Nasal Manifestations of Systemic Illnesses

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This article is focused on the nasal and sinusal manifestations of systemic diseases, such as infections, immunodeficiencies, chronic multisystemic disorders, inflammatory bowel diseases, deposition diseases, hematologic diseases, respiratory diseases, and smell and taste disorders. A concise review of some of the systemic diseases that commonly present complaints in the nose and paranasal sinuses, including their prevalence, sinonasal manifestations, diagnosis, and treatment, is provided.

Introduction

Systemic diseases comprise a heterogenous group of inflammatory disorders that affect several organs. The nose and paranasal sinuses are involved in many of these uncommon diseases. In this article, we try to give a new approach to the field by including some common respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), that show a high prevalence of nasosinusal manifestations, such as rhinitis and sinusitis. Because the sense of smell should be considered a part of the nose physiology, diseases affecting the sense of smell are also described at the end of the manuscript.

Infectious Diseases

Tuberculosis

In 2001, the Centers for Disease Control and Prevention reported approximately 16,000 cases of tuberculosis (TB) in the United States, a significant decrease from the 28,000 cases reported in 1981 [1]. Most countries located in the eastern part of Europe, Portugal, and Spain reported 20 cases per 100,000 people. *Mycobacterium tuberculosis* is the organism that is the causative agent for TB. There are other "atypical" mycobacteria, such as *M. kansasii*, that might produce similar clinical and pathologic appearances of disease. Nasal manifestations in TB-affected patients are similar to common catarrh with rhinorrhea and nasal obstruction. The nasopharynx is the nasal site most commonly involved. Nasal endoscopy might reveal an adenoid hypertrophy normally associated with rhinorrhea and nasal obstruction, with no characteristic features. Nasopharyngeal TB is mainly a primary infection often accompanied by cervical adenopathies. Nasal polyps can be observed predominantly growing from the inferior turbinate. TB should also be included in the differential diagnosis of septal perforation. The laboratory diagnosis of TB is based on acid-fast smear, culture, and tuberculin skin test. Recently, polymerase-chain reaction (PCR) as a diagnostic and confirmatory test has been introduced [2]. The treatment is based on a multidrug anti-TBC regimen.

Leprosy

Also known as Hansen's disease, after G.A. Hansen who, in 1878, identified the bacillus *M. leprae* that causes the disease, leprosy is a slowly progressing bacterial infection that affects the skin, peripheral nerves in the hands and feet, and mucous membranes of the nose, throat, and eyes. Lepromatous leprosy is characterized by a chronic stuffy nose, due to invasion of the mucous membranes, and the presence of nodules and lesions covering the body and face [3]. Diagnosis of leprosy is most commonly based on the clinical signs and symptoms. Skin-scraping examination for acid-fast bacteria (typical appearance of *M. leprae*) is definitive. A lepromin skin test can be used to distinguish lepromatous from tuberculoid leprosy, but is not used for diagnosis. Medications used to eliminate the microorganism and to reduce symptoms include: dapsone, rifampin, clofazimine, and ethionamide.

Invasive fungal sinusitis

Invasive fungal sinusitis (IFS) predominantly affects diabetes mellitus, immunodeficient (primary or acquired), oncology, and elderly patients, who present a high rate of mortality (50%–80%). The *Mucor* family and *Aspergillus fumigatus* are the fungi most commonly associated with an aggressive behavior capable of inducing bone destruction. Early diagnosis is critical for survival. Histopathologic evidence of hyphal forms within sinus mucosa, submucosa, blood vessels, or bone confirms the diagnosis. The treatment consists of a surgical aggressive débridement plus prolongated intravenous antifungal (amphotericin B) medication [4].

Table 1. Most common primary immune deficiencies

Primary combined immunodeficiencies: severe combined immunodeficiency, Wiscott-Aldrich syndrome (asthma), ataxia-telangiectasia, defects of antigen presentation, trisomy 21.
Structural defects: cystic fibrosis, primary ciliary dyskinesia.
Phagocyte function defects: MPO deficiency, chronic granulomatous disease, Chediak-Higashi syndrome, leukocyte adhesion deficit, hyper-IgE syndrome, complement defects.
Cell-mediated immunity defects: DiGeorge syndrome, chronic mucocutaneous candidiasis.
Humoral immunity defects: newborn transient agammaglobulinemia, Bruton agammaglobulinemia, common variable immunodeficiency, selective IgA deficiency, IgG subclass deficiencies, hyper-IgM syndrome.

MPO—myeloperoxidase.

Syphilis

In the United States, there are approximately 6000 cases of primary or secondary syphilis diagnosed per year. *Treponema pallidum* is transmitted through sexual contact with infectious lesions in skin or mucous membrane. In primary syphilis, the nose is not the typical location, although cases with a nasal vestibule chancre have been reported. Secondary syphilis presents as an acute rhinitis with copious nasal discharge that irritates the nares. Tertiary syphilis shows gummata of the nose, septum perforation and deformation, and saddle-nose deformity, but the nasopharynx is rarely involved. Nasal discharge is the main manifestation of congenital syphilis, occurring 2 weeks before the rash. Septum perforation and deformation can also occur [5]. Diagnosis of syphilis is most commonly based on the clinical signs and symptoms, physical examination, lesion-based test (darkfield microscopy, fluorescent antibody staining), and nontreponemal (rapid plasma regain [RPR], Veneral Disease Research Laboratory [VDRL]) or treponemal (fluorescent treponemal antibody absorption [FTA-ABS], IgG, Western-Blot) serologic tests. Microorganism detection is useless for the diagnosis. The antibiotic of choice is penicillin-G. Doxycycline is an alternative in patients with penicillin allergy [6].

Immunodeficiencies

Immunodeficiencies, usually leading to recurrent and severe infections, can be caused by primary immune defects, such as structural defects, defects of the phagocyte function, cell-mediated and humoral immunity, or combined immunodeficiency or acquired immune defects. Immunodeficient patients often present with infections in the head and neck area. Sinusitis, otitis, cervical polyadenopathy, and infections of the oral cavity are the most frequent. The occurrence of two or more severe sinusitis episodes within 1 year is an indication to carry out an immunologic study.

Primary immune defects

Primary immune deficiencies are inborn genetic defects of the immune system. It is estimated that at least 500,000 people worldwide suffer from at least one of these disorders (Table 1). These patients suffer from recurrent and persistent infections. Gene therapy offers the expectation of a potential future cure, obliterating the need for antibiotic and immunoglobulin therapy and bone marrow transplantation.

Acquired immune defects

AIDS

The natural history of HIV infection has been described as a consequence of an insidious and progressive decline of the immune function. A recent document (November 2003) of the United Nations reported 40 million HIV-infected people around the world. An association between opportunistic infections and CD4-positive cell count is observed. HIV-infected patients develop a higher rate of diseases earlier than individuals with a normal immune system. The most common opportunistic diseases and infections consist of bacterial diseases (tuberculosis, bacterial pneumonia and septicemia, *M. avium* complex disease), protozoal diseases (*Pneumocystis carinii*, toxoplasmosis, microsporidiosis, cryptosporidiosis, leishmaniasis), fungal diseases (candidiasis, cryptococcosis), viral infections (cytomegalovirus, herpes simplex, herpes zoster), and HIV-associated malignancies, such as Kaposi sarcoma, lymphoma, and squamous cell carcinoma. These patients might present with nasal obstruction commonly caused by nasopharyngeal hypertrophy (early in the infection stage), allergic rhinitis, neoplasms, and sinusitis. Occasionally, nasopharyngeal hypertrophy causes otitis media with effusion that is refractory to medical treatment. Nasal endoscopy might reveal a hypertrophic, asymmetric, and heterogeneous nasopharyngeal mass with suspicion of a malignant process, such as Kaposi sarcoma or non-Hodgkin lymphoma. Due to humoral and cellular immunodeficiency, decreased ciliar clearance, increased allergic component, increased consumption of tobacco and intranasal drugs, recurrent acute sinusitis, and chronic sinusitis are frequent. An exacerbation of allergic rhinitis is very common in HIV-infected patients [7,8]. Positive HIV antibodies are detected with enzyme-linked immunosorbent assay (ELISA), and the diagnosis is confirmed by analyzing the viral proteins with Western blot.

Therapy with protease inhibitors and nucleoside reverse transcriptase inhibitors, together with prophylaxis and treatment of the opportunistic infections, have an important role in decreasing the morbidity and mortality in HIV-infected patients.

Transplantation

Sinusitis caused by fungi and gram-negative bacteria are a frequent complication of bone marrow transplantation (BMT). Invasive fungal sinusitis is a hazardous complication of BMT. When bone destruction was found, fulminant infection was already present, usually with significant orbital and/or brain invasion [9]. Solid-organ transplantation (SOT) is increasingly becoming more common in the treatment of end-stage organ failure. Opportunistic fungal infections of the sinuses are a frequent complication of transplantation. *Candida* and *Aspergillus* species have been found in most of these invasive fungal infections in organ transplantation recipients. Prompt recognition and treatment of infection become mandatory for any successful therapy [10].

Multisystemic Disorders

Sarcoidosis

Sarcoidosis is a chronic multisystemic disorder of unknown etiology that commonly affects young and middle-aged adults and is characterized by bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The incidence of sarcoidosis greatly varies with race and country. Prevalence as high as 50 per 100,000 people have been reported [11]. Sinonasal involvement occurs with an incidence of 1%, but is not a typical presenting symptom of sarcoidosis.

Nonspecific symptoms, such as nasal obstruction, postnasal drip, crusting, congestion, epistaxis, chronic sinusitis, and headache, are the typical initial complaints. The most consistent finding in the nose and sinuses is an erythematous, edematous, friable, hypertrophied mucosa. Subcutaneous granulomatous infiltration might also occur in the form of yellowish nodules, predominantly in the septum and inferior turbinate. Epiphora or anosmia might also occur, due to an occupation of lachrymal or olfactory cleft, respectively. Nasal polyposis, rhinophyma, and septal perforations can also exist in sarcoidosis. Aggressive, noncaseating granulomas can cause hard and/or soft-palate erosions creating an oral-nasal fistula, as well as provoke a saddle-nose deformity [12]. In the earlier stages of sarcoidosis, there is no treatment. Tissue for diagnosis is typically obtained by transbronchial lung biopsy. Other sites of biopsy are skin lesions, minor salivary glands, and lymph nodes. However, systemic steroids are needed as the disease progresses. Other treatments are chloroquine, immunosuppressors, and lung transplantation.

Wegener's granulomatosis

Wegener's granulomatosis (WG) is a systemic, idiopathic disease described as a necrotizing, granulomatous inflammation involving the upper and lower respiratory tracts in combination with glomerulonephritis. WG is a necrotizing vasculitis that takes the form of fibrinoid necrosis affecting the walls of small to medium arteries and veins. A limited form has been described in the upper respiratory tract, presenting a midline destructive lesion of the nose and sinuses. WG affects approximately one to three people per million [13]. Sinonasal involvement occurs with an incidence of 75%, and the nose is involved in 30% of cases. Most common nasal symptoms are progressive nasal obstruction, discharge, rhinorrhea, minor and recurrent epistaxis, pain over the nasal dorsum, and crusting. Hyposmia/anosmia might also occur and are predominantly caused by secretions [14••]. *Staphylococcus aureus* is the most frequent microbial agent found in the upper airways and has been associated with a higher relapse rate of the disease. Epiphora might also occur due to obstruction or compression of the lachrymal system. The most consistent finding in the nose and sinuses is an erythematous, friable mucosa with nasal crusting and granulation that predominates in the septum and inferior turbinate. Aggressive WG can induce nonvascular necrosis, causing bone destruction that initially affects the nasal septum (perforation) and typically spreads to turbinates, antrum wall, ethmoid sinus, lamina paprika, and cribriform palate, with conservation of the hard palate [15]. Progressive loss of supporting nasal structures might lead to the characteristic saddle-nose deformity. It is the combination of symptoms, results of physical and radiologic examinations, laboratory tests (positive cytoplasmic antineutrophil cytoplasm autoantibodies [c-ANCA] in 60%–90%), and sometimes a biopsy of affected tissue (skin, nose, sinus, lung, or kidney) that together confirm the diagnosis of WG. Treatment usually includes corticosteroid medication, such as prednisone and chemotherapy drugs, such as cyclophosphamide or methotrexate.

Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) was first described in 1951 as a pathologic syndrome of allergic granulomatosis and angiitis. The estimated prevalence of CSS is 1.3 cases per 100,000 people. The cause of CSS remains unknown but its characteristic histologic findings and association with asthma make it distinguishable from other vascular lesions. The syndrome is often associated with the presence of perinuclear antineutrophilic cytoplasmic antibodies that target myeloperoxidase. In 1990, the American College of Rheumatology identified six major criteria for the disease: asthma, peak blood peripheral eosinophilia more than 10%, peripheral neuropathy attributable to a systemic vasculitis, transient pulmonary infiltrates, paranasal sinus abnormality, and a biopsy specimen of a blood vessel with extravascular eosinophils.

Diagnosis of CSS should be considered in patients with asthma accompanied by a raised peripheral-blood eosinophil count or pulmonary infiltrates. Systemic symptoms, such as fever, fatigue, and weight loss, are prominent. Allergic rhinitis occurs in 75% of patients and is often the first manifestation of CSS. Nasal polyps and recurrent sinusitis are also identified in approximately 50% of patients. Less common is nasal pain with purulent or bloody nasal discharge, nasal crusting, or nasal perforations revealing necrosis [16,17]. Treatment usually includes high doses of corticosteroids, to reduce the inflammation, and suppression of the active immune system with cyclophosphamide.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect virtually any body system. SLE predominantly affects women (10:1). The incidence of SLE is 5.6 per 100,000 people, with an estimated prevalence of 130 per 100,000 [18]. Although those with the disease might have different symptoms, the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems. The skin of the nose and nasal vestibule can be involved in the skin rashes. Shallow ulcers of the nasal mucosa and chronic bacterial sinusitis have been reported with an increased frequency [19]. Nasal perforations are uncommon. The disease has multiple manifestations with variable severity, which determine individual treatment. There is no cure for SLE, but corticosteroid therapy or medications to suppress the immune system might be prescribed to control the various symptoms of this severe disease.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) typically develops subacutely, with the onset of constitutional symptoms over weeks to months. Many of the initial symptoms are retrospectively recognized. Fever is a common feature at diagnostic ranging from intermittent low fever to high fever with chills. PAN tends to involve medium-sized muscular arteries. Nasal involvement has only been occasionally reported in polyarteritis nodosa, including perforation of the nasal septum and sinusitis [16,20].

Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic inflammatory disease of the exocrine glands with a broad range of extraglandular involvement characterized by xerostomia and keratoconjunctivitis sicca. SS affects 1% to 3% of the general population, predominantly women. The most common nasal symptoms are epistaxis, crusting, hyposmia/anosmia, and hypogeusia. Nasal mucosa atrophy can be found in approximately 50% of patients at nasal endoscopy. Chronic sinusitis and nasal perforations are less common [21].

Once SS is suspected, the physician should request a variety of blood tests including: anti-nuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, and immunoglobulins. Other tests might also be helpful: Schirmer test measures tear production, parotid gland flow, and sialography. Lip biopsy can be used to confirm lymphocytic infiltration of the minor salivary glands. Treatment is based on the symptoms. Dry eyes are treated with artificial tears, a tear stimulant, or eye lubricant. Dry mouth might be helped by frequent small drinks of water, or chewing gum to stimulate saliva production. Arthritis symptoms are treated with anti-inflammatory drugs, such as aspirin, acetaminophen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) [22].

Other multisystemic diseases

Scleroderma

This is a chronic, autoimmune disease of the connective tissue with an overproduction of collagen. The nasal mucosa shows several changes, such as goblet cell hyperplasia, loss of cilia, and increased serous glandular activity without mucous elements [23].

Antiphospholipid syndrome

The most frequent clinical manifestation is renal dysfunction due to the presence of renal thrombotic microangiopathy. Pulmonary manifestations range from multiple pulmonary emboli to the fatal acute respiratory distress syndrome. Nasal examination occasionally demonstrates a silent nasal septum perforation [24].

Recidivant polychondritis

At least three of the following criteria are needed for the diagnosis of recidivant polychondritis: chondritis of the pinna, nose, larynx, or trachea; ocular alterations; sensorineural hearing loss; and seronegative arthritis. Nasal chondritis can lead to the characteristic saddle-nose deformity, without nasal mucosa inflammation and without sinonasal affectation, which differentiates Wegener's granulomatosis from recidivant polychondritis. Nasal chondritis might resolve with nonsteroid/steroid anti-inflammatory treatment [25].

Cryoglobulinemia

A variety of nonspecific nasal manifestations are present in cryoglobulinemia: nasal obstruction, epistaxis, postnasal discharge, whistling, and crusting. Asymptomatic forms are frequent. Cases of nasal septal perforation secondary to cryoglobulinemia have also been reported [26].

Gastrointestinal Diseases

Inflammatory intestinal diseases

Crohn's disease

Crohn's disease (CD) is a granulomatous inflammatory bowel disease (IBD). The etiology of CD is still unknown, but genetic and environmental factors have been suggested, given the existence of familial aggregation. Several environmental factors, such as domestic hygiene during childhood,

use of oral contraceptives, diet, and smoking, have been suggested in the pathogenesis of CD [27]. The estimated prevalence of CD is 1 to 10 cases per 100,000 inhabitants. Pathologic findings include noncontiguous chronic inflammation and noncaseating granulomas. Any segment of the gastrointestinal tract can be affected, but it is uncommon to find CD spreading beyond the intestine. Nasal manifestations of CD are rare. Chronic mucosal inflammation, nasal discharge, bleeding, obstruction, and, occasionally, septal perforation are the most frequent symptoms. Nasal manifestations can precede the typical manifestations of CD. Reviews of the literature show some cases of nasal involvement in CD and few associations between this illness and other systemic diseases, such as Wegener's disease or relapsing polychondritis. Most patients are first treated with drugs containing mesalamine, a substance that helps to control inflammation. Some patients take corticosteroids to control inflammation. These drugs are the most effective for active Crohn's disease. Drugs that suppress the immune system, such as 6-mercaptopurine and azathioprine, are also used [28•].

Ulcerative colitis

Ulcerative colitis is an inflammatory disorder of a presumed autoimmune etiology. The estimated prevalence of ulcerative colitis is 2 to 3 per 100,000 people. The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Although ulcerative colitis can occur at any age, the most common groups affected are those between 15 and 30 and those between 50 and 70 years old. One million people in the United States are estimated to suffer from IBD, equally split between ulcerative colitis and Crohn's disease. Approximately 50% of patients present with chronic sinonasal disease. Chronic mucosal inflammation, nasal obstruction, and, occasionally, septal perforation have also been associated with ulcerative colitis. Medications that can be used to decrease the frequency of attacks include 5-aminosalicylates, such as mesalamine, and immunomodulators, such as azathioprine and 6-mercaptopurine. Corticosteroids might be prescribed to reduce inflammation. Occasionally, surgery to remove the affected colon will cure ulcerative colitis and remove the threat of colon cancer [29]. Several groups have recently demonstrated the efficacy of cyclosporin-A (CSA) in acute flares of ulcerative colitis [30].

Gastroesophageal reflux

Gastroesophageal reflux (GER) is the retrograde flow of gastric content back into the esophagus. It is one of the most common problems encountered by physicians in all specialties, affecting nearly 30% of the population. Prolonged pH manometry has become the gold standard for the diagnosis. Many articles in the literature include attempts to explain an association between GER and otitis media, pharyngitis, sinusitis, and laryngeal malignancy, but the definition and method of diagnosis of GER are not well standardized. Sinusitis, otitis media, and cancer have many risks factors that make it difficult to isolate the only effect of GER. Controlled studies are now needed to demonstrate this association more accurately [31]. Bothwell *et al.* [32] demonstrated that after reflux treatment, the number of children requiring sinus surgery was dramatically reduced. These study results indicate that GER should be evaluated and treated before sinus surgical intervention.

Deposition Diseases

Among deposition diseases, amyloidosis constitutes a large group of diseases in which misfolding of extracellular protein has a prominent role. These amyloid deposits are identified on the basis of their apple-green birefringence under a polarized light microscope after staining with Congo red, and the presence of rigid, nonbranching fibrils. Amyloidosis can be acquired or hereditary, local or systemic, and is classified according to the precursor protein. The clinical presentation is similar to that of other diseases of the sinonasal area. The most frequent involvement areas affected are the maxillar sinus and the nasal fossa, with symptoms consisting of unilateral nasal respiratory insufficiency, hemifacial paresthesias, hemifacial pain, and rhinorrhea. Nasopharynx amyloidosis is rare. Few cases are reported in the literature [33]. Adenoidectomy with adenotome or curettes and endoscopic sinus surgery are the most frequent surgical treatments. Current treatment consists of support or replacement of impaired organ function and measures to reduce the production of amyloidogenic precursor proteins. Median survival after diagnosis is 4 to 8 years [34].

Hematologic Diseases and Epistaxis

Multiple myeloma

Multiple myeloma (MM) is a cancer of the bone marrow in which antibody-producing plasma cells grow in an uncontrolled and invasive (malignant) manner. MM is the second most common cancer of the blood. It is the most common type of plasma cell neoplasm. Poor blood circulation or Raynaud's phenomenon can affect any part of the body, but particularly the nose, causing nasal bleeding (epistaxis) [35]. The diagnosis of MM is confirmed when bone marrow plasmocytosis (>10%), lytic bone lesions, and monoclonal immunoglobulin in serum or urine are found. There are two variants of MM: solitary bone plasmocytoma and extramedullary plasmocytoma. These variants are seen in younger people, and they respond well to radiotherapy.

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common leukemia of the Western world and accounts for 30% of all cases of leukemia. CLL is a disorder of morphologically mature but immunologically less mature lymphocytes. It manifests as a progressive accumulation of these cells in the blood, bone marrow, and lymphatic tissues. Symptom-

Table 2. The most common causes of epistaxis

- Idiopathic: most cases of epistaxis do not have an easily identifiable cause
- Local trauma (*ie*, nose picking)
- Iatrogenic causes: nasogastric and nasotracheal intubation
- Cocaine sniffing
- Upper respiratory infection (usually in children)
- AIDS (splenomegaly, thrombocytopenia, or platelet disorders)
- Vascular fragility (secondary to chronic hypertension)
- Endocrine causes: pregnancy, pheochromocytoma (causing hypertensive crisis)
- Hepatic cirrhosis
- Renal failure
- Vascular abnormalities:
  - —Sclerotic vessels
  - —Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)
  - —Arteriovenous malformation
  - —Neoplasm
  - —Coagulopathy (hemophilia, anticoagulant overdose, and vitamin K deficiency)
  - —Endometriosis
  - —Wegeners' granulomatosis

atic CLL features lymph node and spleen enlargement, weight loss, and malaise. Unrelenting bone marrow replacement by leukemic cells often results in immunosuppression, anemia, and thrombocytopenia. CLL in the paranasal sinus mucosa is extremely rare. Patients present with chronic sinusitis and nasolacrimal duct obstruction as a result of mucosal infiltration by neoplastic cells [36]. Treatment with conventional doses of chemotherapy is not curative. Selected patients treated with allogeneic stem cell transplantation have achieved prolonged disease-free survival. The overall 5-year survival is approximately 60% but depends on the stage of the disease [37].

Epistaxis

Epistaxis is classified on the basis of the primary bleeding site as being anterior or posterior. Nasal hemorrhage is most commonly anterior, having commonly originated in the nasal septum. Posterior hemorrhage originates from the posterior nasal cavity or nasopharynx, usually below the posterior half of the inferior turbinate or roof of the nasal cavity. Local trauma is the most common cause, followed by facial trauma, foreign bodies, nasal or sinus infections, and prolonged inhalation of dry air. A disturbance of normal nasal airflow, as occurs in a deviated nasal septum, might also be a cause of epistaxis. Although local lesions are the most common causes, systemic diseases can also cause epistaxis [38] (Table 2). Treatment of epistaxis consists of direct digital pressure to the nose over the bleeding site for 10 minutes. If this is not effective, clots should be removed, and cauterization of the bleeding point (chemical or electric cauterization) or anterior nasal packing should be performed. If bleeding originates from far back in the nose, postnasal pack under general anesthesia should be done. If all the above measures fail, surgical intervention using endoscopic sinus surgery or ligation of the internal maxillary artery should be done.

Respiratory Diseases

Much has been written in the recent literature on the association between nasal manifestation and inflammatory respiratory diseases, such as COPD, allergic bronchopulmonary aspergillosis, asthma, cystic fibrosis (CF), and primary ciliary dyskinesia (PCD). Following is an update on this topic and a discussion of the current management options for these diseases.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease, which encompasses both chronic bronchitis and emphysema, is one of the most common respiratory diseases of adults in the developed world. In the United States, COPD affects 4% of population, making it the fourth leading cause of death, surpassed only by heart attacks, cancer, and stroke [39]. COPD is a disorder characterized by reduced maximal expiratory flow and slow, forced emptying of the lungs. The primary cause is cigarette smoking (accounting for 82% of COPD deaths). A smoker is 10 times more likely to die of COPD than a nonsmoker. Other indoor and outdoor air pollutants can also damage the lungs and contribute to COPD, and genetic factors might also play a role in determining susceptibility.

There is an association of nasal symptoms, including nasal discharge, sneezing, nasal congestion, decreased sense of smell, and postnasal drip with respiratory symptoms, suggesting that there is a relationship between the upper and lower airway in COPD [40]. Several therapeutic options are available for COPD, such as respiratory rehabilitation, corticosteroids, and lung-volume reduction surgery.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease of the lungs that is almost always caused by *Aspergillus fumigatus*. ABPA accounts for approximately 10% of pulmonary exacerbations. This category also includes allergic *Aspergillus* sinusitis (AAS). ABPA is described as a disease characterized by episodic bronchial obstruction (asthma), peripheral blood eosinophilia, immediate scratch-test reactivity to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated serum IgE concentrations, history of pulmonary infiltrates (transient or fixed), and central bronchiectasis [41•]. Nasal symptoms of ABPA consist of watery or mucopurulent discharge, sneezing and nasal blockade, passage of golden-brown plugs/casts along with nasal secretion, and episodes of fever during exacerbation [41•]. The sinus occupation in AAS is usually unilateral, predominating in younger patients and presenting a high rate of association with asthma (50%)

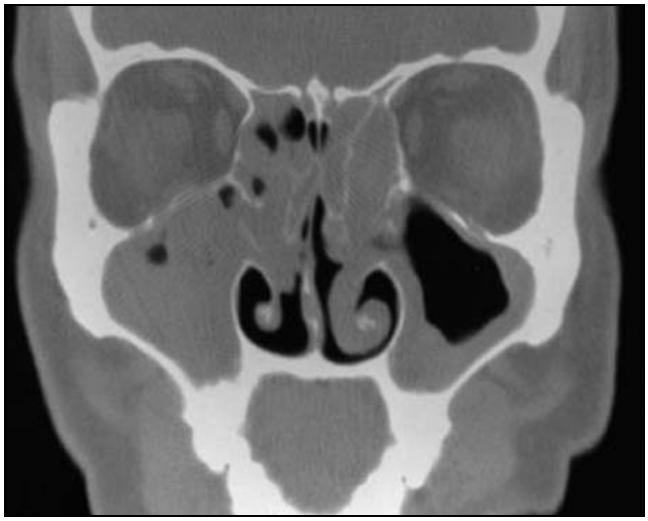

Figure 1. Paranasal sinus CT scan demonstrating endonasal as well as maxillary and ethmoidal sinus affectation.

[42]. Systemic glucocorticosteroids remain the mainstay of ABPA treatment. Itraconazole has an established role as a steroid-sparing agent if the patient has a slow or poor response to steroids, relapses, or is at risk for developing steroid toxicity.

Asthma

Asthma is an inflammatory airway disease associated with intermittent respiratory symptoms, bronchial hyperresponsiveness (BHR), and reversible airflow obstruction. Asthma results from a combination of factors, including genetics, environmental exposure to allergens, and prior respiratory virus infection. In 1997, more than 30.5 million prescriptions for asthma medications were filled, and patients had 1.2 million emergency visits and 445,000 hospitalization days [43]. Several observations have suggested the hypothesis of the unity of the upper and lower respiratory tract and that a common pathogenic mechanism underlies rhinitis and asthma [44]. It has long been recognized that diseases of upper and lower airways might coexist. Indeed, as many as 80% of patients with allergic asthma have allergic rhinitis, and more than 15% of patients with allergic rhinitis have asthma [45,46••]. Radiographic findings of sinus abnormalities, such as mucosal thickening, air–fluid levels, and total opacification of the paranasal sinuses, have been shown to be common (40% to 60%) in adults and school-age children with asthma [47]. The prevalence of nasal polyposis is 7% in asthmatic patients. Aspirin-induced asthma (Widal triad) is a clinical syndrome characterized by nasal polyposis and asthma attacks after the intake of aspirin and other NSAIDS [48]. Nasal polyposis is present in approximately 80% of Widal triad patients (Fig. 1).

Treatment of asthma, allergic rhinitis, and nasal polyposis is based in the use of anti-inflammatory agents (corticosteroids) that reduce airway inflammation.

Cystic fibrosis

Cystic fibrosis is the most prevalent fatal, autosomal, recessive genetic disease in white people, affecting approximately one in 3000 to 10,000 live births. The diagnostic criteria for CF require the presence of one or more typical clinical features: a family history of CF or a positive newborn screening test, plus laboratory evidence of the CF transmembrane conductance regulator (CFTR) dysfunction. The most common mutation in CF is a deletion of phenylalanine 508 (Delta F508) of the *CFTR* gene. This CF-associated mutation is found on at least one chromosome of 90% of affected individuals [49].

Nasal obstruction is the most frequent symptom in these patients, and nasal polyps are found in up to 20%. Different clinical patterns of rhinosinusitis are observed: nasal polyposis, chronic purulent rhinosinusitis, and mucopyosinusitis (purulent secretion in the maxillary antrum with bulging of the lateral wall). This last case is described as maxillary pseudomucocele. A major focus of CF treatment is the obstructed breathing that causes frequent lung infections. Physical therapy, exercise, and medications are used to reduce the mucus blockage of the airway.

Primary ciliary dyskinesia

Primary ciliary dyskinesia is an autosomal-recessive disorder that affects approximately one in 16,000 live births. Among affected individuals, 50% have the Kartagener's syndrome triad of bronchiectasis, chronic sinusitis, and situs inversus [50]. Rhinitis with mostly thin discharge is almost universally present, accompanied by nasal polyposis. Chronic ethmoid and maxillary sinusitis are almost universally found. Frontal sinuses are usually hypoplastic. Diagnosis is made with a combination of the saccharine test, nasal nitric oxide, ciliary beat frequency, and electron microscopy. Management of patients with PCD involves daily chest physiotherapy, including postural drainage and coughing. Antibiotics are used for respiratory symptoms and pulmonary exacerbations. Polypectomy or endoscopic sinus surgery relieving chronic sinusitis have been beneficial in many patients.

Smell Disorders

Smell and taste disorders are common, with loss of smell occurring more frequently. Although these disorders can have a substantial impact on quality of life and might represent significant underlying disease, they are often overlooked by the medical community. The most common causes of smell disturbance are nasal and sinus disease, upper respiratory infection, and head trauma, and frequent causes of taste disturbance include oral infections, oral appliances (*eg*, dentures), dental procedures, and Bell's palsy. Medications can interfere with smell and taste, and should be reviewed in all patients with reported dysfunction. In addition, advancing age has been associated with a natural impairment of smell and taste ability [51] (Table 3).

Table 3. Selected causes of smell disorders

Infectious disease	Immunologic disorders
Bacteria	AIDS
Fungi	Sjögren's syndrome
Viruses	Asthma and aspirin sensitivity
Rickettsia	Drugs
Neurologic diseases	Antibiotics
Central nervous system tumors	Anticancer drugs
Head trauma	Clofibrate
Cerebral vascular accidents	Cholestyramine
Arteriovenous malformations	Antithyroid drugs
Multiple sclerosis	Radioactive iodine
Postsurgical interruption of olfactory tract	Cocaine abuse
Psychiatric conditions	Others
Epilepsy	X-irradiation
Alzheimer's disease	Vitamin deficiencies (A, B_6, B_{12})
Parkinson's disease	Trace metal deficiencies (Zn, Cu, Mg)
Endocrine disorders	Kallman's syndrome
Hypothyroidism	Chronic renal failure
Adrenal cortical insufficiency	Hepatic cirrhosis
Panhypopituitarism	
Cushing's syndrome	
Cystic fibrosis	
Diabetes mellitus	

Conclusions

A variety of systemic diseases are associated with nasal manifestations. Primary care physicians, as well as ear, nose, and throat specialists and allergologists, should keep these differential diagnoses in mind when treating nasal or paranasal sinus pathology.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

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