Abstract

In this chapter, we examine the chronic inflammatory diseases of the nasal cavity and paranasal sinuses. First, we examine the basic characteristics of the various chronic inflammatory diseases of the nasal cavity and paranasal sinuses and chronic inflammatory diseases of the oral cavity. Further, we discuss the etiopathogenesis, diagnosis, differential diagnosis, and treatment options for the various conditions. The chapter is aimed at helping gain some insight into the current views regarding chronic inflammatory conditions of the nasal cavity and paranasal sinuses as well as the oral cavity.

Chronic Inflammatory Disease of Nasal Cavity and Paranasal Sinuses

Currently, the prevalence of chronic inflammatory diseases of the nasal cavity and paranasal sinuses is high. It has been reported that every 10th European has chronic inflammation of the nose and paranasal sinuses [1]. A basic understanding of the various nasal and paranasal diseases is paramount to approaching them clinically. Below is a short description of various chronic inflammatory diseases affecting the nasal cavity and the paranasal sinuses.

Rhinosinusitis

Sinusitis, or rhinosinusitis, is defined as the inflammation of the paranasal sinuses and nasal cavity [2]. Rhinosinusitis is the more preferred term because it encompasses the inflammation of both the nasal cavity and the inflam-
mation of the paranasal sinuses. Rhinosinusitis may present in the acute or chronic form, and chronic rhinosinusitis (CRS) may present with or without nasal polyps. The most common symptoms of CRS are nasal obstruction, nasal congestion, discharge, fatigue, headache, facial pressure, and dysosmia, which may also show worsening in certain seasons, such as winter [3]. CRS frequently occurs in conjunction with nasal polyps and asthma, presenting as a complex allergic entity. Thus, CRS tends to compromise the patient’s quality of life and daily functioning. The diagnostic modalities commonly used for the diagnosis of this condition are paranasal sinus computed tomography (CT), fiberoptic endoscopy, and anterior rhinoscopy [3]. The mainstay in the treatment of CRS is nasal corticosteroids, both in the presence and absence of nasal polyps [3]. Other predominant treatment options in the absence of nasal polyps are nasal wash, nasal decongestants, and systemic corticosteroids [3].

**Sinonasal Inflammatory Polyp**

In 20–40% of the cases of CRS, nasal polyps are detected [3]. Inflammatory nasal polyps are inflammatory, polypoidalsinosasal mucous tissues that arise in response to inflammatory stimuli, such as allergy and infections, or as a component of a systemic process such as aspirin intolerance or cystic fibrosis [4]. The diagnosis of sinonasal polyps is generally established by CT or MRI. Sinonasal polyps are generally considered benign, and the condition is generally treated symptomatically, unless severe. In 20-35% of the cases, surgery is required [3]. The mainstay in the medical treatment of sinonasal polyps is nasal corticosteroids [3]. The treatment of chronic rhinosinusitis with polyps is discussed in subsequent sections in detail.

**Paranasal Nasal Sinus Mucocele**

Mucoceles are defined as benign cystic lesions limited by the mucosa of the paranasal sinus itself and occurring most frequently in the paranasal sinus[5]. The condition generally does not give rise to any specific group of symptoms and is most often manifested by pressure symptoms giving rise to ophthalmic or intracranial complications [6]. In fact, studies have shown that even in the presence of large lesions with significant erosion of involved tissue, the condition may remain asymptomatic [7]. A long-term study showed that a very high percentage of patients with paranasal sinus mucoceles develop ophthalmologic complications [8]. Surgical excision is the standard treatment for these lesions, with the endoscopic approach being the gold standard [6].

**Infections**

Fungal sinusitis may occur as allergic fungal sinusitis, mycetoma and acute or chronic invasive fungal sinusitis [9].
**Allergic Fungal Sinusitis**

Allergic fungal sinusitis affects atopic immunocompetent individuals with fungal colonization of the sinuses. The fungus acts as an allergen triggering inflammatory reactions and thereby leading to sinus obstruction and stasis, which further promotes fungal proliferation [9]. The diagnostic criteria for this condition are detection of allergic mucin; detection of fungal specific IgE; absence of fungal invasion of the submucosa, blood, or bone; absence of immunosuppression; and radiologic evidence of opacity of the involved sinua. Typical CT findings of air-fluid level seen in bacterial sinusitis are rare in fungal sinusitis, and in fact, the absence of air-fluid levels may be considered diagnostic for this condition [10,11]. Allergic fungal sinusitis has been often linked with socioeconomic conditions, and it has been observed to affect low income groups [12,13].

**Mycetoma**

Mycetoma, sometimes referred to as “fungal ball” typically occurs in immunocompetent nonatopic individuals[9]. In this condition, the fungus remains in the secretion, without invading the mucosa. Mycetomas are masses of fungal hyphae that elicit a low-grade chronic noninvasive inflammation of the sinuses. Most commonly, only one sinus, often the maxillary sinus, is affected [9]. The condition may lead to sclerosis or calcification of the sinus walls, which may be evident radiologically [9]. Clinically, the condition is mildly symptomatic or may be asymptomatic [9].

**Invasive fungal sinusitis**

Chronic invasive fungal sinusitis extending to the orbits or the brain may occur in patients who are immunocompetent[9]. Fungal pathogens in this condition proliferate in the sinuses, eventually invading the mucosa [9].

**Sinonasalmucormycosis**

Sinonasalmucormycosis is a rare fulminant disease affecting immunocompromised individuals. In the pediatric population, it is rare but potentially fatal [14].

**Rhinosporidiosis**

Rhinosporidiosis is an infectious disease predominantly reported from India and Sri Lanka [15]. It is caused by Rhinosporidiumseeberi. The nasal form of the disease presents with chronic mucoid discharge with painless unilateral obstruction and possible involvement of para-nasal sinuses. It is also likely to affect other tissues such as conjunctiva, orapharyngeal, laryngeal mucosa, and urethra [15].
Bacterial Infection

Rhinoceroma

Rhinoceroma is a chronic granulomatous disease of the nasal cavity, nasopharynx, and paranasal sinuses caused by *Klebsiella rhinoscleromatis*. The clinical disease progresses through the catarrhal/rhinitic stage to the granulomatous/florid and sclerotic/cicatricial stages. Initial presentation involves non-specific rhinitis, followed by chronic foul purulent discharge, frequent epistaxis, nasal obstruction, crustation, and granulation, eventually resulting in permanent nasal and oral deformities [16].

Leprosy

Leprosy is caused by *Mycobacterium leprae* and is characterized by involvement of the skin and peripheral nerves. Depression of the nasal bridge is a characteristic feature of leprosy. The nasal mucosa is the main point of entry and exit of the bacteria [17].

Tuberculosis

Tuberculosis is caused by *Mycobacterium tuberculosis*. It is clinically characterized by prolonged cough, night sweats, and weight loss, often presenting as a prolonged low-grade fever of unknown origin. The diagnosis is confirmed by detection of acid-fast bacilli in pathological examination of sputum and radiological evidence. Vacancies are now administered in countries where the condition is endemic, and the treatment involves administration of isoniazid, rifampicin, and pyrazinamide for six months [18].

Protozoal

Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis is caused by *Leishmania braziliensis*. Almost 40% of patients develop mucocutaneous involvement, with the typical early symptoms being nasal obstruction associated with a nodule or polyp at the inferior turbinate. The disease eventually progresses to destroy the nasal septum and destroy the nose and mouth if not controlled [19].

Viral Infection

Herpes

Herpes simplex is caused by herpes simplex virus (HSV) type I or II and manifests as painful blisters or ulcers around the nose and mouth [20]. Oral lesions are generally caused by HSV type I. Tingling, itching, or burning may be experienced before the appearance of the blisters [20].

CMV

Cytomegalovirus infection (CMV) is a self-limiting disease caused by human herpes simplex virus 5. CMV is clinically similar to CMV and characterized by fever, gen-
Chronic Inflammatory Diseases

Infectious mononucleosis

Infectious mononucleosis is caused by Epstein-Barr virus and manifests as fever, pharyngitis, and lymphadenopathy. The condition is self-limiting and generally occurs in immunocompetent individuals [22].

Chronic Inflammatory Diseases of the Oral Cavity

Periodontal Disease

Periodontal diseases are diseases affecting the gingiva and alveolar bone. It is a growing public health concern, with many risk factors, including poor oral hygiene; tobacco use or smoking; psychological factors such as stress; related systemic conditions such as diabetes mellitus, obesity, and cardiovascular disease; use of drugs influencing salivary flow; being the main risk factors for periodontal diseases [23].

Gingivitis

Chronic gingivitis is the chronic inflammation of the gingiva.

Plasma Cell Gingivitis

Plasma cell gingivitis is a rare condition that is characterized by the diffuse and extensive infiltration of plasma cells into the sub-epithelial tissue [24]. It may be caused by allergens, be neoplastic in origin, or idiopathic [25] and is manifested by hypersensitivity [24].

Drug-Related Gingival Hyperplasia

Some anticonvulsants such as phenytoins, calcium-channel blockers such as nifedipine, and immunosuppressants such as cyclosporine cause clinically and histologically similar gingival enlargement in susceptible patients [26].

Gingival Fibromatosis

Gingival fibromatosis is defined as the overgrowth of the collagenous portion of the non-epithelial gingival tissue [27]. It may be hereditary, idiopathic, or drug-induced.

Bacterial Infection

Streptococcal tonsillitis with pharyngitis

Streptococcal tonsillitis generally presents with high-grade fever (above 100°F), pharyngitis, tonsillar exudates, and cervical lymphadenopathy. The diagnostic standard is detection of the bacteria in throat culture.

Tuberculosis

Although TB usually affects the lungs, it can also have extra-pulmonary manifestations. The oral lesions are typically asymptomatic appearing in the oral buccal mucosa and may be either primary or secondary [28]. They gener-
ally affect the oral mucosa, especially the tongue, or the gingival tissue and appear as chronic ulcers, nodules, or granulomas. Diagnostic confirmation by pathology and proper treatment are necessary.

**Leprosy**

Oral manifestations of leprosy range from non-specific lesions such as enanthema of palate to specific lesions such as nodules or ulcers that may show positivity for the pathogenic bacteria (*Mycobacterium leprae*). The lesions are insidious and may be asymptomatic [29].

**Actinomycosis**

Actinomycoses is a rare chronic bacterial infection caused by anaerobic bacteria of *Actinomyces* spp., which colonize in the mouth and the digestive and genital tracts. Typical microscopic findings include necrosis with yellowish sulfur granules and filamentous gram-positive fungal pathogens [30]. Apart from the common respiratory tract presentation, the disease can also manifest in a cervicofacial form, which is acquired via a mucosal breach and presents as an slow-growing indurated mass with subsequent abscess formation and appearance of yellowish exudates containing sulfur granules.

**Cat scratch disease**

Cat scratch disease is a bacterial zoonotic disease generally presented as lymphadenopathy near the site of cat scratch or bite, fever, and fatigue. It is caused by *Bartonella henselae*.

**Fungal and Protozoal Disease**

**Candidiasis**

Oropharyngeal candidiasis is caused by *Candida* spp., most often *Candida albicans*. The infection is generally regarded as an opportunist infection, mainly affecting immunocompromised individuals. Clinically, the lesions are characterized by pseudomembranous, erythematous, or hyperplastic appearance. Chronic atrophic candidiasis is a form of the disease that is associated with denture use. [31].

**Zygomycosis**

Zygomycosis or mucormycosis is a fungal disease caused by fungi of the order *Mucorales*. The disease is characterized by a high mortality rate and generally affects immunocompromised lesions. Oral lesions such as ulcers serve as point of entry for the organism, which evades the hard palate, maxillary bone, paranasal sinuses, and the orbital and intracranial cavities [32].

**Aspergillosis**

Aspergillosis of the sinonasal tract is caused by *Aspergillus* sp. Predisposing factors are immunosuppression and obstructive nasal lesions [33].

**Viral Disease**

**Herpes simplex virus**

Oral lesions of herpes simplex are generally caused by HSV I. The lesions typically occur as localized clusters of
painful blisters or ulcers occurring around the mouth.

**Cytomegalovirus infection**

Cytomegalovirus infection is caused by CMV. Although similar in clinical presentation to infectious mononucleosis, CMV infection rarely includes pharyngitis.

**Clinical Feature Site**

**Etiology**

Lam et al discussed the current understanding on the etiopathogenesis of CRS in their review [34]. These hypotheses suggest the notion that CRS occurs due to an interplay between individual host characteristics and exogenous factors. They grouped the current concepts on CRS etiology and pathogenesis into the following categories: (1) the “fungal hypothesis,” (2) the “superantigen hypothesis,” (3) the “biofilm hypothesis,” and (4) the “microbiome hypothesis,” all of which emphasize key environmental factors, and (5) the “eicosanoid hypothesis” and (6) the “immune barrier hypothesis,” which describe specific host factors [34].

Some of the common bacterial infections are caused by the pathogenic transformation of bacteria that are normally present in the nasal and oral mucosa, e.g., actinomycosis and candidiasis. Certain viral infections such as cytomegalovirus occur in those immunocompromised.

**Risk**

With regard to CRS and allergic fungal rhinosinusitis, a recent cohort study of patients from North Carolina showed that patients with CRS have higher income, more access to primary care, and lower markers of disease severity than those with allergic fungal rhinosinusitis [13]. The role of socioeconomic factors in the occurrence of allergic fungal rhinosinusitis has also been reported by others [12]. Miller et al [35] have shown that markers of disease severity (namely, bone erosion and orbitocranial involvement) in AFRS were associated with low income, rural residence, poor housing quality, and less health care access. Several diseases of the oral cavity such as tuberculosis also spread because of overcrowding, poor oral hygiene, and denture use.

**Gender and Age**

Diseases such as infectious mononucleosis are common in adolescents and young adults, while CSR is mostly seen in middle aged adults. No particular gender predilection is seen for these diseases.

**Histology**

The main histological characteristics of chronic rhinosinusitis with nasal polyps are proliferation of pseudostratified respiratory epithelium, thickening of the basement membrane, focal fibrosis and eosinophilic and lymphocytic infiltration of the lamina propria [36].
though the exact etiopathogenesis of nasal polyps remains elusive, currently two hypotheses are predominantly implicated: “hypothesis of staphylococcal superantigens” and “hypothesis of immune barrier dysfunction” [36]. Further, more recent findings indicate that HMG B1 may play a crucial role in the pathogenesis of CRS with nasal polyps [37].

**Differential Diagnosis**

The diagnosis of CRS on the basis of the symptom presentation alone is difficult.

Bhattacharya [38] conducted a study on the correlation between reported symptoms and radiographic evidence of chronic sinusitis and found that there is little correlation between the two, thereby suggesting that the diagnosis of CRS based on symptom criteria alone is difficult because most symptoms (other than dysosmia) do not distinguish between radiographically normal and diseased patients. The presence of a polyp and dysosmia were found to be the only criteria that successfully distinguished between radiographically diseased and normal individuals. Similarly, Lange et al investigated the value of questionnaire-based and clinical-based diagnosis and evaluation of CRS and found only moderate agreement self-reported questionnaire scores and clinical-based assessment. As stated above, the absence of air-fluid levels may be suggestive of the diagnosis of allergic fungal sinusitis. [10,11]. In cases of allergic fungal sinusitis, CT scans may show opacity in the affected sinus, and the absence of the typical air-fluid levels in the case of acute bacterial sinusitis. In cases of mycetoma, sclerosis or calcification of the sinus wall may be seen in later stages [9].

Most diseases of the oral cavity, such as herpes, present with typical lesions. Isolation of the pathogenic bacteria, such as acid-fast bacilli, from oral mucosa or secretions is generally necessary to establish the diagnosis. Others such as tuberculosis, which may present with non-specific lesions need to be investigated by histopathological studies to confirm the diagnosis. Diseases with systemic manifestations such as leprosy may be distinguished by their typical clinical presentation and diagnostic features.

**Treatment**

The mainstay in the treatment of CRS is nasal corticosteroids, nasal washes, and decongestants [3]. About 20–35% of the patients require surgery [3]. For CRS with nasal polyps, evidence for short-term use of systemic corticosteroids has been shown to be favorable, but not as much in CRS without nasal polyps [39]. Topical corticosteroids improve symptom scores in both CRS subgroups. The role of microbes in CRS is still controversial. Culture-directed antibiotics are recommended for CRSSNP with exacerbation. Long-term use of low dosage antibiotics is recommended for CRSSNP for their anti-inflammatory effects [39].
With respect to allergic fungal rhinosinusitis, the treatment mainly relies upon the surgical removal of fungal hyphae in eosinophilic mucin [40]. A recent review [40] suggested that although several uncontrolled studies support the beneficial effect of antifungal agents in AFRS, but randomized trials of topical and systemic antifungal therapies have not shown beneficial results in CRS. Antifungal treatment within the sinonasal cavities does not appear to be an effective approach for most chronic sinusitis, and antifungal therapy for AFRS is unproven [40].

Recent studies [41] have shown that refractory CRS that significantly affect the patient’s quality of life does not respond to continued medical therapy. A recent meta-analysis showed that current trend is to recommend endoscopic sinus surgery after failure of 8-week course of topical intranasal corticosteroids and 3-week course of oral antibiotics, and in some cases the use of systemic corticosteroids [42]. On the other hand, studies have also indicated that no clear evidence is available to prove the superiority of surgical treatment over medical treatment for chronic sinusitis with polyp, in terms of symptom scores or quality of life scores; therefore, further investigations are necessary to determine the most suitable forms of treatment for this condition [43].

Watt and Petersen [23] highlighted the importance of shifting from individual focus to developing effective public health measures to combat periodontal disease. Infective diseases such as tuberculosis and leprosy need to be tackled by widespread, effective public health measures, particular in countries where the conditions are endemic. Further, awareness regarding the maintenance of oral hygiene and the effects of tobacco use, which are causes for several types of oral lesions, need to be generated in the public. This will help reduce the incidence of diseases such as chronic gingivitis.

**Figure 1:** Paranasal sinuses (From Mosby’s Medical Dictionary, 8th edition. S.v. “Paranasal sinus diseases.” Retrieved on January 09, 2016 from http://medical-dictionary.thefreedictionary.com/Paranasal+sinus+diseases)
Figure 2 and Figure 3: Treatment for chronic rhinosinusitis. (From Piromchai P, Kasemtsiri P, Laohasiriwong S, Thanavigaratnanich S. Chronic rhinosinusitis and emerging treatment options. Int J Gen Med. 2013 Jun 7;6: 453–464. doi: 10.2147/IJGM.S29977. Print 2013.)

Figure 4: Chronic gingivitis. (a) Histopathologic characteristics in a biopsy section of the epithelial and connec-tive tissues of mild non-specific chronic gingivitis: Epithe-
lial hyperplasia, mild inflammatory lymphocyte infiltrate. HE. Original magnification ×100. (b) Histopathologic characteristics in a biopsy section of the epithelial and connective tissues of moderate non-specific chronic gingivitis: Proliferation of epithelial crests, moderate inflammatory lymphocyte infiltrate, congestion. HE. Original magnification ×100. (c) Histopathologic characteristics in a biopsy section of the epithelial and connective tissues of severe non-specific chronic gingivitis: Epithelial atrophy, spongiosis, severely lymphoplasmocytic infiltration. HE. Original magnification ×200. (From Myriam A. Koss, Cecilia E. Castro, Silvia Carino, and Maria E. López. Histopathologic and histomorphometric studies and determination of IL-8 in patients with periodontal disease. J Indian Soc Periodontol. 2014 Mar-Apr; 18(2): 145–149.)

Figure 5: Allergic fungal rhinosinusitis: CT image demonstrating heterogenous signal intensity that is characteristic of AFS. (From Daniel Glass, MD* and Ronald G. Amedee, MD. Allergic Fungal Rhinosinusitis: A Review. Ochsner J. 2011 Fall; 11(3): 271–275. PMCID: PMC3179194).

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