Romanian Journal of Rhinology, Vol. 4, No. 14, April-June 2014

LITERATURE REVIEW

Nasal manifestations of systemic diseases – a literature review

Codrut Sarafoleanu, Claudiu Manea
ENT&HNS Department, "Sfanta Maria" Hospital, Bucharest, Romania
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Multiple systemic diseases may have an expression in the sinonasal area, developing various, slow and atypical clinical manifestations, difficult to diagnose. An increased index of suspicion on behalf of the otolaryngologist and also a good multidisciplinary collaboration is required in order to establish a correct diagnosis and to treat this kind of pathology.
This article is a review of the most common clinical entities with sinonasal manifestation, emphasizing on the diagnosis and therapeutic algorithm used for each pathological entity.
KEYWORDS: granulomatous diseases, Wegener's granulomatosis, sarcoidosis, Churg-Strauss syndrome, mucociliary diseases

INTRODUCTION

Although nowadays the incidence of systemic diseases affecting the upper airway appears to be increasing, the diagnosis is being made earlier because of the heightened degree of suspicion on the part of otolaryngologists, as they play an important role in the early and differential diagnosis of these diseases. A thorough clinical examination and paraclinical evaluation as well as a multidisciplinary approach are essential for the diagnosis and treatment of these illnesses[1,2].

Multiple systemic diseases may have an expression in the sinonasal area developing various, slow and atypical clinical manifestations, difficult to diagnose. Evaluation of such patients must consider the multisystemic effects of these pathologies and combine the exhaustive clinical examination and the thorough anamnesis with a multidisciplinary approach. There are two ways of dealing with such disorders: understanding the pathophysiology of the systemic diseases and using the specific diagnostic tools necessary to confirm or rule out different diagnoses[2].

Systemic diseases with rhinosinusal symptoms can be divided in inflammatory, infectious, malignant and genetic. The nasal signs that may lead us to search for a systemic disease, even if they are not pathognomonic or specific, are the presence of crusting, septal perforation and a granular mucosa. Also, we should expect for a head and neck manifestation in the patients with primary antibody deficiencies, uncontrolled diabetes mellitus, leukaemia, AIDS, bone marrow or organ transplantation[3].

In this literature review, we will try to present the most common systemic diseases with sinonasal manifestation, emphasizing on the diagnosis and therapeutic algorithm used for each pathological entity.

GRANULOMATOUS DISEASES

There are several granulomatous diseases that may cause head and neck manifestations, characterized by a local inflammatory response mainly in the upper nasal passages. These include Wegener's granulomatosis (WG), the most common of them, Churg-Strauss syndrome (CSS) and sarcoidosis[3].

The key element of granulomatous condition is, of course, the presence of a granuloma containing macrophages, epithelioid cells and multinucleated giant cells. Unfortunately, this histologic configuration is

Corresponding author: Codrut Sarafoleanu, MD, PhD, Professor of Otorhinolaryngology
email: csarafoleanu@gmail.com

encountered in a number of ***infective***, ***inflammatory*** and ***neoplastic*** conditions that complicates in this way the differential diagnosis (Table 1).

Wegener's granulomatosis

The WG is a systemic disease characterized by necrotizing granulomas with vasculitis of the upper and lower respiratory tract, systemic vasculitis, and focal necrotizing or proliferative glomerulonephritis[5]. It is the most common granulomatosis, its prevalence being estimated around 3/100000 and the mean age is 55 years[6]. Rhinologic symptoms may include nasal congestion, rhinorrhea and anosmia that may progress to rhinitis, sinusitis, septal perforation or nasal airway stenosis. Nasal endoscopy reveals mucosal cobblestoning, edema and crusting[7].

The classic triad of WG includes the upper respiratory tract, lungs and kidneys. There are three types of WG (Table 2): type 1 is the limited form, type 2 indicates a patient with more systemic symptoms and type 3 involves multiple organs such as airway, lungs and kidneys, and sometimes may be accompanied by cutaneous lesions[1,8]. Patients with type 1 present upper respiratory tract infection for several weeks, unresponsive to antibiotics and with serosanguineous nasal drainage and pain especially over the dorsum of the nose[3]. Of particular notice are the large nasal crusts in both nostrils. This severe crusting is not seen in other disease than WG[1]. The nasal symptoms involved in type 2 are similar to type 1, but, in this case, there is also a pulmonary involvement shown by hemoptysis and the cavitating lesions on chest radiographs[1]. In type 3,

Table 1
Classification of granulomatous diseases (adapted after Howard D.J and Lund V.J.[4])

	Infective	Inflammatory	Neoplastic
Bacteria			
Tuberculosis	Myobacterium tuberculosis	Wegener's granulomatosis	T-cell lymphoma (Midline lethal granuloma)
Leprosy	Myobacterium leprae	Sarcoidosis	
Rhinoscleroma	Klebsiella rhinoscleromatis	Churg-Strauss syndrome	
Syphilis	Treponema pallidum	Cholesterol granuloma	
Actinomycosis	Actinomyces israelii	Eosinophilic granuloma	
Fungal			
Aspergillus	Asp. Fumigatus, flavus, niger		
Zygomycosis	Conidiobolus coronatus		
	Rhizopus oryzae		
Dermatacietes	Curvularia		
	Alternaria		
	Bipolaris		
Rhinosporidiosis	Rhinosporidiosis seeberi		
Blastomycosis	Blastomyces dermatitidis		
	Cryptococcus neoformans		
Histoplasmosis	Histoplasma capsulatum		
Sporotrichosis	Sporotrichum schenckii		
Coccidioidmycosis	Coccidioides immitis		
Protozoa			
Leishmaniasis	Leishmania spp.		

there is a cutaneous involvement represented by tick-bite-like lesions of the lower limbs and renal involvement with hematuria and abnormal urinary sediment or renal failure[1]. WG may concern the orbits alone or in conjunction with nasal involvement and the nasolacrimal duct, which may be obstructed due to ethmoid and nasal disease[9,10].

The positive diagnosis of WG is provided by erythrocyte sedimentation rate, hemoglobin, serum creatinine and cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) in conjunction with nasal biopsy[3]. Immunofluorescence distinguishes c-ANCA for anti-PR3 from perinuclear antineutrophil cytoplasmic antibody (p-ANCA) for antimyeloperoxidase[11]. The high sensitivity and specificity of c-ANCA for WG may preclude the need for biopsy and may be used as an indicator of disease relapse. However, a negative result does not exclude the diagnosis of WG. Nasal biopsy offers supportive evidence for the diagnosis, as long as the nasal crusts and the tissue from the septum, nasal floor and turbinates are removed in order to provide ample tissue for stains and culture (useful to rule out granulomatous agents like fungi and mycobacteria)[12].

There are some disorders mimicking WG, such as nasal cocaine abuse. The patient presents isolated, large septal perforation with total normal nasal mucosa, inflamed and crusty edges of the perforation. There is no history of nasal trauma or previous surgical procedures and also nonspecific biopsy results, normal results in blood tests and negative ANCA results. There are also other entities causing midface destruction or midline granulomas like lymphomas, carcinomas and infectious processes[13] (Table 3).

Table 2
Clinical features of Wegener Granulomatosis (adapted after McCaffrey[3])

WG type	Clinical features
Type 1	• upper airway symptoms • few systemic findings. • several weeks of symptoms after a respiratory tract infection unresponsive to antibiotics. • associated with nasal pain and serosanguineous rhinorrhea and crusting.
Type 2	• initial presentation similar to type 1 • systemic features • prolonged upper respiratory tract infection with nasal discharge, nasal pain, tenderness, serosanguineous discharge, ulceration and crusting. • pulmonary involvement associated with cough, hemoptysis and cavitary lesions on chest x-ray.
Type 3	• widely disseminated form with: ▪ upper and lower airway involvement, ▪ cutaneous lesions, ▪ progressive renal involvement. • systemic features are more profound with nasal ulcerations and symptoms.

Table 3
Differential diagnostic between T-cell lymphoma and Wegener's granulomatosis (after Strickler J.G.)[14]

	T-cell lymphoma	Wegener's granulomatosis
Distribution of the ulceration	Focal, localised and explosive	Diffuse ulceration
Systemic features	Lung infiltrates Otologic, tracheal and renal	Lung infiltrates
Morphologic examination	Polymorphic lymphoid infiltrate with angioinvasive features	Vasculitis

Immunosuppression uses agents like cyclophosphamide (2 to 200 mg/kg/day), methotrexate (0.25 mg/kg/w to 25 mg/w) and/or glucocorticoids (prednisone 0.5 to 1 mg/kg/day). Daily cyclophosphamide is used in life- or major organ-threatening disease. Methotrexate and Azathioprine are an alternative to cyclophosphamide in Type 1 patients and are also used to sustain remission. Glucocorticoids (prednisone) are given concurrently with cyclophosphamide or methotrexate. Trimethoprim-sulfamethoxazole has the role of preventing relapses and has minimal side effects[1,3,15-17]. Rituximab has been proven to be effective in treating resistant WG[18].

Local treatment is often necessary and consists of upper airway hygiene, local antibiotics and nasal irrigation using water picks or customized irrigation systems. These methods lead to the reduction of nasal Staphylococcus aureus colonization that otherwise is associated with a higher rate of disease relapse[19]. Antibiotics or lubricants like glyceryl monooleate would be applied within the outer one-third of the nasal vestibule for reducing symptoms from dry mucosa. If there is severe destruction of the nasal structures, the large crusts must be mechanically removed. Oral antibiotics are necessary for recurrent rhinosinusal infections[20].

Surgical treatment is best to be considered when disease is controlled and the glucocorticoids doses are minimal, excepting severe symptoms that need prompt relief or diagnosis. Repair of septal perforations is not recommended because the risk-benefit ratio favours the risk[21].

Sinus surgery, endoscopic or by external approach, includes removing diseased tissue, restoring natural drainage and/or obtaining tissue to aid in diagnosis[22].

Saddle nose deformity repair may be a therapeutic challenge due to the possibility of graft resorption and a worse deformity than the original one. This is more common in patients that were not in remission or that did not minimized medication before surgery[23].

Sarcoidosis

Sarcoidosis is a chronic systemic granulomatous disease involving almost any organ in the body, like lymphatic system, lungs, liver, spleen and bones[3,8]. Although, sinonasal involvement is a rare disease manifestation of sarcoidosis[24], it is of our interest because of its predilection to involve many head and neck organs[8]. Nasal involvement of sarcoidosis can be external or internal and is observed in about 1-6% of patients with sarcoidosis, and may be the first manifestation of this disease. In 10% of cases, there is a progression to pulmonary fibrosis, although the clinical course is usually benign with spontaneous resolution within 2 years. 90% of patients may have enlarged intrathoracic lymph nodes or pulmonary parenchymal infiltrates and 40% of patients may have granulomatous changes in extrapulmonary organs[3].

The pathogenesis of sarcoidosis results from exposure to environmental agents in a genetically susceptible host. The most commonly associated genes are class I HLA-A1 and –B8 and class II HLA-DR3, the inheritance being polygenic. The disease begins with an alveolitis consisting of T cells that elaborate chemotactic factors that attract monocytic cells, which transform into epithelial cells[25,26]. These cells form the granuloma that may lead to fibrosis[1]. This granuloma has not a specific histologic feature, similar ones occurring in tuberculosis, berylliosis, leprosy, hypersensitivity pneumonitis, fungal disease and chronic inflammatory processes[27,28].

Externally, the patient may present papular lesions on the nose that can coalesce to form bluish-red swellings. These lesions are firm and elastic when palpated and involve the entire thickness of the dermis. There is another form of nasal sarcoidosis called *lupus pernio* that describes violaceous cutaneous lesions on the cold-sensitive areas such as the nose, cheeks, ears and fingers[29].

Intranasal involvement consists of diffuse nasal crusting or a vasomotor-like appearance to the nasal mucosa, causing diffuse mucosal swelling of the septum and inferior turbinate. Also, one may note the characteristic yellow color of submucosal nodules that are the equivalent of the intramucosal granulomas seen in mucosal biopsies. The most frequent signs and symptoms that may be present are nasal polyps that are friable and bleed readily, epistaxis, nasal crusts, dyspnea, epiphora, nasal pain and anosmia[3,30].

Paranasal sinus involvement is represented by mucous membrane thickening or opacification and destruction of the nasal bones, appearing like osteoporosis or zones of frank destruction[31].

To make the diagnosis of sarcoidosis, three criteria must be fulfilled: the compatibility of the clinical and radiographic findings with sarcoidosis, noncaseating granulomas and other causes for granulomatous changes excluded[1]. Biochemical data involves elevated serum or urinary calcium and elevation of angiotensin-converting enzyme (ACE). ACE converts angiotensin 1 in angiotensin 2 and is correlated with the clinical activity of sarcoidosis in 83% of cases. Therefore, it is useful for both the diagnosis and the monitoring of sarcoidosis. It is important to know that ACE levels can also be elevated in tuberculosis, lymphoma, leprosy and Gaucher's disease. Histologic findings confirm the clinical diagnosis by the presence of noncaseating granulomas in the nasal mucosa. Sinus CT and x-ray are abnormal, as well as the pulmonary x-ray that may reveal hilar lymphadenopathy or pulmonary fibrosis[3]. Gallium-67 uptake is elevated in the nasal mucosa because the isotope is taken up in the inflammatory tis-

sues and accumulates there, remaining yet nonspecific[1,32].

The management of sarcoidosis consists of systemic corticosteroids. In stage 1 pulmonary involvement, "watchful waiting" with periodic examinations is indicated[1]. The stage 2 and 3 patient with no spontaneous improvement or that show worsening 6 months after diagnosis will usually require treatment. 10 to 40 mg per day of prednisone will control the symptoms[1,33]. The oral dosage may be reduced by using intranasal steroids[3]. In patients unresponsive to corticosteroids or if there are contraindications to the use of systemic corticosteroids, methotrexate may be used at a dose of 30 mg weekly[34].

Unfortunately, despite systemic immunosuppressive treatment and repeated sinus surgery, the clinical course of sinonasal sarcoidosis can be complicated by relapse[25].

Churg-Strauss Syndrome (allergic granulomatosis angiitis)

It is defined as an eosinophil-rich, granulomatous inflammation and necrotizing vasculitis of the upper respiratory tract, affecting small to medium vessels associated with asthma, allergic rhinitis, nasal or sinus polyps and eosinophilia[1,35]. CSS is rare and its prevalence is not known, but it affects all age groups and has no gender predilection[36]. ENT features are common in CSS, sinusitis being one of the major manifestations and may precede the diagnosis in 60% of patients[37].

There are three phases:

1. a prodromal phase consists of allergic disease (allergic rhinitis, nasal polyposis)
2. peripheral blood and tissue eosinophilia (eosinophilic pneumonia or gastroenteritis)
3. a life-threatening systemic vasculitis.

Although CSS may be similar to WG, it distinguishes from WG by the presence of nasal polyps and asthma and by not having the diffuse mucosal destruction that typifies WG[1]. In addition, the p-ANCA is positive in 70% of patients, while c-ANCA is negative. The differential diagnosis with sarcoidosis may be made by the presence of asthma, eosinophilia and vasculitis with necrotizing granulomas that are absent in sarcoidosis[37].

The management of CSS is represented by glucocorticoids as standard treatment. CSS does not respond to cyclophosphamide, as does WG, but may be used in life-threatening disease or in poor prognostic cases[1,38].

CUTANEOUS DISEASES

Although nasal findings in autoimmune or collagen-vascular disorders are uncommon, there are a few disorders with nasal manifestations that may be mentioned, like pemphigus vulgaris and pemphigoid[3].

Pemphigus vulgaris

It is a mucocutaneous bullous disorder characterized by nonscarring bullous dermatitis involving the oral cavity and the nasal mucosa as head and neck manifestation of this disease. Its origin is presumed to be autoimmune[39].

The clinical features involving the nasal mucosa are present in 10% of all patients and include desquamative ulcerative lesions and ulceration with anterior perforation of the septum. Also, it has been noticed that the external nose is more likely to be affected.

The medical treatment consists of steroids combined with other immunosuppressant drugs[3].

Pemphigoid

Presumed to be an autoimmune disease, the pemphigoid is characterized by blisters and scars. Therefore, it is divided into two categories represented by bullous pemphigoid affecting the skin and cicatricial pemphigoid affecting the mucosa[40].

The nasal findings occur in 25-50% of patients and involve the anterior nasal region as painful ulcerative crusting. The scar formation is found more frequently in the nasal valve area, but it may also affect the nasopharynx. If the scarring is bilateral, it can lead to partial or total nasal obstruction[41].

The treatment includes Dapsone and/or immunosuppressive agents, and is usually managed by the dermatologist[3].

MUCOCILIARY DISEASES

Normal mucociliary function in the nose is oriented toward the nasopharynx except for the anterior end of the septum and its direction is independent of the body position. The mucociliary system plays an essential role in the nose and paranasal sinuses defense mechanism against infection. This is seen in the effects of mucociliary deficiencies in dysfunctional cilia syndrome and cystic fibrosis[3,40].

Primary Ciliary Dyskinesia

It is a chronic respiratory tract disease beginning in childhood, as an autosomal recessive disease, and which can express by chronic rhinitis, sinusitis, bronchiectasis, chronic cough, otitis media and sterility[42].

The diagnostic may be revealed after the saccharin test or after the morphologic studies of the ciliated epithelium[3]. Through brushing or biopsy, we may observe the ciliary movements on photometry or their appearance on electronic microscopy.

The medical treatment uses antibiotics and nasal irrigations.

Surgery is indicated for chronic or recurrent infections. But, even if it establishes an appropriate drainage pattern, the antibiotics and nasal irrigations will still be necessary for a proper control of the disease[3].

Cystic Fibrosis

It is an autosomal recessive disease affecting the mucous component of mucociliary transport, unlike the ciliary dyskinesia, in which the cilia themselves are affected.

Clinical features of cystic fibrosis include chronic lung disease, chronic sinusitis and pancreatic insufficiency, and the diagnosis is confirmed by the sweat chloride test[43].

The nasal symptoms specific for cystic fibrosis include intermittent nasal obstruction, clear and thick rhinorrhea, nasal polyps, grayish-green putty-like material in the sinuses made by *Pseudomonas aeruginosa* and *Staphylococcus Aureus* as the most frequent germs[3].

The purpose of the treatment of the nasal symptoms is to maintain a patent airway and to prevent infection at the same time. That is why it comprises long term antibiotics and nasal irrigations[3].

Even though the nasal polyp and sinus surgery have controversial benefits, they may be indicated in cases of failed medical management, depending upon the degree of nasal obstruction, the severity of sinusitis symptoms and the motivation of the patient and family[3].

EXTRANODAL NK/T-CELL LYMPHOMA NASAL TYPE (ENKL)

Lymphomas represent 3-5% of all malignant tumors. 60% of lymphomas are Non-Hodkin type. The rhinosinusal localisation of this T-cell lymphoma is rare and uncommon[44].

Extranodal NK/T-cell lymphoma (ENKL) represents about 75% of the rhinosinusal lymphomas, 25% being B-cell lymphomas. It is observed in adults, but it may affect children too, with a male to female ratio of 2:1 to 3:1. The etiology is indefinite; Epstein-Barr virus (EBV) is found in most cases of NK-cell leukaemia/lymphoma, first in 1990[45]. However, the oncogenic role is not reliable because patients may have polyclonal or biclonal populations of malignant cells, malignant cells based on differential EBV genome incorporation[46,47].

The first case of face and midline destruction was described in 1897 by McBride[48]. ENKL is characterised by aggressive, necrotizing lesions of cartilage, bone and soft tissues, the predominant location being in the nasal cavity.

The clinical manifestation of the early stages includes: nasal obstruction, foul smelling, chronic purulent rhinorrhea, serosanguineous discharge, pain. As symptoms progress, perforation of the septum occurs in 40% of cases, swelling of the soft palate may precede the necrotic ulcerate lesions of the midline position, oronasal fistula being a consequence of the palatal destruction. The mucosa is often pale, friable with extensive crusting. Systemic symptoms such as malaise, night sweats, febrile episodes and arthralgias are typically noted in advanced cases[49].

The key of the diagnosis of the T-cell lymphoma is the nasal biopsy. The Laboratory workup is similar to that for Wegener granulomatosis and includes HIV testing[49].

Diagnosis of malignant lymphoma is frequently dependent on the identification of atypical hematopoietic cells amid an intense inflammatory, necrotic and degenerating cellular milieu. Under these conditions, it is essential that the biopsy be of sufficient size and adequate technical quality in order to allow the identification of atypical cells[49].

Histopathological examination of the lesion exhibits a polymorphic lymphoid infiltrate with mature, immature and atypical lymphocytes, histocytes and eosinophils and macrophages. The infiltrate is characterized by angiocentricity and angioinvasion, and can lead to vessel occlusion and local tissue infarction, causing the rapid tissues necrosis and ischemia[49].

The treatment depends on the extension of the tumor. For the localized disease, the treatment was for many years radiotherapy alone, but the 5-year overall survival is approximately 50%. Now, the treatment consists of a short irradiation of 50 Gy, followed by chemotherapy, with an increased 5-year overall survival (70%)[49].

In disseminated disease or relapses, the chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone or third-generation anthracycline-containing regimens are used, but most patients respond poorly and die within several months[48].

A phase I trial of a new combination of chemotherapy named SMILE has started. SMILE is a treatment based on steroid hormone, methotrexate, ifosfamide, L-asparaginase and etoposide and is a dose-finding study for methotrexate and etoposide[45].

IMMUNODEFICIENCY DISEASES

The immunodeficiency diseases with rhinosinusal manifestation can be represented by AIDS or iatrogenic immunodeficiency (resulting from chemo / radiotherapy)[50].

AIDS is a chronic incurable disease caused by a HIV, a retrovirus of the family Lentivirus characterised

by a progressive immune deficiency with the affectation of CD4 lymphocytes. The infection has 3 stages: A - primary HIV infection (>500CD4/mm3, >29%) B - symptomatic infection (200-499CD4, 14-29%), C - AIDS (<200CD4/mm3, <14%)[51].

The complications of AIDS are represented by opportunistic infections such as bacterial infections, fungal sinusistis and chronic rhinitis[52]. Rhinosinusitis is common in HIV-infected patients, with a reported prevalence of between 20 and 68%[52].

The **bacterial infection** is usually due to the same pathogens affecting the general population (Streptococcus pneumoniae, Moraxella catarrhalis and Haemophilus influenzae), with more subtle clinical signs, an antibiotic treatment being always necessary. HIV-infected patients do seem to have a higher incidence of Staphylococcus aureus and Pseudomonas aeruginosa cultured from patients with acute and chronic sinusitis, often in association with anaerobic bacteria[53-56]. The complications of rhinosinusal infection in a patient with AIDS are periorbital and orbital abscess; in these cases, a surgical treatment may be applied[50].

Fungal sinusitis are caused by Aspergillus sp. and Mucor sp., which in immune deficiency state have an invasive, rapid manner to cause facial cellulitis, gangrenous mucosal changes in the nose and paranasal sinuses, obtundation, cranial nerve palsies, vision loss and proptosis. The pacients accuse bloody nasal discharge, facial pain and swelling, fever and edema[57].

The clinical examination reveals pale or gray mucosa of the nasal cavity, palate or the classic black middle turbinate and destructive bony lesions can be observed on the CT scan[58].

The treatment of fungal sinusitis consists of amphotericin B systemically and nasal irrigations (voriconazole and posaconazole) after a biopsy or a culture confirmed Mucor or Aspergillus. If the patient can tolerate a surgical intervention, it is highly recommended an aggressive surgical debridement[50].

Chronic rhinitis is the most common nasal manifestation of AIDS. Patients present with partial obstruction, pain, nasal congestion, crusting and drying. The infectious agents that cause rhinitis are Streptococcus pneumoniae, Haemophilus influenzae, Legionella pneumophilia, Alternaria, Cryptococcus neoformans, and Acanthamoeba castellanii, CMV, and the treatment is based on antibiotics and decongestants, after an antral lavage and culture[52].

Allergic rhinitis is very frequent too, twice as common in HIV as in the general population, determined by the increased circulating immune complexes with increased production of IgA, IgG and IgE, produced by polyclonal B-cell activation[59].

Allergic rhinitis can be treated with topical nasal steroid sprays, second-generation antihistamines or ipratroprium bromide, a topical anticholinergic spray[59].

INFECTIOUS SYSTEMIC DISEASES

Rhinoscleroma is a chronic granulomatous bacterial disease of the upper respiratory tract, determined by Klebsiella Rhinoscleromata[60]. Rhinoscleroma is endemic to areas of Africa, South-East Asia, Mexico, Egypt, Central and South America, and Central and Eastern Europe, and it has been associated with low socioeconomic status[61].

The stages of the infection are: catarrhal stage – long lasting foul-smelling, purulent rhinorrhea, atrophic stage – large nasal plaques or crusts (foul smelling and simulating atrophic rhinitis), granulomatous stage – multiple granulomatous nodules in the nose, pharynx, larynx, trachea or bronchi, fibrosis and stenosis – may evolve with the complete stenosis of the nostrils and may extend to the nasopharynx and trachea[1].

Rhinoscleroma's diagnosis is based on identification of the Mikulicz's cell in biopsy specimens; it is pathognomonic and is represented by a large, foamy histiocyte[62]. The disease is difficult to cure and prone to recur; currently a combination of surgical debridement and long term antibiotic therapy are recommended[62]. The antibiotic treatment consists of Streptomycin (1 g/day for 4 weeks) and tetracycline (2 g/day). The cure rate is about 60-70% and it is not improved by radiotherapy or corticosteroids.

Tuberculosis is a chronic, with worldwide prevalence granulomatous infection disease caused by Mycobacterium tuberculosis and Mycobacterium bovis[63], less often. M. tuberculosis is an aerobic, non-spore forming bacillus, with a thick cell wall, resistant to common antibiotics[64]. The nasal localization of the infection is very rare, so, it may fail to be suspected and the diagnosis is often delayed[1]. Destructive tuberculomas in the nasal cavity are part of the differential diagnosis for other destructive lesions such as Wegener's granulomatosis or lymphoma[63]. The diagnosis starts with a Mycobacterium tuberculosis culture, on Lowenstein-Jensen or Middlebrook culture medium, smears and cultures for acid-fast bacilli, histopathological examination of a biopsy specimen. The definite diagnosis is established on the basis of the results of nasal mucosa biopsy[64].

In early stages, nasal tuberculosis determines partial obstruction, pain, crusting, nasal bleeding and nasal discharge. The nasal examination reveals a red, nodular thickening, with or without ulceration, sometimes with septal perforation, on the anterior part of the septum or turbinates[1].

The treatment strategies of tuberculosis are represented by a combination of 3 or 4 antituberculosis an-

tibiotics (isoniazid, rifampicin, ethambutol, pyrazinamide), for 6 - 9 months, combined with local treatment such as alkaline antiseptic solutions irrigations with hydrogen peroxide tampons for crusts, acids such as lactic, trichloracetic and chromic applied on the ulcers, and use of galvanocautery and diathermy for destruction of the lesions[65]. Failure occurs due to primary drug resistance or because of the nonadherence to the long-term therapeutic regimen[64].

Syphilis is an infectious venereal disease caused by the spirochete Treponema pallidum, transmissible by sexual contact with infectious lesions, which progresses through 4 stages: primary, secondary, latent and tertiary[66].

The nasal lesions have a multi-site location: in the nose, the external nose, the nostrils and on the tip of the nose. They are very tender, swollen, congested, and can lead to septal perforation accompanied by thin watery discharge[67].

The diagnosis is difficult because syphilis can mimic other infections and immune-mediated processes in advanced stage. TPHA (Treponema Pallidum Haemagglutination Assay) is the specific test for syphilis. Syphilis is cured with antibiotic treatment with Penicillin, or, in case of allergy, Doxycycline can be used[68].

Histoplasmosis is a granulomatous fungal disease due to Histoplasma capsulatum that can involve any part of the head; the infection is made by inhalation of the spores, especially in patients with the acquired immunodeficiency syndrome (AIDS)[69].

The symptoms depend on the immunological condition and the fungal load inhaled. Most of the people with normal immune systems develop either trivial clinical histoplasmosis or are totally asymptomatic. The pulmonary symptoms consist of cough, chest pain and hoarseness, and they are accompanied by nasal manifestations like nodules or ulcers[70-72].

COCAINE ABUSE

About 11% of American adults have tried cocaine and 4 million have used cocaine in the past year[73]. The nasal complications determined by nasal administration (nasal hair loss, nasal crusting, sinusitis, epistaxis, saddle nose deformity, palatal perforation erosion of turbinates, ethmoids, loss of smell and visual acuity[74] have a 4,8% incidence[75].

Cocaine (benzoylmethylecgonine) is a naturally occurring alkaloid, a purified extract from Erythroxylum coca plant[75] that has a vasoconstrictor effect, which can lead to ischemia of the nasal mucosa and perforation of the septum, nasal abscess or the whole septum destruction.

The effects on other organs include: irritability, paranoia, restlessness, anxiety, heart attack, arrhythmia, ulcers, acute renal failure, skin infections, allergic reactions and coma[75,76].

EPISTAXIS – DIFFERENTIAL DIAGNOSIS

Long time ago called "Hippocrates' bleeding", the epistaxis is a frequent symptom among young people, but, on the other hand, it may engage the vital prognosis among the elderly, who may be weakened by a medical condition whose revealing sign may be. The approach of epistaxis must be led to show a nasal pathology or, at the same time, a vascular one, general, traumatic or a neurosurgical pathology[77].

Systemic factors contributing to epistaxis include *vascular disorders, blood dyscrasias, alcohol consumption, hypertension, various infectious diseases, vitamin deficiencies, inflammatory diseases and granulomatous diseases.* There are also several indicators significant for haemostasis disorders, such as bruising without significant trauma, prolonged bleeding after dental work or minor cuts, and unusually heavy menorrhea.

The Von Willebrand's disease is the most common hereditary bleeding disorder associated with epistaxis and can be associated with the severity of the disease. Therefore, the bleeding time must be performed as a part of the preoperative evaluation. The diagnosis is made with quantitative immunoelectrophoresis or enzyme-linked immunoassay.

Hemophilia A due to a functional defect of factor VIII and *Hemophilia B* secondary to factor IX deficiency may cause epistaxis that can be associated with the severity of the disease[78].

Factor XIII deficiency may be hereditary or acquired. Factor XIII deficiency is a rare autosomal-recessive disorder that can cause epistaxis, but only a homozygote shows the bleeding tendency. Acquired factor XIII deficiency can result from inflammatory bowel diseases and acute leukaemia[79-82].

In *the Rendu-Osler disease*, the vessels are thin-walled, without smooth muscles, and the increased angiogenesis is present; it results in vascular proliferation that may cause epistaxis by rupture of the telangiectasias and the arteriovenous malformations, even after minor trauma, such as nose blowing[78,83,84]. Epistaxis is the presenting symptom in 90% of patients diagnosed with Rendu-Osler disease, from which 62% become symptomatic by age 16 and almost all by age 40[85,86].

The management of epistaxis consists of decongestants, chemical cautery, electrocautery, nasal packing, angiography and embolization, depending on the severity of the bleeding, the cause of epistaxis and the patient's comorbidities. Of course, the underlying systemic disease should also be treated properly. These manoeuvres are well tolerated in childhood.

Micro-endoscopic surgical technique results in minimal surgical trauma, decreased surgical time and improved visualisation.

Electrocoagulation of the main nasal branches must be selective and performed by endonasal approach.

External approach is reserved for severe cases (ethmoidal arteries).

NASAL OBSTRUCTION'S IMPACT IN SLEEP RELATED BREATHING DISORDERS

Nasal obstruction may have a negative impact on sleep quality and must be considered to be a co-factor in the pathophysiology of sleep-related breathing disorders (SRBD). Patients with nasal obstruction (sensitized subjects during high allergen exposure, patients with common cold) frequently complain of poor sleep quality and daytime fatigue[87].

Many studies suggested that nasal obstruction must be considered a co-factor in the pathophysiology of SRBD, but the relation between cause and effect remains a matter of debate. The experimental nasal occlusion on sleep quality in normal subjects reveal that patients with nostrils occluded (using petroleum jelly and cotton or adhesive tapes) and carrying out polysomnographic studies report sleep quality worsened; complete nasal packing has also induced similar effects[88-90].

The experimental nasal occlusion on sleep quality conclusions are that nasal obstruction may trigger the induction of SRBD in normal individuals and nasal breathing increases ventilation efficiency by stimulating certain sensory trigeminal receptors in the nasal mucosa. Another study analyzes the relation between nasal patency and SRBD in patients with abnormal nasal patency. Miljeteig et al. studied 683 patients referred for snoring and/or apnea evaluation and assessed nasal resistance and sleep parameters. This was also confirmed by others studies[91-93].

Patients with a complaint of nasal obstruction and SRBD are at higher risk of developing OSAS. But the contribution of nasal resistance to OSAS is however weak (2.3% of the variance in the apnea-hypopnea index (AHI) was explained by nasal resistance). A correlation between Mallampati score, nasal examination and some sleep parameters was found by Liistro et al.[94,95].

Nasal occlusion and the presence of a high MS obstruction is associated with an increased risk of OSAS[94] and patients with SRBD switch more frequently from nasal to oronasal breathing during sleep if nasal obstruction is present, which can be a cause for an increase in respiratory effort and may result in alveolar hypoventilation.

CONCLUSIONS

Multiple systemic diseases may express in the sinonasal area, developing various, slow and atypical clinical manifestations difficult to diagnose.

Evaluation of such patients must consider the multisystemic effects of these pathologies and combine the exhaustive clinical examination and the thorough anamnesis with a multidisciplinary approach.

There are two ways of dealing with such disorders: understanding the pathophysiology of the systemic diseases and using the specific diagnostic tools necessary to confirm or rule out different diagnoses.

When you are facing a patient with extensive nasal crusting, septal perforation, mucoid bloody discharge, you have to be aware that you may deal with a patient with a systemic disease with nasal manifestation. In this case, the treatment of the systemic disease will have a beneficial impact over the nasal alterations.

REFERENCES

1. Mc Donald T.J. – Manifestations of Systemic Diseases of the Nose. In: Cummings C.W. -Otolaryngology-Head and Neck Surgery. 3rd ed. Mosby: Maple Vail Book Manufacturing Group, St. Louis Missouri, U.S.A., 1999;p.844-850.
2. Prokopakis E., Nikolaou V., Vardouniotis A., Jorissen M. - Nasal manifestations of systemic diseases. B-ENT., 2013;9(3):171-84.
3. McCaffrey T.V. - Nasal manifestations of systemic dieseases. Otolaryngol Pol., 2009;63(3):228-235.
4. Howard D.J., Lund V.J. – Granulomatous conditions of the nose. In: Scott-Brown's Otorhinolaryngology, Head and Neck Surgery. 7th ed. Hodder Arnold : Hodder Education, London, UK, 2008;p.1645-1659.
5. Wegener F. - Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arteriensystems und der Nieren. Beitr Pathol Anat., 1939;109:36.
6. Cotch M.F., Hoffman G.S., Yerg D.E., et al. - The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. Arthritis Rheum., 1996;39:87-92.
7. Tami T.A. - Granulomatous diseases and chronic rhinosinusitis, Otolaryngol Clin North Am., 2005;38:1267-1278.
8. McDonald T.J. - Vasculitis and granulomatous disease. In: McCaffrey T.V., editor - Rhinologic diagnosis and treatment. Thieme, New York, 1996;370-381.
9. Bullen C.L., Liesegang T.J., McDonald T.J., De Remee R.A. - Ocular complications of Wegener's granulomatosis. Ophthalmology, 1983;90:279.
10. Kalina P.H., Garrity J.A., Herman D.C., DeRemee R.A., Specks U. - Role of testing for anticytoplasmic autoantibodies in the differential diagnosis of scleritis and orbital pseudotumor. Mayo Clin Proc., 1990;65:1110-7.
11. Erickson V.R., Hwang P.H. - Wegener's granulomatosis: current trends in diagnosis and management. Curr. Opin.Otolaryngol. Head Neck Surg., 2007;15:170-176.
12. McDonald T.J., DeRemee R.A., Kern E.B., Harrison E.G. Jr. - Nasal

manifestations of Wegener's granulomatosis. Laryngoscope. 1974 Dec;84(12):2101-12.
13. Armengot M., García-Lliberós A., Gómez M.J., Navarro A., Martorell A. - Sinonasal involvement in systemic vasculitides and cocaine-induced midline destructive lesions: Diagnostic controversies. Allergy Rhinol (Providence)., 2013 Summer;4(2):e94–e99. Doi:10.2500/ar.2013.4.0051.
14. Strickler J.G., Meneses M.F., Habermann T.M., Ilstrup D.M., Earle J.D., McDonald T.J., Chang K.L., Weiss L.M. - Polymorphic reticulosis: a reappraisal. Hum Pathol., 1994;25(7):659-65.
15. Specks U. - Wegener's granulomatosis and pulmonary vasculitis. Clin Pulm Med., 1995;2(5):267.
16. DeRemee R.A., McDonald T.J., Weiland L.H. - Wegener's granulomatosis: observations on treatment with antimicrobial agents. Mayo Clin Proc., 1985;60(1):27-32.
17. Valeriano-Marcet J., Spiera H. - Treatment of Wegener's granulomatosis with sulfamethoxazole-trimethoprim. Arch Intern Med., 1991 Aug;151(8):1649-52.
18. Sanchez-Cano D., Callejas-Rubio J.L., Ortego-Centeno N. - Effect of rituximab on refractory Wegener granulomatosis with predominant granulomatous disease. J Clin Rheumatol., 2008;14(2):92-93.
19. Stegeman C.A., Tervaert J.W., Sluiter W.J., et al. - Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Ann Intern Med., 1994;120(1):12–17.
20. Villa-Forte A., Santos A.S., Hoffman G.S. – Granulomatous Diseases: Wegener's Granulomatosis, Churg-Strauss Syndrome and Nasal Natural Killer (NK)/T-Cell Lymphoma. In: Harris J.P., Weisman M.H. - Head and Neck Manifestations of Systemic Disease. New York, Informa Healthcare, U.S.A., 2007;p.97-115.
21. Rasmussen N. - Management of the ear, nose, and throat manifestations of Wegener granulomatosis: an otorhinolaryngologist's perspective. Curr Opin Rheumatol., 2001;13(1):3–11.
22. Lebovics R.S. - Sinonasal complications of vasculitic diseases. Cleve Clin J Med., 2002;69(suppl 2):SII152–SII154.
23. Congdon D., Sherris D.A., Specks U., et al. - Long-term follow-up of repair of external nasal deformities in patients with Wegener's granulomatosis. Laryngoscope, 2002;112(4):731–737.
24. Kirsten A.M., Watz H., Kirsten D. - Sarcoidosis with involvement of the paranasal sinuses - a retrospective analysis of 12 biopsy-proven cases. BMC Pulm Med., 2013 Sep 26;13:59. Doi:10.1186/1471-2466-13-59
25. Statement on Sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med., 1999;160(2):736–755. doi: 10.1164/ajrccm.160.2.ats4-99
26. Grunewald J., Wahlstrom J., Berlin M., et al. - Lung restricted T cell receptor AV2S3+ CD4+ T cell expansions in sarcoidosis patients with a shared HLA–DR beta chain conformation. Thorax, 2002;57(4):348–352.
27. Coup J., Hopper I.P. - Granulomatous lesions in nasal biopsies. Histopathology, 1980;4:293-308.
28. Waldman R.H. - Tuberculosis and atypical mycobacteria. Otolaryngol Clin North Am., 1982;15(3):581-96.
29. Arnold H.L. Jr, Odom R.B., James W.D. - Andrews' diseases of the skin: clinical dermatology. ed 8, WB Saunders, Philadelphia, 1990.
30. McCaffrey T.V., McDonald T.J. - Sarcoidosis of the nose and paranasal sinuses. Laryngoscope., 1983 Oct;93(10):1281-4.
31. James D.G., Barter S., Jash D., MacKinnon D.M., Carstairs L.S. - Sarcoidosis of the upper respiratory tract (SURT). J Laryngol Otol., 1982;96:711-718.
32. Sulavik S.B., Palestro C.J., Spencer R.P., Swyer A.J., Goldsmith S.J., Tierstein A.S. - Extrapulmonary sites of radiogallium accumulation in (sarcoidosis). Clin Nucl Med., 1990 Dec;15(12):876-878.
33. Milton C.M. - Sarcoidosis in ENT practice. Clin Otolaryngol., 1985;10:351-355.
34. Fenton D.A., Shaw M., Black M.M. - Invasive nasal sarcoidosis treated with methotrexate. Clin Exp Dermatol., 1985;10:279-283.
35. Lanham J.G., Elkon K.B., Pusey C.D., et al. - Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore), 1984;63(2):65–81.
36. Watts R.A., Carruthers D.M., Scott D.J. - Epidemiology of systemic vasculitis: changing incidence or definition? Semin Arthritis Rheum., 1995;25(1):28–34.
37. Olsen K.D., Neel H.B.I., DeRemee R.A. - Nasal manifestations of allergic granulomatosis and angiitis (Churg-Strauss syndrome). Otolaryngol Head Neck Surg., 1980;86:936-945.
38. Cohen P., Parnoux C., Mahr A., Arene J.P., Mouthon L., Le Guern V., Andre M.H., Gavraud M., Jayne D., Blockmans D., Cordier J.F., Guillecin L., French Vasculitic Study Group - Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum., 2007;57(4):686-93.
39. McCaffrey T.V. - Nasal manifestations of systemic dieseases. Otolaryngologia Polska., 2009;63(3):228-235.
40. Hanson R.D., Olsen K.D., Rogers R.S. III - Upper aerodigestive tract manifestations of cicatricial pemphigoid. Ann Otol Rhinol Laryngol., 1988;97:493-499.
41. Fleming M.G., Valenzuela R., Bergfeld W.F., Tuthill R.J. - Mucous gland basement membrane immunofluoresence in cicatricial pemphigoid. Arch Dermatol., 1988;124:1407-1410.
42. Buchdahl R.M., Reiser J., Ingram D., Ruttman A., Cole P.J., Warder J.O. - Ciliary abnormalities in repiratory disease. Arch Dis Child., 1988;63:238-43.
43. Barker P.E. - Gene mapping and cystic fibrosis. Am J Med Sci., 1990;299:69-72.
44. Neves M.C., Lessa M.M., Voegels R.L., Butugan O. - Primary Non-Hodgkin's lymphoma of the frontal sinus. Case report and review of the literature. Ear Nose Throat J., 2005;84:47–51.
45. Harabuchi Y., Yamanaka N., Kataura A., Imai S., Kinoshita T., Mizuno F., et al. - Epstein–Barr virus in nasal T-cell lymphomas in patients with lethal midline granuloma. Lancet., 1990;335:128–30.
46. Suzuki R. - Leukemia and lymphoma of natural killer cells: Review. Hematopathol. 2005;45:51–70.
47. Batra P., Shah N., Mathur S. - Midline lethal granuloma - A clinical enigma. Indian J Dent Res., 2003;14:174–83.
48. Ratech H., Burke J.S., Blayney D.W., Sheibani K., Rappaport H. - A clinicopathologic study of malignant lymphomas of the nose, paranasal sinuses and hard palate including cases of lethal midline granuloma. Cancer., 1989;64:25–31.
49. Metgud R.S., Doshi J.J., Gaurkhede S., Dongre R., Karle R. - Extranodal NK/T-cell lymphoma, nasal type (angiocentric T-cell lymphoma): A review about the terminology. J Oral Maxillofac Pathol., 2011 Jan-Apr;15(1):96–100.
50. Katsivas T.F. - Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome. In: Harris J.P., Weisman M.H. -

Head and Neck Manifestationsof Systemic Disease. New York, Informa Healthcare, U.S.A., 2007: 229-251.
51. Rubin J.S, Honigberg R.- Sinusitis in patients with the acquired immunodeficiency syndrome. Ear Nose Throat J. 1990 Jul;69(7):460-3[PubMed ID: 2205470]
52. Loulergue P. - The HIV infection. In: Karila L. - Books de ECN. Roumanian edition. "Iulia Hateganu" University Medical Publishing, Cluj Napoca, Roumania, 2011;p.325-328.
53. Greenspan D., Schiodt M., Greenspan J.S., et al. - Aids and the Mouth: Diagnosis and Management of Oral Lesions. Copenhagen: Munksgaard, 1990.
54. Sooy C.D. - Impact of AIDS on otolaryngology head and neck surgery. In: Meyers E.N., ed. Advances in Otolaryngology Head and Neck Surgery. Vol 1. Chicago: Year Book 1987;p.1-27.
55. Milgram L.M., Rubin J.S., et al. - Sinusitis in human immunodeficiency virus infection: Typical and atypical organisms. J Otolaryng., 1994;23(6):450-453.
56. McDonald T.J. - Nasal manifestations of systemic diseases. In Cummings C.W., editor - Otolaryngology Head and Neck Surgery, 4th ed, Philadelphia, 2005, Mosby;p.338-342.
57. Maisel R.H. - Sinusitis in the immunocompromised patient. In McCaffrey T.V., editor - Systemic Disease and the Nasal Airway, 1993, Thieme;p.874-878.
58. Tami T.A., Lee K.C. - Otolaryngologic Manifestations of HIV. In : HIV In Site Knowledge Base Chapter. August 1998 Available at http://hivinsite.ucsf.edu/InSite. Accessed 03.03.2014
59. Bailhache A., Dehesdin D., François A., Marie J.P., Choussy O. - Rhinoscleroma of the sinuses. Rhinology. 2008 Dec;46(4):338-41.
60. Chan T.V., Spiegel J.H. - Klebsiella rhinoscleromatis of the membranous nasal septum. J Laryngol Otol., 2007 Oct;121(10):998-1002. Epub 2007 Mar 15.
61. Hoffmann E.O., Loose L.D., Harkin J.C. - The Mikulicz cell in rhinoscleroma. Light, fluorescent and electron microscopic studies. J Pathol. 1973 Oct;73(1):47-58.
62. Fitzgerald D., Haas D.W. - M. tuberculosis. In: Mandell G.L., Bennett J.E., Dolin R., eds. - Principles and Practice of Infectious Diseases. Vol. 2. 6th ed. New York, NY: Elsevier/Churchill Livingstone, 2005;p.2852–2886.
63. Katsivas Th.F. - Tuberculosis and Atypical Mycobacteria. In Harris: J.P., Weisman M.H. - Head and Neck Manifestations of Systemic Disease. New York, Informa Healthcare, U.S.A., 2007;p.169-177.
64. Dixit R., Dave L. - Primary Nasal Tuberculosis Lung India., 2008 Apr-Jun; 25(2):102–103.
65. Lau S.K., Kwan S., Lee J., Wei W.I. - Source of tubercle bacilli in cervical lymphadenopathy: a prospective study. J Laryngol Otol., 1991;105:558–61.
66. Kinghorn G.R. - Syphilis. In: Cohen J., Powderly W., eds. - Infectious Diseases. Vol. 1. 2nd ed.Edinburgh, NY: Mosby, 2004;p.807–816.
67. Capps F.C.W. - Manifestations of syphilis as see in the nose and throat today. Br J Vener Dis., 1938 Oct;14(4):235-42.
68. Rolfs R.T. - Treatment of syphilis, 1993. Clin Infect Dis., 1995;20(suppl 1):S23–S38.
69. Darling S.T. - A protozoan general infection producing pseudotubercles in the lungs and focal necroses in the liver, spleen, and lymph nodes. JAMA, 1906;46:1283-1285.
70. DeMonbreun W.A. - The cultivation and cultural characteristics of Darling's histoplasma capsulatum. Am J Trop Med Hyg., 1934;14:93-125.
71. McDonald T.J. - Granulomatous diseases of the nose. In: English GM, editor – Otolaryngology. vol 2, JB Lippincott, Philadelphia, 1990;p.435-437.
72. National Institute of Drug Abuse: Epidemiologic Trends in Drug Abuse. Community Epidemology Work Group, December 1997, Vol.1. Hightlights and Executive Summary. (NIH publication no. 98-4297), Rockville., MD, National Institute of Health, 1998.
73. National Institute of Drug Abuse: National Household Survey on Drugs Abuse: Population Estimates 1997. Rockville, MD, Substance Abuse and Mental Health Administration, 1998.
74. Blanksma C.J., Brand H.J. - Cocaine abuse: orofacial manifestations and implications for dental treatment. International Dental Journal. Amsterdam, The Netherlands., 2005;55:365–369.
75. Villa P.D. - Midfacial Complications of Prolonged Cocaine Snorting. J. Can Dent Assoc., 1999;65:218-23.
76. Khalifa N., Calas V, Trémelet L, Cave J-P. - L'epistaxis en urgence. La revue de la société de chirurgie ORL de Tarn-et-Garonne, janvier 2006 - n°02.
77. Santos P.M., Lepore M.L. - Epistaxis in head and neck surgery. In: Bailey B.J., ed. -Otolaryngology. Vol. 1., 2nd ed., PA: Lippincott-Raven, Philadelphia, 1998;p.513–529.
78. Karabulut A.B., Aydin H., Mezdegi A., et al. - Recurrent bleeding following rhinoplasty due to Factor XIII deficiency. Plast Reconstr Surg., 2001;108(3):806–807.
79. Andreoli T.E., Bennet J.C., Carpenter C.C. - Cecil Essentials of Medicine. 3rd ed., PA: Saunders, Philadelphia, 1993;p.400–416.
80. Burrows R.F., Ray J.G., Burrows E.A. - Bleeding risk and reproductive capacity among patients with factor XIII deficiency: a case presentation and review of literature. Obstet Gynecol Surv., 2000;55(2):103–108.
81. Gerlach R., Raabe A., Zimmermann M., et al. - Factor XIII deficiency and postoperative hemorrhage after neurosurgical procedures. Surg Neurol., 2000;54(3):260–265.
82. Klepfish A., Berrebi A., Schattner A. - Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. Arch Intern Med., 2001 Mar 12;161(5):767.
83. Peery W.H. - Clinical spectrum of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Am J Med., 1987;82(5):989–997.
84. Bowie E.J.W., Owen C.A. Jr. - Primary vascular disorders. In: Colman R.W., Hirsch J., Marder V.I., et al., eds. - Hemostasis and Thrombosis: Basic Principles and Clinical Practice. PA: JB Lippincott Co., Philadelphia, 1994;p.134–168.
85. Porteous M.E., Burn J., Proctor S.J. - Hereditary haemorrhagic telangiectasia: a clinical analysis. J Med Genet., 1992;29(8):527–530.
86. Rappai M., Collop N., Kemp S., deShazo R - The nose and sleep-disordered breathing. What we know and what we do not know. Chest, 2003;124:2309-2323.
87. Zwillich C.W., Pickett C., Hanson F.N., Weil J.V. - Disrupted sleep and prolonged apnea during nasal obstruction in normal men. Am Rev Respir Dis., 1981;124:158-160.
88. Olsen K.D., Kern E.B., Westbrook P.R. - Sleep and breathing disturbances secondary to nasal obstruction. Otolaryngol Head Neck Surg., 1981;89:804-810.
89. Wetmore S.J., Scrima L., Hiller F.C. - Sleep apnea in epistaxis patients treated with nasal packs. Otolaryngol Head Neck Surgery., 1988;98:596-599.
90. Miljeteig H., Hoffstein V., Cole P. - The effects of unilateral and bilateral nasal obstruction on snoring and sleep apnea. Laryngoscope, 1993;102:1150-1152.

91. Jessen M., Fryrsmark U. - Is there a relationship between the degree of nasal obstruction and the snoring? Clin Otolaryngol., 1993;18:485-487.
92. Miljeteig H., Savard P., Mateika S., Cole P., Haight J.S., Hoffstein V. - Snoring and nasal resistance during sleep. Laryngoscope, 1993;103:918-923.
93. De Vito A. - The importance of nasal resistance in obstruction sleep apnea syndrome: a study with positional rhinomanometry. Sleep Breath, 2001;5:3-11.
94. Liistro G., Rombaux Ph., Belge C., Dury M., Aubert G., Rodenstein D. - High Mallampati score and nasal obstruction are associated risk factors for obstructive sleep apnea. Eur Respir J., 2003;21:248-252.
95. Ohki M., Ushi N., Kanazawa H., Hara L., Kawano K. - Relationship between oral breathing and nasal obstruction in patients with obstruction sleep apnea. Acta Otolaryngol., 1996;52:228-230.