Nasal manifestations of systemic diseases

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Abstract. Nasal manifestations of systemic diseases. Objectives: Signs and symptoms of the sinonasal tract may be originated in any organ system. Distinguishing these from original sinonasal disease poses a great diagnostic challenge. The ENT specialist usually faces an unresponsive or relapsing case, with an atypical presentation. We address this issue by trying to provide a wider perspective when dealing with sinonasal manifestations.
Methodology: We reviewed the literature exploring heterogeneous groups of diseases and systemic conditions that might interfere with normal sinonasal physiology. The most current and valid information have been included in an effort to delineate such manifestations and clarify the distinguishing signs and tests.
Results: A great variety of systemic conditions with sinonasal manifestations, including connective tissue, autoimmune, infectious, vascular, hematological, gastrointestinal, and endocrine diseases, were included. We address their distinguishing characteristics and diagnostic work-up.
Conclusions: Signs and symptoms of the sinonasal tract can originate from either local or systemic disorders. The keys to dealing with such disorders are understanding the patterns in which systemic diseases can manifest, and using special diagnostic tools specific to each condition to confirm or rule out particular diagnoses.

Introduction

Nasal blockage, nasal drip, crusting, and epistaxis are very common symptoms among patients presenting or referred to an ENT specialist. Although these symptoms are usually related to diseases of the sinonasal tract, in some cases they represent manifestations of conditions that originate in other organs or systems. These cases are challenging for the physician, since the ordinary diagnostic work-up is usually negative for common sinonasal conditions, leading to diagnostic dead ends. Whenever confronted with a strange history or when the evolution of symptoms is not as expected, systemic diseases should be included in the differential diagnosis, and the appropriate diagnostic procedures should be performed. Herein, we review systemic diseases with nasal manifestations, raise diagnostic suspicion, and provide a comprehensive tool to the physician dealing with a challenging sinonasal patient (Table 1).

Diseases presenting with sinonasal signs and symptoms can be generally categorized into six major groups: connective tissue diseases (granulomatous, vasculitis, autoimmune), infectious, respiratory, hematological, gastrointestinal (GI), and endocrine system conditions.

Connective Tissue Diseases

Granulomatosi with Polyangiitis (GPA, formerly Wegener’s granulomatosi)

GPA is an idiopathic disease with a prevalence of about 50 to 100 per million. It is characterized by diffuse necrotizing vasculitis of the small and medium-sized vessels, and granulomatous inflammation affecting the lungs, kidneys, and upper respiratory tract. Although its etiology is unknown, a genetic susceptibility triggered by certain environmental exposures (e.g., solvents, pollen and other allergens, or drugs) is suspected. A special relation between GPA and Staphylococcus aureus has been identified. There is a high incidence of secondary sinonasal infections by S. aureus in patients with GPA, and a high rate of disease relapse has been documented after S. aureus infections. The nasal mucosa becomes friable, ischemic, and ulcerative in nearly 85% of patients. Lesions in nasal and paranasal mucosa lead to nasal obstruction, crusting,
drainage, hyposmia, and nasolacrimal duct obstruction with epiphora. The turbinates, nasal bones, and both bony and cartilaginous septum are affected, resulting in destruction, perforation, and characteristic saddle deformity. The ostia mucosa is affected in the very same way, giving rise to chronic rhinosinusitis (CRS).

Criteria for the classification of GPA include the following:

1. Nasal or oral inflammation: Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph: Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
3. Urinary sediment: Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
4. Granulomatous inflammation on biopsy: Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

For purposes of classification, a patient shall be said to have GPA if at least two of these four criteria are present. The presence of any two or more criteria yields a diagnostic sensitivity of 88.2% and specificity of 92.0%.

Diagnosis, when suspected, is confirmed through serologic examinations (i.e., cytoplasmic ANCA, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)) and biopsy from affected mucosa (not while the patient is being treated with corticosteroids). On endoscopy, the nasal and sinus mucosa usually appear infiltrated, often ulcerated, and occasionally with a granulomatous or “cobbledstone” appearance. Computed tomography (CT) scan reveals mucosal thickening, especially in the maxillary sinus, along with bony erosion in more than one-half of patients. In addition, one must always look for manifestations in the lungs and kidneys.

Treatment should be in line with a clinical immunologist, and includes steroids, immunosuppressants (e.g., cyclophosphamide, methotrexate, azathioprine), antibiotics (e.g., anti-S. aureus, Bactrim) and local agents (e.g., saline rinsing and corticosteroids), as in common sinonasal disease. Functional endoscopic sinus surgery (FESS) is considered, as it may provide a certain degree of relief; however, the altered anatomy and unpredictable wound healing process make FESS quite challenging. Similarly, the role of reconstructive surgery is also questionable because of the relapsing course of the disease, the altered characteristics of the recipient site, and the need for chronic medication that is known to have an adverse effect on wound healing. However, good results can be expected when reconstruction is performed during disease remission and after careful planning.

Sarcoidosis

Sarcoidosis is a chronic inflammatory disease of unknown etiology. It is characterized by the formation of immune granulomas with non-caseating epithelioid cells, and most commonly affects the lungs and intra-thoracic lymph nodes, as well as the skin and the eye. Macrophages aggregate and are then differentiated into epithelioid cells. T-cells then arrange into a rim around these cells, forming a granuloma. If this process continues unchecked, fibroblasts and collagen will encase the granuloma and fibrosis will eventually occur. Both genetic and environmental exposures are believed to play a role in the pathophysiology of sarcoidosis. Its prevalence is less than 40 cases per 100,000 individuals, with higher rates among females in Scandinavian countries and people of African descent. Patients are usually between 25 and 40 years of age at onset.

Presenting symptoms are usually dyspnea, persistent dry cough, erythema nodosum, subcutaneous nodules, fever, and fatigue. Sinonasal involvement is relatively rare, with reported incidences of 1% to 6%. Nasal symptoms include obstruction, congestion, rhinorrhea, anosmia, crusting, and septal perforation.

Endoscopy of the sinonasal tract will reveal mucosal changes, such as small nodules or granulation, crusts, synechia, hypertrophy, and a strawberry-like appearance. Yellowish nodules and granulation of the inferior turbinates and septum, mucosal thickening, and lysis of the septum are also present on CT scan and magnetic resonance imaging (MRI), along with a corrugated iron-like image. Epiphora and anosmia will occur when the lacrimal system or olfactory cleft, respectively, are involved. Palatal erosion can be seen in more aggressive forms, leading to oronasal fistula.

Diagnosis of sarcoidosis is based on chest X-ray (bilateral hilar lymphadenopathy) and serological findings, such as raised serum angiotensin-
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converting enzyme, hypergammaglobulinemia, and ESR. Biopsy of lesions of the affected mucosa reveals the characteristic non-caseating epithelioid giant cell granulomas.

Oral and local steroids are the mainstays of sarcoidosis treatment. Immunosuppressants, such as methotrexate or azathioprine, are also usually required. Monoclonal antibody agents targeted against tumor necrosis factor alpha, such as adalimumab and infliximab, have been used recently with very promising results.4 Endoscopic surgery for sinonasal sarcoidosis alone does not eradicate the disease nor prevent recurrence, but may help reduce symptoms. In cases of severe deformity, reconstruction of the septum may also be considered, but can be very challenging.

Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disease characterized by immune responses against intracellular antigens. Autoreactive T cells and B cells mediate inflammation and/or direct tissue damage by secreting inflammatory cytokines and anti-nuclear autoantibodies, respectively. Immune complex depositions and autoimmune vasculitis lead to destruction in almost any tissue or organ.

The most prevalent presentation of SLE is on the skin, with the characteristic butterfly-like rash on the face. Ulcers on the nasal mucosa and cartilaginous septum perforation may also be observed in less than 5% of patients. Nasal mucosa may be diffusely erythematous, edematous, or atrophic. Epistaxis, crusting, foul smell, and mucopurulent discharge often accompany the defect.

SLE is unlikely to initially present with nasal manifestations, so diagnosis should already be known when the patient is referred to the ENT specialist. Clinical features from other sites (e.g., skin, joints, heart, or renal function) and serology findings (e.g., ANA, anti-dsDNA, anti-Sm, anti-SSA, anti-SSB, hypocomplementemia, ESR, CRP) should always be considered in order to reach a definite diagnosis.

Treatment should always address the autoimmune disorder first. Hydroxychloroquine, non-steroidal anti-inflammatory drugs (NSAIDs), and steroids are usually adequate for acute SLE flares. Medications such as methotrexate may be useful in chronic lupus arthritis, and azathioprine and mycophenolate have been widely used in patients with moderately severe lupus. Nasal lesions should be treated with local care and saline rinses. Surgical intervention should only be employed for severe and annoying deformities.

Churg-Strauss Syndrome (CSS)

CSS, also known as allergic granulomatous angiitis, is a necrotizing granulomatous vasculitis that affects small to medium-sized blood vessels. The most common presentation includes asthma, eosinophilia, sinonasal infections, pulmonary infiltrates, vasculitis, and polyneuropathy. Its incidence is estimated at approximately 1-3 cases per 100,000 individuals. The age of onset tends to be the 30s.

The course of CSS can be divided into three phases. The lungs are invariably involved during the prodromal phase, presenting with asthma accompanied by allergic rhinitis, obstruction, and sinusitis, with nasal polyps present in almost 60% of patients. Nasal involvement of any kind is observed in approximately 70% of patients during the prodromal phase. The second phase is characterized by peripheral blood eosinophilia and eosinophilic tissue infiltration, while the third phase is dominated by systemic vasculitis (i.e., polyneuropathy).

CSS is characterized by eosinophilia (>10%), elevated ESR, CRP, the presence of anti-myeloperoxidase antibodies and ANCA in ~40% of patients, elevated IgE, and rheumatic factor. Diagnosis is based on clinical features, serological findings, and pathology in biopsies of affected tissue.

Treatment with systemic steroids is adequate for mild to moderate cases of CSS. In severe cases, cytotoxic agents are employed (e.g., azathioprine, cyclophosphamide, infliximab, and mycophenolate). Some patients might benefit from immunoglobulin or interferon (IFN)-a treatment. Nasal manifestations respond to classical treatment.

Sjögren’s Syndrome

Sjögren’s syndrome is a chronic inflammatory disorder characterized by autoimmune lymphocytic proliferation in exocrine glands, including the major and minor salivary glands of the airway mucosa. Extra-glandular features include cutaneous findings (e.g., xeroderma, urticaria); arthritis; pulmonary, GI, and renal involvement; and small (i.e., unmyelinated peripheral nerve) fiber neuropathy.
<table>
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<td>Necrotizing vasculitis of small and medium-sized vessels; granulomatous inflammation</td>
<td>c-ANCA, CRP, ESR, biopsy</td>
<td>&gt;80% Crusting, drainage; epistaxis</td>
<td>Steroids, cyclophosphamide, methotrexate, azathioprine, antibiotics, saline rinses, local corticosteroids, FESS, endoscopic sinus surgery (ESS)</td>
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<td>Sarcoidosis</td>
<td>Immune granulomas with non-caseating epithelioid cells</td>
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<td>Churg-Strauss Syndrome</td>
<td>Necrotizing granulomatous vasculitis affecting small to medium-sized blood vessels</td>
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<td>1-3/100,000 &gt;80% Mucosal edema; allergic rhinitis; nasal polyps</td>
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<td>Scleroderma</td>
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<td>ANA, Scl-70, anti-RNP, anti-scl-70, anti-RNP, ANA, anti-RNA, anti-centromere, anti-SSA/Ro, anti-SSB/La, RF, ANA, anti-SSA/Ro, anti-SSB/La, RF, ANA</td>
<td>1/3,000,000 &lt;5% Mucosal remodeling</td>
<td>D-penicillamine, IFN-beta, mycophenolate, cyclophosphamide</td>
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<tr>
<td>Condition</td>
<td>Autoimmune response</td>
<td>&lt;1/1,000,000</td>
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<td>Cryoglobulinemia</td>
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<td>Common Variable Immunodeficiency</td>
<td>Failure in B-cell differentiation</td>
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</tr>
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ACE: angiotensin-converting enzyme; ANA: antinuclear antibody; c-ANCA: cytoplasmic antineutrophil cytoplasmic antibody; CNS: central nervous system; CREST: calcinosis, Raynaud’s, esophageal dysfunction, sclerodactyly, and telangiectasias; CRP: c-reactive protein; CT: computed tomography; ELISA: enzyme-linked immunosorbent assay; ESR: erythrocyte sedimentation rate; FESS: functional endoscopic sinus surgery; GI: gastrointestinal; IFN: interferon; Ig: immunoglobulin; LA: lupus anticoagulans; MPO: myeloperoxidase; MRI: magnetic resonance imaging; NSAIDs: non-steroidal anti-inflammatory drugs; RF: rheuma factor; SSA: sjögren syndrome A antigen; SSB: Sjögren syndrome B antigen; TIA: transient ischemic attack.
Sjögren’s syndrome can be primary, or secondary to other underlying rheumatic conditions (e.g., SLE, rheumatic arthritis, or scleroderma). Its incidence is reportedly 0.1% to 4%; it primarily affects women, with a female-to-male ratio of up to 9:1. The onset age is during the fourth to fifth decade of life. It usually presents as Sicca syndrome, with xerostomia and enlargement of the major salivary glands accompanied by xerophthalmia and keratoconjunctivitis. Mucosal dryness and hypertrophy are also present in the sinonasal tract. Crusting, and secondary microbial infection. This condition commonly presents with fever and malaise accompanied by myalgia/arthritis. The course of the disease is characterized by the involvement of various organs with signs of progressive arthritis; transient ischemic attacks from the central nervous system (CNS); cutaneous ulcerations and nodules; GI bleeding and bowel infarction; and hepatic and renal failure. Head and neck manifestations are rare, and mostly involve sensory neural hearing loss and ulceration of the nasal and oral mucosa with bleeding and crusting.

Diagnosis of PAN is a systemic necrotizing vasculitis that affects the walls of small and medium-sized arteries, especially at bifurcation points. The elastic lamina is destroyed by the formation of fibrinoid necrosis, which leads to aneurysm development. Rupture of microaneurysms leads to hemorrhage, thrombosis, local ischemia, and infarct formation. The most commonly involved organs are the joints, muscles, central nervous system, GI tract, skin, liver, and kidneys. Because of multi-organ involvement, PAN is a potentially lethal condition if untreated. The inflammation involves men more than women, with an incidence of 1.6 to 4.6 cases per 10^6 individuals. PAN is not associated with any specific race or age.

There is currently no cure for Sjögren’s syndrome, so only symptomatic and suppressive measures can be employed. When this condition is associated with other underlying immune conditions, those conditions should be addressed accordingly, as the course of Sjögren’s syndrome will follow. Nasal rinses and optical agents for eye and mouth dryness, such as artificial saliva and tears, are usually adequate. Cholinergic parasympathomimetic agents, such as pilocarpine, are also helpful. More severe organic manifestations might require more drastic solutions (e.g., steroids, cyclophosphamide, and cyclosporine).

**Polyarteritis Nodosa (PAN)**

PAN is a systemic necrotizing vasculitis that affects the walls of small and medium-sized arteries, especially at bifurcation points. The elastic lamina is destroyed by the formation of fibrinoid necrosis, which leads to aneurysm development. Rupture of microaneurysms leads to hemorrhage, thrombosis, local ischemia, and infarct formation. The most commonly involved organs are the joints, muscles, central nervous system, GI tract, skin, liver, and kidneys. Because of multi-organ involvement, PAN is a potentially lethal condition if untreated. The inflammation involves men more than women, with an incidence of 1.6 to 4.6 cases per 10^6 individuals. PAN is not associated with any specific race or age.

This condition commonly presents with fever and malaise accompanied by myalgia/arthritis. The course of the disease is characterized by the involvement of various organs with signs of progressive arthritis; transient ischemic attacks from the central nervous system (CNS); cutaneous ulcerations and nodules; GI bleeding and bowel infarction; and hepatic and renal failure. Head and neck manifestations are rare, and mostly involve sensory neural hearing loss and ulceration of the nasal and oral mucosa with bleeding and crusting.

Diagnosis of PAN can be very difficult, and this condition should be differentiated from other forms of small vessel vasculitis. Imaging studies, including arteriography, CT, and MRI, reveal lesions on small and medium-sized vessels. When the involved tissue is accessible a biopsy should be collected from the edge of the lesion, and should include deep dermis and subcutaneous fat. Pathology demonstrates necrotizing damage to the arterial wall with mixed cellular proliferation. Nerve fibers, when included, exhibit axonal degeneration and demyelination. Serological findings may include ESR and P-ANCA, although non-specific.

Treatment solutions are guided by disease severity and organ involvement. Systemic glucocorticoids are the first-line medication, with cyclophosphamide added for more serious cases. Anti-viral agents should be considered when PAN is associated with hepatitis B. Acute GI manifestations may require surgical intervention. Lesions of the sinonasal mucosa only need local care, with rinses and tamponade if epistaxis occurs. Surgery to correct septal perforation is not recommended due to high rates of failure.

Scleroderma

Scleroderma is a connective tissue disease characterized by inflammation, progressive tissue fibrosis, and occlusion of the microvasculature by excessive production and deposition of collagen fibers I and III. It usually affects the skin (e.g., epidermal atrophy, skin thickening) but can also affect any other organ. The small blood vessels present fibrosis and
perivascular cellular infiltration with activated T cells. Its prevalence rises to approximately 200 cases per 1 million individuals; risk is 4- to 9-fold higher among women than men, with age of onset at 30-50 years.

Scleroderma presents in four forms: (1) diffuse cutaneous; (2) limited cutaneous (also known as calcinosis, Raynaud’s, esophageal dysfunction, sclerodactyly, and telangiectasias, or CREST); (3) systemic sclerosis sine scleroderma; and (4) systemic sclerosis in overlap. Head and neck manifestations usually include dysphagia, perioral and nasal skin lesions, xerostomia/xerophthalmia (Sicca syndrome), and Raynaud’s of the tongue. The nasal mucosa and overall respiratory mucosa exhibit significant changes (e.g., goblet cell hyperplasia, loss of cilia and microvilli, exfoliation of the superficial epithelial layers, and increased glandular activity).

Aside from the characteristic clinical presentation, serological tests play a very important role in the diagnosis of scleroderma. ANA are observed in more than 90% of patients; markers include Scl-70, anti-ribonucleoprotein (anti-RNP), anti-RNA, and anti-ThRNP. Imaging provides information about the state of involved organs, especially the pulmonary system (e.g., ground-glass appearance on CT). Skin biopsy will reveal extensive fibrosis, as well as increases in collagen fibers and T-cell infiltration.

There is no widely accepted treatment for scleroderma, although several agents have been tested (e.g., D-penicillamine, IFN-g, mycophenolate mofetil, and cyclophosphamide). Organ-oriented problems are addressed accordingly. Mucosal lesions in the sinonasal tract need only local care; although severe deformities of the nose may be considered surgical candidates, harvesting grafts can be very difficult.  

Relapsing Polyarthritis

Relapsing polyarthritis is a recurring cartilage inflammation that can affect any cartilaginous structure and lead to fibrosis. This condition involves the nose, auricle, larynx, trachea, and even the heart valves and large arteries. There is an autoimmune response against type II collagen fibers, with T-cell infiltration and the presence of antigen-antibody complexes. It is very rare, with an annual incidence of less than 1 per million.

Relapsing polyarthritis presents as recurring, non-erosive inflammation of the auricle and nasal cartilages, polyarthritis, and sometimes inner ear involvement (e.g., SSNHL, vertigo). Nasal chondritis is very painful, and destroys the cartilage architecture. Several recurrent episodes can lead to saddle nose deformity. The mucosa is also affected by the inflammation, becoming congested and highly friable with episodes of epistaxis, and the nose appears red and swollen.

The diagnosis of relapsing polyarthritis is based on the history of recurrence. The laboratory workup is nonspecific and aims to exclude other autoimmune diseases. Pulmonary function tests and imaging can help determine upper respiratory tract stenosis. Biopsy of the affected cartilage will reveal chondrolysis and perichondritis, with a decrease in the number of chondrocytes, and lymphocyte and macrophage infiltration. Late biopsy will reveal major destruction of the cartilage, with replacement of the cartilaginous matrix by fibrous tissue.

Treatment is the same as for common cartilage inflammation. Systemic steroid therapy is the preferred agent for controlling the acute phase, as well as for maintenance at low doses. Other medications reported to control symptoms and, perhaps, progression of the disease, include dapsone, azathioprine, methotrexate, cyclophosphamide, and cyclosporine. Reconstructive surgery should be considered when the disease is in remission and well controlled with medication. Although there is argument regarding whether to use cartilage or bony grafts, both seem to work and this decision is left to the surgeon’s experience.

Antiphospholipid Syndrome

Antiphospholipid syndrome is a very rare autoimmune disorder characterized by high levels of antibodies against the anionic phospholipids of the cell membrane. This syndrome can be primary, or it may be secondary in association with SLE or another rheumatic or autoimmune disorder. It clinically manifests as recurrent arterial or venous thrombosis in any tissue and organ, and fetal loss. Although the nose is rarely involved, nasal involvement in antiphospholipid syndrome is in the form of septal perforation.

This disorder is highly heterogeneous, as thrombosis can affect practically any part of the body. Suspicion should be raised by a history of multiple thrombotic episodes (not necessarily in the same organ) in young patients or patients that lack risk
factors for thrombosis. A history of spontaneous, late-term fetal losses or premature births of healthy children is also a suspicious finding.

Diagnosis of antiphospholipid syndrome is based on positive history with accompanying laboratory evidence. Elevated anticardiolipin (IgG or IgM), anti beta 2 glycoprotein I, and LA are considered indicative, although not specific to this condition. When dealing with a solitary attack, other studies may be needed to determine the site and magnitude of a thrombotic event (e.g., imaging and functional tests).

There is no definite treatment for antiphospholipid syndrome. The thrombotic events are handled in accordance with site and severity. Prophylactic measures include eliminating known risk factors, prescribing low-dose salicylates, and treating other immune conditions that may coexist.

**Cryoglobulinemia**

Cryoglobulinemia is an autoimmune condition characterized by high levels of serum cryoglobulins. Cryoglobulins are immunoglobulins that undergo reversible precipitation at low temperatures. The formation of cryoglobulin-containing immune complexes leads to intravascular cryoglobulin formation of cryoglobulin-containing immune complexes, allowing clot formation prior to centrifuging. Then, the serum sample should be incubated at 4°C. As mentioned above, the levels and composition of immunoglobulins determine the type of cryoglobulinemia. Other blood tests include RF, ESR, renal and hepatic function tests, and complement evaluation.

Depending on the site of clinical manifestation, additional imaging and functional tests may also apply (e.g., angiography, CT scanning, echocardiography). When possible, skin biopsy can be employed to reveal vasculitis with intraluminal cryoglobulin deposits.

The treatment of cryoglobulinemia aims to limit the serum levels of cryoglobulins, as well as any underlying condition (e.g., HCV). Another concern is the treatment of symptoms that arise from the inflammatory manifestations of the disease. NSAIDs are used for arthralgia and myalgia, while immunosuppressants (e.g., corticosteroids, cyclophosphamide, or azathioprine) are indicated for vital organ vasculitis. Rituximab is also used to control the disease, along with plasmapheresis to reduce circulating cryoglobulins. IFN-a and ribavirin may be needed for HCV control.

**Immunodeficiency**

**Acquired Immune Deficiency Syndrome (AIDS)**

AIDS, which is caused by human immunodeficiency virus (HIV), is the most widely recognized acquired immunodeficiency. HIV-1 and HIV-2 are retroviruses of the Retroviridae family. They are enveloped, single-stranded, RNA viruses with an integrated DNA intermediate that is integrated into the host DNA and persists there as a provirus. The HIV infection attacks the CD4 T-helper cells, causing a significant decline in their population and an inversion of the normal CD4/CD8 ratio. Antibody production by B cells is thereby deregulated, leading to impaired immune responses to certain antigens. HIV is a bloodborne, sexually transmitted virus. Infection can occur through sexual intercourse, intravenous drug administration with shared needles, mother-to-child transmission during birth or lactation, and uncontrolled blood transfusion. Its incidence is higher among males, homosexuals, drug addicts, and patients that receive multiple blood transfusions. The United Nations estimated that approximately 33.4 million people were in-
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infected with HIV globally in 2008, with region-dependent variations in incidence.

HIV infection develops through three phases. Acute seroconversion, which takes place weeks to months after initial infection, is characterized by the creation of a provirus reservoir with a very high viral load and very low CD4 count. During the same period of time, the CD8 response is initiated and anti-HIV antibodies help lower the viral load and return the CD population to near normal. Only general symptoms are likely to develop (e.g., fever, flu-like syndrome, and lymphadenopathy).13 The second stage, known as the asymptomatic phase, can last from months to years. During the asymptomatic phase, no clinical evidence of the disease is present and the viral load remains steady; however, the CD4 count steadily drops. Fully developed AIDS is the third phase of HIV infection. The immune system is heavily impaired, with a CD4 count at or below 200 CD4+ cells/µl. This impairment predisposes the patient to a much higher risk of opportunistic and recurrent infections, even by otherwise harmless organisms, affecting almost any tissue. Sinonasal involvement can include recurrent rhinosinusitis (often of uncommon etiology), obstruction, allergic rhinitis, and neoplasms. Poor response to common therapy, uncommon pathogens in cultures/biopsies, and short intervals between relapses should raise suspicion. Characteristic malignancies (e.g., Kaposi’s sarcoma, lymphoma) should also be considered.

Diagnosis and staging are both serological and clinical. It is very important to remain highly alert, since infected individuals can remain asymptomatic for long periods. Screening for HIV is essential in blood transfusions and when assessing members of high-risk groups (e.g., homosexuals, drug addicts, health professionals, individuals who have received multiple transfusions, or individuals living in endemic areas). An enzyme-linked immunosorbent assay is the first line of detection, followed by a Western blot assay for confirmation. The most important marker, and the one directly related to the risk of opportunistic infections, is the CD4 count, with 200 CD4+ cells/µl considered the accepted cut-off. The viral load is also very important; it provides a good screen for treatment effectiveness, and is measured by nucleic acid sequence-based amplification and reverse transcription polymerase chain reaction (PCR). Other tests include viral culture, proviral DNA, PVR, and lymph node biopsy, as well as any test needed to ascertain other HIV-associated disorders.

Treatment should address the underlying immunodeficiency, as well as opportunistic infections depending on the disease phase. Highly active antiretroviral therapy (HAART) is very effective in preventing immune deterioration and restoring the CD4 population. A combination of a nucleoside analogue reverse transcriptase inhibitor with a protease inhibitor is recommended.14 Prophylaxis from opportunistic infections should aim to maintain a high level of personal hygiene, to avoid contact with pathogens, and to initiate chemoprophylaxis. When infections occur, they must be addressed aggressively with pathogen-specific agents. Although FESS may be considered for symptomatic relief of CRS, clinicians should keep in mind that a less favorable outcome is likely.

Common Variable Immunodeficiency (CVID)

CVID is a diverse condition affecting both the humoral and cell-mediated immune responses. Its basic pathophysiological feature is a failure in B-cell differentiation due to either the inability of T cells to present antigens or the inability of B cells to respond.15 The disconnect results in low levels of immunoglobulins, defective immune resistance to common pathogens, and recurrent and opportunistic infections. The prevalence of the disease is approximately 1 case per 50,000 individuals, with no sex or race predilection. Onset age shows peaks at 1-5 years of age and 16-20 years of age.16 Patients usually present with a history of recurrent infections of the upper respiratory, lower respiratory, and GI tracts. Sinonasal infections are common, exhibiting a pattern of resistance to common treatment and recurrence. Suspicion should be raised when treating such patients, especially when they report infections of other organ systems (e.g., GI tract, urinary tract). Other manifestations include autoimmune phenomena and malignancies, especially B-cell lymphoma.

Diagnosis of CVID is a combination of positive history and serological and blood count tests. Serum IgG and IgA levels are lowered, skin immunologic responses are negative, and T-cell activity is also reduced.

The first-line treatment for CVID is immunoglobulin replacement therapy. Infections should be aggressively addressed at the first sign, preferably
with an agent of known effectiveness, which should be replaced by a culture-specific agent when results are available.

**Transplantation**

Immunosuppressive preparation prior to transplantation is becoming an increasingly frequent cause of acquired immunodeficiency. Allogeneic bone marrow transplantation is particularly notorious for causing impairment of both cellular and humoral immunity. Treatment advances through three stages: induction, the perioperative phase, and maintenance. The latter phase must continue for as long as the graft remains in the host, although sometimes it can be altered.

Because there is no way to limit immuno-suppressant treatment against graft antigens alone, an unavoidable side effect is high susceptibility to opportunistic infections. Rhinosinusitis is a common entity caused by a plethora of pathogens (e.g., gram-negative bacteria, including *Pseudomonas aeruginosa* and *Serratia marcescens*; gram-positive bacteria; and various fungi). Heightened suspicion is not sufficient to protect this subgroup from opportunistic infections, and sometimes prophylactic measures should be taken.19

Diagnostic considerations are limited to effectively pinpointing the site of infection, since immunodeficiency is already known. Topics of special concern include the need to aggressively treat any infectious condition (preferably with culture-guided agents), balanced against all kinds of limitations in therapeutic measures due to the graft and immunosuppressant drugs.

**Infectious Diseases**

**Tuberculosis (TB)**

TB, caused by *M. tuberculosis*, was very common during the 19th and 20th centuries. Even though immunization programs and effective pharmaceutical treatment have suppressed the prevalence of the disease, an increase in new cases has been noted during the last years. Although TB is transmitted aerially, inhalation of mycobacteria will not lead to infection in most cases. An intermediate state can be reached in some individuals that develop latent TB infection under immune suppression. The typical histological finding is the tubercle, an epithelioid granuloma with central caseation necrosis.

Although TB predominantly affects the lungs, cases of extra-respiratory involvement (which include most other tissues) account for one-fifth of cases of TB. Cervical lymphadenopathy and laryngeal TB are the second most common presentation; there are also nasal manifestations, although these are rather rare. Rhinorrhea, nasal obstruction, septal perforation, and nasal polyps are signs of nasal TB.

TB is diagnosed using the tuberculin skin test (which employs a purified protein derivative), sputum or other specimen culture, and PCR, as well as biopsy. A thorough systemic investigation should always be performed to identify other affected sites.

Multiagent treatment is necessary, and includes combinations of isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin18. Comorbidities should be addressed accordingly.

**Leprosy**

Leprosy, or Hansen’s disease, has been known since ancient times; however, it was not until the 19th century that its pathophysiology and etiology was discovered, and proper therapeutic measures became available in the 20th century. It is caused by *M. leprae*. According to the World Health Organization (WHO), in 2004, 69 new cases of leprosy were detected and 131 individuals total reportedly had the disease. Incidence of leprosy is not correlated with sex, race, or age. It has a mean incubation period of 10 years, which makes difficult to track sources of transmission.

Leprosy is found in two forms. The tuberculoid form is expressed in patients with vigorous cellular immunity and involves the skin and peripheral nerves. Dry, hypoesthetic skin lesions exhibit very low numbers of bacteria in tissue. The lepromatus form affects the skin extensively and is observed among patients with impaired cellular immunity. Symmetric, hypopigmented macules, nodules, plaques or papules on cooler parts of the skin are characteristic, and the nose is invariably affected. Nasal involvement can present as nasal congestion, mucosal nodules, or nose bleeding, as well as collapse and saddle deformity when cartilage is involved.

Diagnosis is made by nasal smear and skin biopsy, which turn positive for acid-fast (resistant) bacilli.20 Detection of phenolic glycolipid-1 in the serum is specific for *M. leprae*. 
The WHO recommends multidrug treatment to control and eradicate the infection. The treatment regimen includes dapsone, rifampin, clofazimine, and minocycline administered weekly or monthly for several months. Post-treatment monitoring of patients is essential to prevent relapse. Nasal reconstruction can be performed after full remission of the disease.

**Syphilis**

Caused by *Treponema pallidum*, syphilis is one of the most famous venereal diseases. It can be transmitted through sexual contact, or vertically across the placenta.

Syphilis progresses in four stages: primary, secondary, latent, and tertiary. After direct exposure, the primary stage affects the lips, tongue, and nasal passages. The skin and mucosa are affected during the secondary stage, with white macules and papules especially in the nose, pharynx, and larynx. Although the skin manifestations of secondary syphilis resolve during the latent stage, patients remain seropositive. Tertiary syphilis is characterized by granuloma formation at affected sites. The clinical presentation of the disease during these four stages can mimic almost any infection or immune condition.

Nasal manifestations are nonspecific and include vestibule painless chancre, septal perforation, saddle deformity, and hard palate perforation. *T. pallidum* can only be seen under dark field microscopy. The VDRL, rapid plasma reagin, and ICE Syphilis recombinant antigen tests provide a definitive diagnosis. Penicillin remains the treatment of choice.

**Leishmaniasis**

Leishmaniasis is a parasitic disease caused by various species of *Leishmania*. It is mediated by female sandflies, and humans are only occasional hosts. After inoculation of the parasite, it enters the reticuloendothelial system and incubates within the lysosomes of macrophages for months before the development of disease. The WHO reports an annual incidence of 1.5 million in 88 countries, and especially in hot climates.

Leishmaniasis can present in four forms: cutaneous, mucocutaneous, visceral, and viscerotropic. Cutaneous leishmaniasis is characterized by painless papules that turn into ulcers that resolve within 2-12 months, leaving a scar and pigmentation changes. The exposed parts of the body are at greater risk of cutaneous leishmaniasis. The mucocutaneous form develops several years after an apparently healed cutaneous case. It is characterized by hematogenous spread to the respiratory mucosa. Necrotic lesions in the nasal mucosa leave severe, even mutilating deformity. The visceral form, also known as Kala-azar, is the most fatal. It involves the abdominal viscera, liver, kidneys, spleen, and bone marrow, leading to multi-organ failure. Finally, viscerotrophic leishmaniasis has similar multi-organ involvement, although not of the same severity.

Leishmaniasis is easily diagnosed by staining tissue samples that present the characteristic Leishman-Donovan bodies. Species-specific diagnosis is possible with PCR techniques.

Therapy is necessary only for severe forms of visceral or mucocutaneous leishmaniasis and extended cutaneous cases. Available medications include sodium stibogluconate (a 10-day course), meglumine antimoniate, and amphotericin B. Surgical intervention is not recommended for cutaneous lesions because it may exacerbate the disease; however, it may be considered to repair nasal and facial deformities when the disease is in remission.

**Rhinoscleroma**

Rhinoscleroma is a granulomatous infection of the nose and upper respiratory tract. The responsible agent, *Klebsiella rhinoscleromatis*, is a gram-negative bacillus that is endemic in the soil and is transmitted by the inhalation of contaminated droplets.

The disease progresses through three discrete stages: catarrhal, granulomatous, and sclerotic. The catarrhal stage has persistent purulent rhinorrhea with yellow crust. The granulomatous stage is characterized by nasal polyposis, septal destruction, epistaxis, and thickening of the soft palate. Affected mucosa exhibit painless nodules as far as the subglottis. The sclerotic stage marks lesion healing, leaving extensive scarring that can cause narrowing of the nasal passages. Anosmia and nasal deformity can also occur. Progression through the stages of rhinoscleroma can last many years, and its generic clinical presentation can delay diagnosis.

Cultures of tissue samples should be performed using McConkey agar as growth media, and identification should employ immunoperoxidase staining. Biopsy provides a definite diagnosis, with
characteristic Mikulicz cells, Russell bodies, and positive Warthin-Starry stain.

Treatment solutions depend on culture and sensitivity tests, but generally include streptomycin, rifampin, or tetracycline. Sometimes reconstructive plastic surgery may be needed.\textsuperscript{22}

\textbf{Fungal Sinusitis}

The nose and sinuses are exposed to fungal spores that are present in inhaled air. When local mucosa conditions are suitable, fungal rhinosinusitis can develop, presenting with symptoms and signs that do not differ from those of common bacterial sinusitis. Immunodeficiency and diabetes are two conditions often associated with dismal outcome after fungal infection.\textsuperscript{20}

Several fungal species present with nasal manifestations. These include: \textit{Histoplasma capsulatum} is communicated via inhaled spores. The resulting histoplasmosis presents as a common viral infection, but then enters a chronic phase that is characterized by dyskataposia, pharyngalgia, mucosal ulcers, and chest X-ray findings.

Blastomycosis, which is caused by \textit{Blastomyces dermatitidis}, has a more systematic course affecting the lungs, bones, and skin. Verrucoid lesions leading to scarring are characteristic. Mucosal involvement includes erythematous hyperplasia and fibrosis.

Mucormycosis is a very aggressive, potentially lethal infection. It affects patients with diabetes mellitus or immunodeficiency. After a local sinus infection with bloody rhinorrhea, it spreads locally, causing bone erosion, eye involvement, and even CNS neuropathy. A biopsy is necessary for diagnosis. The treatment of choice is surgical debridement followed by amphotericin B therapy.\textsuperscript{24}

\textit{Aspergillus} can cause a common, noninvasive sinusitis with dark nasal discharge, or a more severe invasive form like mucormycosis. A CT scan is necessary to determine the extent of erosion, and a biopsy is needed to confirm the diagnosis. Surgical excision followed by amphotericin B is the treatment of choice.

\textit{Candida} affects patients with immunodeficiency. It produces painful mucosal involvement with pseudomembrane formation. A swab culture usually provides a clear diagnosis.

\textit{Rhinosporidium seeberi} affects the mucosa of the nose, palate, and conjunctiva, producing mucous discharge and epistaxis, and later developing polypoid, friable lesions.

\textbf{Hematologic Diseases}

\textit{Rendu-Osler-Weber Syndrome}

Also called hereditary hemorrhagic telangiectasia (HHT), Rendu-Osler-Weber syndrome is an autosomal dominant disorder of tumor growth factor beta (TGF\textbeta{}), which is central to vascular formation and repair. This condition causes localized vessel wall weakness because of abnormal repair of vessel wall lesions, which leads to telangiectasia, arteriovenous malformations, and aneurysms in the mucocutaneous and visceral vessels. Onset can be delayed until the fourth decade of life.

Common presenting symptoms are recurrent epistaxis and visceral (e.g., GI, pulmonary, hepatic, and CNS) bleeding, along with visual mucocutaneous telangiectasia. A positive family history reporting at least one first-degree relative with the disease is also indicating.

Although many methods are available for symptomatic treatment, none is definite. Nasal bleeding is treated with packing, electrocautery, ND:YAG LASER ablation, and ligation or embolization of the sphenopalatine and ethmoidal arteries.\textsuperscript{23} Septodermoplasty (Saunders) can be used to repair nasal mucosa, with limited and transient results.\textsuperscript{25} Another method, developed during the 1960s and recently renewed, is nasal closure with a local mucocutaneous flap. The results are remarkable in lowering the incidence of relapse, and the procedure remains reversible.

\textbf{Multiple Myeloma}

Multiple myeloma is a form of malignancy involving proliferation of plasma cells, a type of B cell. Bone marrow infiltration by plasma cells affects almost all blood cell series, resulting in anemia, neutropenia, and thrombocytopenia. Plasma cells can also cause formation of soft tissue masses and bone lytic lesions. Overproduction of monoclonal IgG, IgA, and light chains results in impaired humoral immunity and hyperviscosity.

A common presentation is the combination of skeletal pain, infections, anemia, and renal failure. Sinonasal manifestations include recurrent epistaxis and rhinosinusitis (often fungal due to humoral immunodeficiency).\textsuperscript{26}
Diagnosis is based on history and can be confirmed by findings on complete blood count, monoclonal protein in urine, immunoglobulin levels, and CRP.

Chemotherapy, immunosuppression, and autologous bone marrow transplantation are the main therapeutic solutions. Skeletal, renal, neurological, and hematological manifestations also require treatment.

**Chronic Lymphocytic Leukemia (CLL)**

CLL is the most common type of leukemia. Bone marrow B-cell production gets out of control, which results in B cells outgrowing other healthy series and overwhelming peripheral blood with massive numbers of non-functional B cells.\(^2^8\)

CLL is commonly discovered incidentally during a random blood cell count or lymph node enlargement work-up. Humoral immunodeficiency renders the patient prone to opportunistic infections, including rhinosinusitis, while thrombocytopenia usually presents as nosebleeds.

Hematological findings and history can lead to diagnosis, which is confirmed by bone marrow biopsy. The treatment approach includes chemotherapy, immunosuppression, and autologous bone marrow transplantation.

**GI Diseases**

**Inflammatory Bowel Disease (IBD), Ulcerative Colitis, and Crohn’s Disease**

IBD is an autoimmune disease of the GI tract. Ulcerative colitis is limited to the large intestine, while Crohn’s disease can affect any part of the GI tract. Depending on the site of the intestines involved, IBD can cause irritable bowel syndrome, malabsorption, mucus and blood in the stools, and irregular bowel movements. Systemic symptoms are also common, including fever, sweating, malaise, and arthralgias.

In addition to GI manifestations, extra-intestinal involvement occurs in almost 20% of patients, and can include anemia and osteoporosis due to malabsorption, uveitis, erythema nodosum, arthritis, and aphthous stomatitis. Nasal manifestations include chronic rhinosinusitis. It can present as nasal drip, obstruction, nosebleeds, septal perforation, and sometimes even precedes the actual intestinal manifestations.\(^2^9\)

There is no specific diagnostic tool, and diagnosis is based on history, stool studies, histological findings, and serological testing. Treatment is symptomatic and can include aminosalicylates, steroids, azathioprine, and antibiotics (e.g., metronidazole, ciprofloxacin).

**Endocrine Disorders**

**Thyroid Disease**

Thyroid gland disorders affect the metabolism of the whole body, with signs and symptoms arising in almost every organ. The nose is affected, especially in hypothyroidism, presenting blockage, rhinorhea, and recurrent rhinitis.\(^3^0\) These manifestations have been shown to resolve after proper hormonal therapy.

**Pregnancy**

During pregnancy, the altered hormonal environment leads to substantial changes in mucosa and the immune reaction. Rhinitis is very common among mothers-to-be, presenting with very annoying obstruction, rhinorhea, and nasal bleeding. Allergic subjects experience an increase in allergen sensitivity during pregnancy. Only conservative treatment can be offered during pregnancy, including nasal lavage and corticosteroids.\(^3^1\)

**Conclusion**

Sinonasal signs and symptoms are very common among patients with a highly heterogeneous group of diseases. We have reviewed such systemic conditions in an effort to emphasize their distinguishing characteristics, provide diagnostic tools, and guide proper treatment. Thorough knowledge of and alertness for such conditions is key to successfully addressing difficult sinonasal cases.

**References**


