognosis
- Systemic corticosteroids and/or cyclophosphamide
- Prognosis depends on extent of disease

GRANULOMATOSIS WITH POLYANGIITIS—PATHOLOGIC FEATURES

Gross Findings
- Nasal ulcer with crusting and/or perforation

Microscopic Findings
- Classic histologic triad: biocollagenolytic necrosis (necrobiosis), vasculitis, and granulomatous inflammation
- Granulomas tend to be poorly formed and often consist simply of giant cells
- It is uncommon to see all three classic findings in a biopsy, with vasculitis being the least common

Ancillary Studies
- Vessels with vasculitis can be highlighted by elastic stains
- Presence of serum c-ANCA and PR3 autoantibodies are quite specific

Pathologic Differential Diagnosis
- Infectious rhinosinusitis, cocaine use, Churg-Strauss disease, NK-/T-cell lymphoma, nasal type

Differential Diagnosis

The differential diagnosis includes infectious granulomatous rhinosinusitis (e.g., chronic fungal sinusitis). Infectious granulomatous disease tends to produce granulomas that are better developed than those seen in GPA. Special stains for microorganisms (e.g., GMS, AFB) are helpful in addressing this possibility. Churg-Strauss disease shows granulomatosis and vasculitis and is an allergic reaction, showing asthma and tissue and peripheral eosinophilia, and may even have elevated ANCA titers. Another consideration is lymphomas in general but the NK-/T-cell lymphoma, nasal type specifically. This malignancy often exhibits vascular involvement resulting in large zones of necrosis, and the inflammatory infiltrate can be deceptively mixed and, at times, not obviously malignant. Nevertheless, on close inspection, overtly malignant lymphoma cells with marked nuclear atypia and a high mitotic rate can be found in NK-/T-cell lymphoma. In addition, NK-/T-cell lymphoma lacks granulomatous inflammation and is positive for Epstein-Barr virus (EBV) by in situ hybridization for EBV-encoded small nuclear RNA (EBER). Finally, cocaine abuse can result in nasal ulcers and perforation. The histopathologic features of cocaine abuse are typically nonspecific, but occasionally polarizable material from talc or other material used to "cut" cocaine can be identified.

Prognosis and Therapy

GPA is treated with immunosuppressive agents such as corticosteroids or cyclophosphamide. The prognosis of GPA depends on the extent of disease. Localized disease has a good prognosis, but relapses are common. However, renal and pulmonary disease can be life-threatening.

SINONASAL HAMARTOMAS

The sinonasal hamartomas consist of three lesions: REAH, seromucinous hamartoma (SH), and chondromesenchymal hamartoma (CMH). Despite the "hamartoma" terminology, there is evidence to suggest that each of these lesions is actually a benign neoplasm.

Clinical Features

All three hamartomas are rare. REAH and SH have a similar clinical profile: they tend to arise in adults with a slight male predominance and have a predilection for the posterior nasal septum (Fig. 1.20). REAH and SH present as unilateral polyps that cause nasal obstruction or epistaxis. In contrast, CMH arises most often in infants as a slow-growing, expansile lesion within the paranasal sinuses, nasal cavity, and/or orbit that can be locally aggressive. CMH has a strong association with the pleuropulmonary blastoma tumor predisposition disorder.

Pathologic Features

Gross Findings

REAH and SH have the appearance of a nasal polyp. CMH is firm and white.

Microscopic Findings

REAH consists of downward-growing proliferations of branching glands originating from the surface epithelium (Fig. 1.21A). The glands are lined by a pseudostratified ciliated epithelium and are surrounded by a hyalinized or edematous stroma (see Fig. 1.21B), usually showing a prominent and thickened basement membrane. SH consists of a dense proliferation of variably sized submucosal seromucinous glands lined by a single layer of cuboidal cells (Fig. 1.22A). In both REAH and SH, the

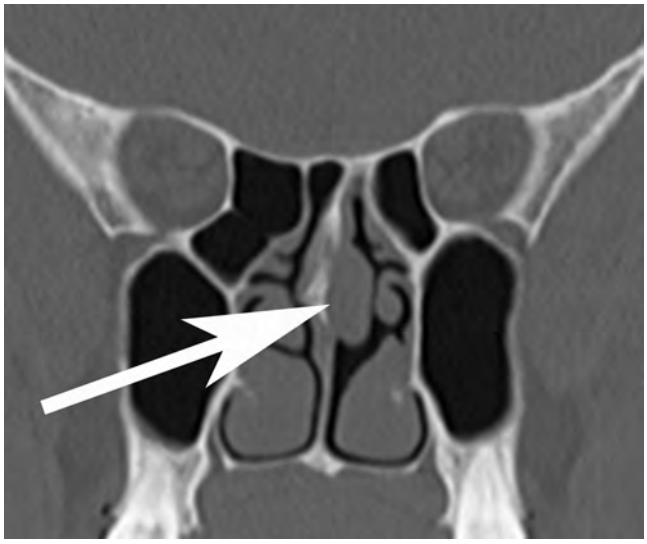

FIGURE 1.20

Respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma have a similar radiographic appearance—a polypoid mass of the posterior nasal septum (*arrow*).

SINONASAL HAMARTOMAS—DISEASE FACT SHEET

Definition
- Benign proliferations of epithelium (REAH and SH) or stroma (CMH)

Incidence
- All three are rare
- REAH and SH most frequently occur on the posterior nasal septum
- CMH involves the paranasal sinuses, nasal cavity, or orbit

Morbidity and Mortality
- REAH and SH are localized lesions
- CMH may be locally aggressive

Sex and Age Distribution
- REAH and SH involve middle-aged patients with a male predominance
- CMH usually affects infants with a male predominance

Clinical Features
- REAH and SH present with unilateral nasal obstruction, bleeding, and polyps
- CMH presents as nasal obstruction or a mass

Treatment and Prognosis
- Surgical excision
- Excellent prognosis

CMH, Chondromesenchymal hamartoma; *REAH*, respiratory epithelial adenomatoid hamartoma; *SH*, seromucinous hamartoma.

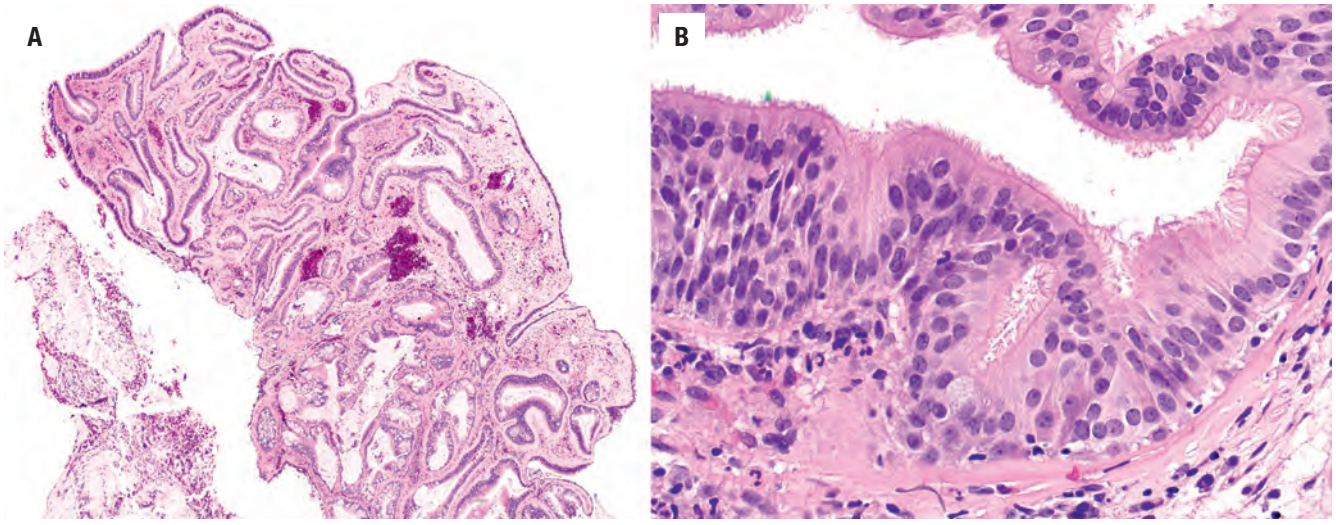

FIGURE 1.21

Respiratory epithelial adenomatoid hamartoma consists of a polypoid mass with a downward growth of surface epithelium (**A**). The glands are ciliated, pseudostratified, and often surrounded by a thick basement membrane (**B**).

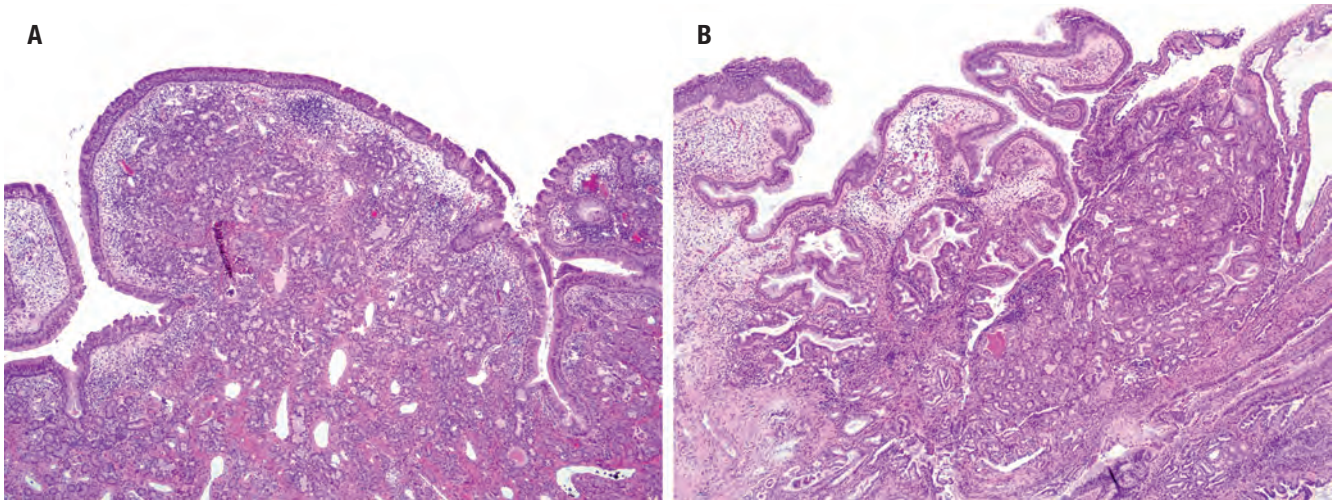

FIGURE 1.22

Seromucinous hamartoma consists of an increased number of normal-appearing seromucinous glands in the submucosa (**A**). Some examples of seromucinous hamartoma have areas that closely resemble respiratory epithelial adenomatoid hamartoma (*left*), suggesting these lesions are closely related (**B**).

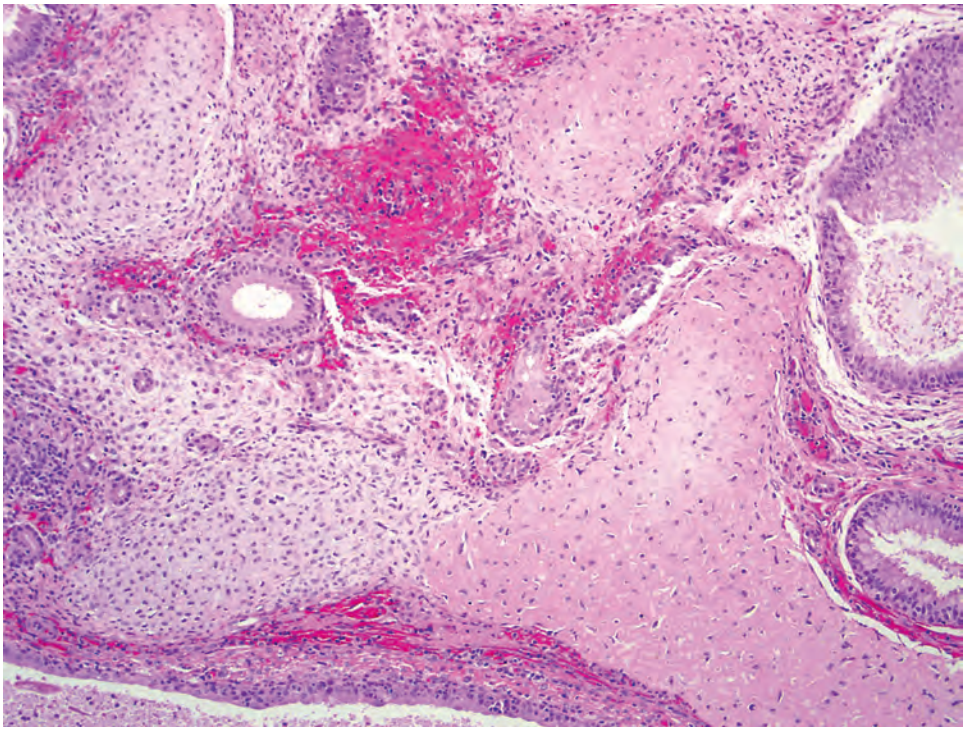

FIGURE 1.23

Chondromesenchymal hamartoma demonstrates scattered, ill-defined nodules of variably mature cartilage in the sinonasal submucosa.

glands can be dilated and lined by flattened, atrophic epithelium. REAH and SH are both frequently accompanied by chronic inflammation with edema and inflammatory polyps. In is not uncommon to see lesions with hybrid features of both REAH and SH, suggesting that the lesions exist at ends of a spectrum (see Fig. 1.22B).

CMH consists of irregular nodules of cartilage or chondromyxoid stroma haphazardly arranged in the sinonasal submucosa (Fig. 1.23). The cartilage may be mature or immature, and the islands are typically surrounded by a cellular fibrous stroma, often with atypical cells and even mitoses. Bony trabeculae, fat, or entrapped glands may also be seen.

Ancillary Studies

The role for immunohistochemistry in the diagnosis of sinonasal hamartomas is limited. The glands of REAH are

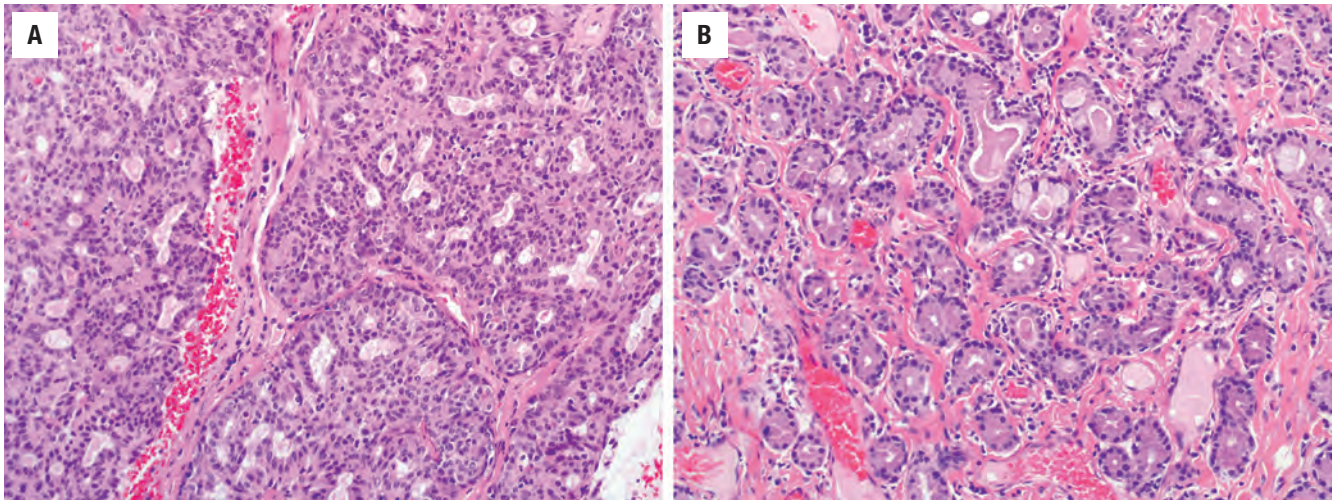

FIGURE 1.24

Low-grade nonintestinal sinonasal adenocarcinoma has fused, complex, back-to-back seromucinous glands without intervening stroma (**A**). In contrast, seromucinous hamartomas have stroma between the seromucinous glands (**B**).

usually surrounded by basal cells that are positive for p63, p40, and CK903, but SH typically lacks surrounded basal or myoepithelial cells. Patients with CMH usually harbor germline or somatic mutations of *DICER1* as part of the pleuropulmonary blastoma tumor predisposition disorder; CMH can be the presenting lesion of this syndrome.

Differential Diagnosis

REAH may be confused with sinonasal inflammatory polyps, although glandular proliferation not commonly seen in polyps. Inverted sinonasal papilloma also exhibits downward growth of surface epithelium, but the epithelium of inverted sinonasal papilloma tends to be squamous or squamoid, thickened, and infiltrated by neutrophils with microabscesses. Biphenotypic sinonasal sarcoma shows invaginations of the surface epithelium reminiscent of REAH, but the cellular stromal spindle cell component and mixed neural and myogenic differentiation is unique. REAH and especially SH can be confused with a low-grade nonintestinal sinonasal adenocarcinoma. Although low-grade nonintestinal sinonasal adenocarcinoma is composed of similar-appearing small glands, it is architecturally more complex, with fused glands and papillary structures (Fig. 1.24A). Importantly, the glands of SH and REAH, while proliferative, are also surrounded by intervening stroma (see Fig. 1.24B). The absence of basal/myoepithelial cells is not useful in the diagnostic distinction.

CMH is more likely to be confused with a mesenchymal process such as chondromyxoid fibroma or chondroma. The young age of the patient and haphazard distribution of the cartilaginous nodules are more in keeping with CMH. Moreover, chondromyxoid fibroma typically lacks well-formed hyaline cartilage.

SINONASAL HAMARTOMAS—PATHOLOGIC FEATURES

Gross Findings

- REAH and SH appear as an edematous nasal polyp
- CMH is a firm tan-white mass

Microscopic Findings

- REAH—downward proliferation of surface epithelial glands lined by pseudostratified ciliated epithelium
- SH—proliferation of small seromucinous submucosal glands lined by eosinophilic cuboidal epithelium
- CMH—irregular proliferation of variably mature cartilage nodules in the sinonasal submucosa with fibrotic stroma

Pathologic Differential Diagnosis

- REAH: sinonasal inflammatory polyp, inverted sinonasal papilloma, biphenotypic sinonasal sarcoma
- SH: low-grade nonintestinal sinonasal adenocarcinoma
- CMH: chondromyxoid fibroma, chondroma

CMH, Chondromesenchymal hamartoma; *REAH*, respiratory epithelial adenomatoid hamartoma; *SH*, seromucinous hamartoma.

Prognosis and Therapy

All sinonasal hamartomas are treated with surgical excision, and the prognosis for each is excellent with recurrences being uncommon.

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The complete Suggested Readings list is available online at ExpertConsult.com.

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2

Benign Neoplasms of the Nasal Cavity, Paranasal Sinuses, and Nasopharynx

Lester D.R. Thompson

SINONASAL PAPILLOMAS

The mucosa of the nasal vestibule and the superior wall of the nasal cavity are lined by squamous and olfactory mucosa, respectively. The remaining nasal mucosa consists of ciliated columnar epithelium of ectodermal origin known as the schneiderian membrane. Three benign neoplastic papillomatous proliferations arise from the schneiderian membrane: inverted or endophytic papillomas (IP; most common), exophytic, fungiform, or everted papillomas (EPs; second most common), and columnar, cylindrical cell, or oncocytic papillomas (OPs; rare). They are defined as a group of benign epithelial neoplasms arising from sinonasal (schneiderian) mucosa. Although these entities share a number of findings and are classified as "sinonasal papillomas" (SPs), there are sufficient clinical and microscopic differences to regard them as three distinctive clinicopathologic entities. The overall lack of mixed papillomas and their relation to human papillomavirus (HPV) are sufficiently different to lend further credence to this separation.

Clinical Features

SPs are a rare disease with an estimated annual incidence of ~2.3 cases per 100,000 population, representing < 5% of all sinonasal tract tumors. Males are affected much more commonly than females (2 to 10:1), depending on subtype, with patients presenting over a wide age range (mean, 20 to 70 years), also type dependent. Children are rarely affected. Clinical symptoms are nonspecific and include unilateral nasal obstruction, followed by epistaxis, an asymptomatic mass, polyps, rhinorrhea, facial pressure, and headaches. Symptoms are often present for a long duration. Often, patients report previous intranasal surgery before a diagnosis of SP is firmly established. Physical examination usually demonstrates a unilateral polypoid mass in the nasal cavity. There is well-documented evidence that exophytic papillomas have a strong HPV association (38% to 65%) and a weaker association with IPs but usually low-risk types 6 and 11, with only rare cases of types 16 and 57b. The association is not established for oncocytic type. p16 at this time does not have the same surrogate expression as seen in oropharyngeal carcinoma.

SPs show a remarkable anatomic distribution according to histologic type: EPs arise almost exclusively on the nasal septum (lower anterior); IPs and OPs affect the lateral nasal wall, middle meatus, and the paranasal sinuses (maxillary, ethmoid, sphenoid, frontal sinuses). Rarely, exceptions are noted. Less than 3% of cases are bilateral and usually reflect extension or secondary involvement of the disease from one side to the other. Rarely, cases are seen as primary lesions in nasopharyngeal, lacrimal sac, or middle ear mucosa.

Radiographic Features

Plain x-rays, computed tomography (CT), and magnetic resonance imaging (MRI) routinely show a unilateral polypoid mass filling the nasal cavity, although variable based on the extent of disease (Fig. 2.1). Displacement of the nasal septum and opacification of sinuses are also frequently seen. Pressure erosion of the bone is present in ~45% of cases.

Pathologic Features

Gross Findings

EPs have been described as gray-tan cauliflower-like, papillary, warty, or mulberry-like verrucous papillary

Sinonasal papilloma—disease fact sheet

	Exophytic Type	Inverted Type	Oncocytic Type
Definition	A papilloma derived from the schneiderian membrane composed of exophytic, papillary fronds with fibrovascular cores lined by multiple layers of well-differentiated stratified epithelial cells	A papilloma derived from the schneiderian membrane with proliferation and invagination into the underlying stroma	A papilloma derived from the schneiderian membrane displaying exophytic fronds and endophytic invaginations lined by multilayered columnar oncocytic cells
Incidence and Location	Uncommon (0.6/100,000 population) Nasal septum	Uncommon (~2.3/100,000 population) Lateral nasal wall, middle meatus, paranasal sinuses Rarely nasopharynx and middle ear	Rare Lateral wall of nasal cavity, paranasal sinuses
Morbidity and Mortality	Morbidity associated with nasal obstruction and epistaxis No mortality	Intracranial invasion Carcinoma in 2% of cases	Nasal obstruction, bleeding Rare cases of carcinoma
Sex and Age Distribution	Males > females (10:1) Adults (mean, 20-50 years)	Males > females (3:1) Adults (mean, 5th-6th decade), uncommon in children	Equal sex distribution 6th decade
Clinical Features	Unilateral nasal obstruction Epistaxis Rhinorrhea Headaches	Nasal obstruction Epistaxis Rhinorrhea Facial pressure Headaches	Nasal obstruction Epistaxis
Prognosis and Treatment	Excellent long-term prognosis, although recurrences develop (up to 50%) Meticulous and complete surgical resection	Excellent long-term prognosis (excluding cases with malignant transformation) Recurrences up to 60%, depending on type of surgery Carcinoma in ~2% of cases Meticulous, complete surgical resection	Excellent prognosis Very rare examples of carcinoma Meticulous and complete surgical resection

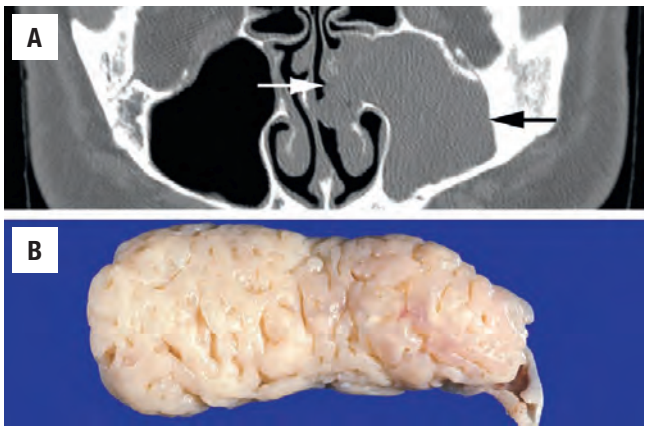

FIGURE 2.1

(**A**) A computed tomography scan showing opacification and expansion of the left maxillary sinus and lateral nasal wall *(arrows)*. (**B**) Surgical specimen of an inverted sinonasal papilloma with a polypoid appearance. The cerebriform surface shows numerous clefts due to exuberant endophytic epithelial proliferation.

proliferations attached to underlying mucosa by a narrow stalk, up to ~2 cm. IPs usually are large, multinodular, firm, bulky, polypoid lesions with deep clefts and intact mucosa (Fig. 2.1), creating a cerebriform appearance. Often, resections for IP include fragments of bone. Grossly, OPs are usually small and fragmented and consist of soft pink, tan to brown papillary fragments of tissue. All of them are nontranslucent.

Microscopic Findings

Exophytic Papilloma

EPs consist of branching, exophytic proliferations composed of fibrovascular cores lined by well-differentiated multilayered (up to 20 cells thick) squamous epithelium (Fig. 2.2). The epithelium ranges from basal and parabasal cells (Fig. 2.3) to well-differentiated keratinized cells with a granular cell layer and surface keratin with hyperkeratosis (Figs. 2.4 and 2.5). Koilocytic atypia may be seen. Surface keratinization is uncommon. There may be intraepithelial or luminal ciliated or goblet cells. The stroma usually contains variable numbers of seromucous glands. Mitotic figures and atypical mitoses are uncommon. Malignant change is exceptional.

Inverted Papilloma

IP consists of a markedly thick, inverted, or endophytic growth of multiple layers (up to 30 cells thick) of nonkeratinizing transitional cells (Fig. 2.6) associated with transmigrating neutrophils. The inverted areas are surrounded

Sinonasal papilloma—pathologic features

	Exophytic Type	Inverted Type	Oncocytic Type
Gross Findings	Gray-tan, cauliflower-like or verrucous papillary proliferation attached to mucosa by narrow stalk	Large, multinodular, firm polypoid lesions Deep clefts of inverted but intact mucosa Fragments of bone in surgical specimen	Small fragments of soft, fleshy, pink, tan, papillary tissue
Microscopic Findings	Branching, exophytic proliferations with fibrovascular cores lined by well-differentiated stratified squamous epithelium Basal and parabasal cells, well-differentiated keratinized cells, granular cell layer, surface keratin Intraepithelial or luminal ciliated or goblet cells Stroma with seromucous glands	Markedly thick, inverted neoplastic proliferation Transitional/squamoid epithelium Transepithelial neutrophils with numerous intraepithelial microcysts containing neutrophils, mucin, and cellular debris Distinct cell borders with glycogenation May have ciliated columnar cells or surface keratinization Foci of cytologic atypia Stroma ranging from edematous, myxomatous, to fibrous No seromucous glands in stroma	Both exophytic and endophytic patterns Multiple layers of columnar oncocytic epithelium Tumor cells have well-defined borders with eosinophilic or granular oncocytic cytoplasm Round nuclei with small nucleoli Cilia may be present focally on the surface Intraepithelial cysts Rare malignant transformation
Immunohistochemical Findings		Coexpression of columnar and squamous epithelial keratins by the same cells	Mitochondrial histochemical stains (phosphotungstic acid haematoxylin, PTAH)—positive Cytochrome c oxidase positive
Pathologic Differential Diagnosis	Cutaneous squamous papilloma, inflammatory nasal polyp, papillary squamous cell carcinoma	Sinonasal polyp, REAH, carcinoma	Rhinosporidiosis and low-grade papillary sinonasal adenocarcinoma

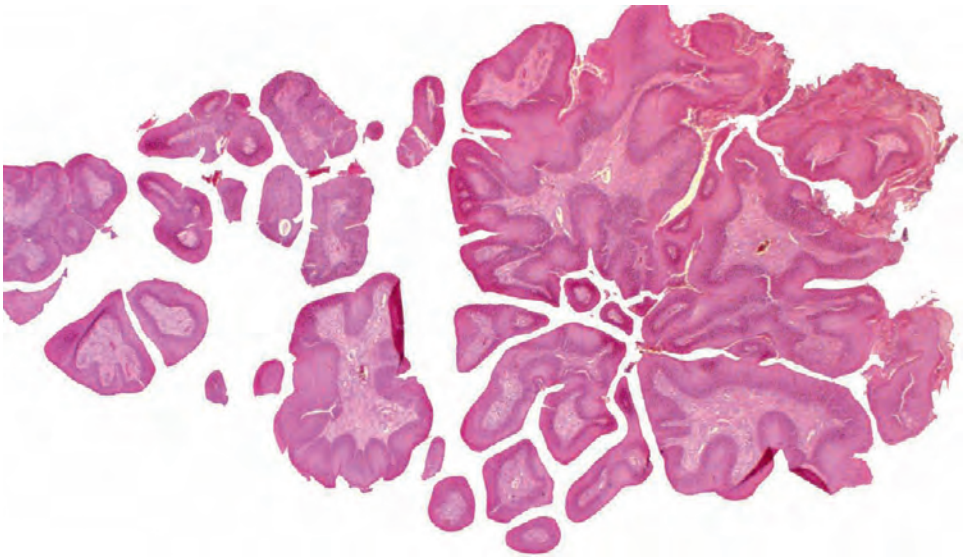

FIGURE 2.2

Multiple, complex papillary projections in an exophytic sinonasal papilloma.

by a well-formed basement membrane and do not show irregular, "invasive" growth (Fig. 2.7). The epithelium in IP undergoes squamous maturation with superficial cells adopting a flattened orientation, but ciliated columnar epithelium is usually seen, whereas surface keratinization and a granular cell layer are uncommon (< 10 %). Distinct cell borders and cleared cytoplasm (due to glycogen) are frequent findings. Cellular pleomorphism may be present but is focal and not associated with dyskeratosis or increased mitotic activity. A characteristic feature is the presence of numerous intraepithelial microcysts containing macrophages, neutrophils, mucin, and cellular debris (Fig. 2.8). These microcysts are more numerous close to the luminal surface. Mucous cells may be interspersed. Mitotic activity is variable but usually limited to basal and parabasal cells. The stroma ranges from edematous, myxomatous, to fibrous, usually showing a conspicuous absence of seromucous glands. An inflammatory infiltrate is composed of a variable mixture of neutrophils, eosinophils, and small lymphocytes (Fig. 2.8). Concurrent

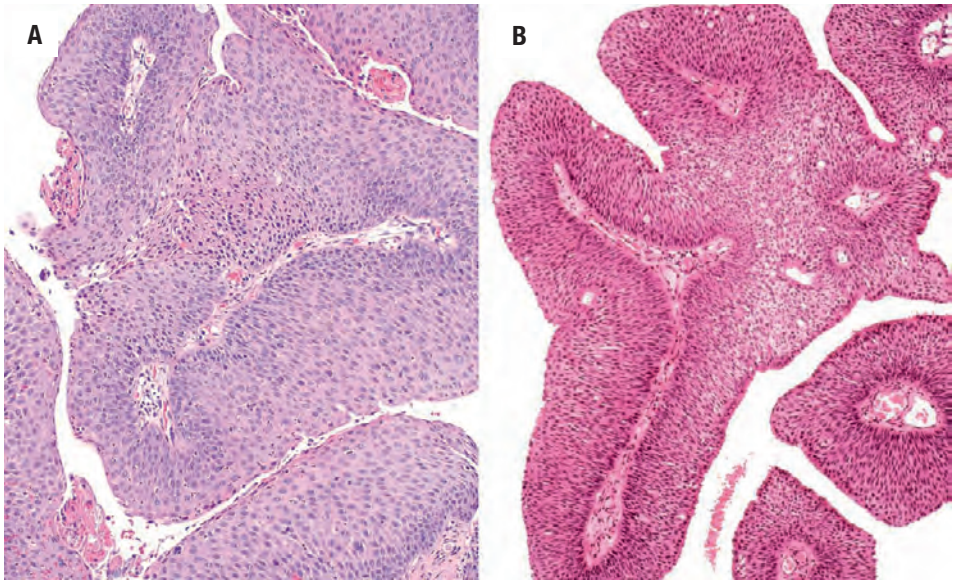

FIGURE 2.3

(**A** and **B**) Exophytic sinonasal papilloma lined by markedly thickened well-differentiated squamous epithelium. There are isolated inflammatory cells.

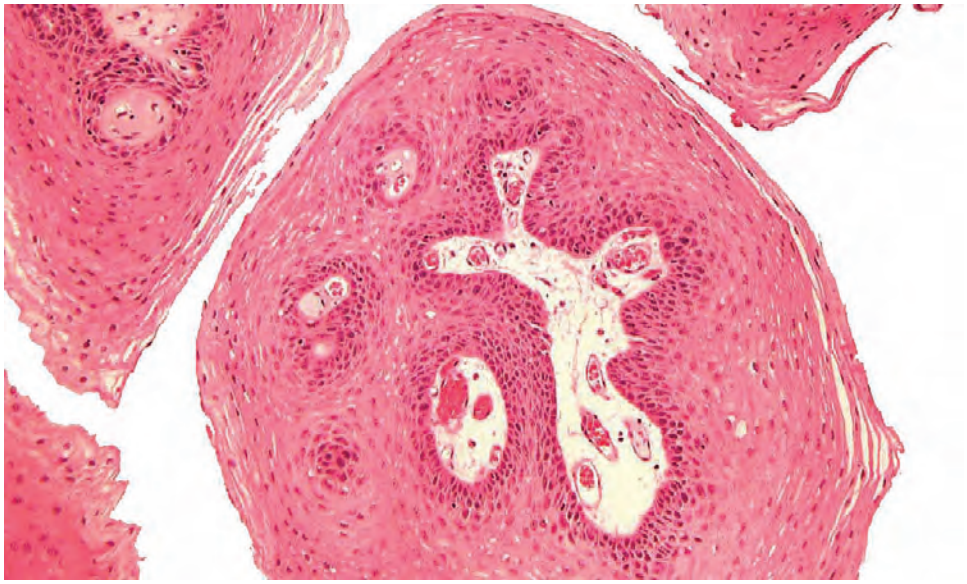

FIGURE 2.4

Exophytic sinonasal papilloma with papillary "finger-like" projections with a fibrovascular core lined by squamous cells.

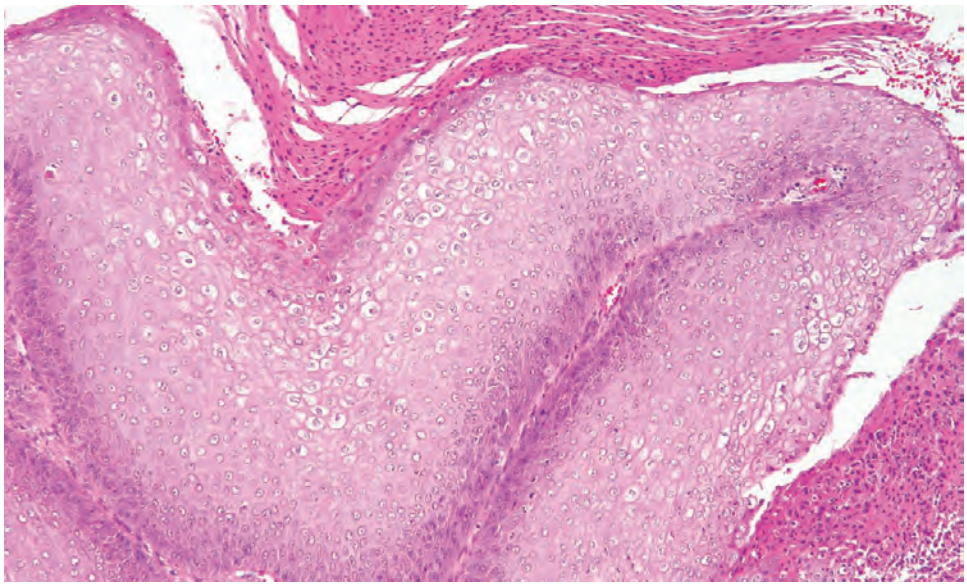

FIGURE 2.5

An exophytic sinonasal papilloma with koilocytic atypia, hyperkeratosis, and parakeratosis.