Human immunodeficiency virus and salivary gland pathology: an update

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Salivary gland disease is a common manifestation of human immunodeficiency virus (HIV) infection, with a significant increase in prevalence over the last two decades. This review summarizes contemporary knowledge of non-neoplastic salivary gland disease in HIV infection. The aim is to update information on and bring attention to those lesions, which are almost exclusive to the salivary glands in the HIV setting. The associated conditions include xerostomia or salivary gland hypofunction; Sjögren syndrome–like illness; salivary gland enlargements, including benign lymphoepithelial cysts (cystic lymphoid hyperplasia); diffuse infiltrative CD8+ lymphocytosis syndrome; and mucous extravasation phenomena, especially ranula. Many of these conditions show considerable overlap, and thus, the term *HIV-associated salivary gland disease* is used to designate HIV infection with xerostomia or salivary gland hypofunction, enlargement of one or more of the major salivary glands, or both. These manifestations may be related to HIV infection, and therefore, prompt recognition is invaluable in the diagnosis and treatment of both the salivary gland disease and HIV infection. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:52–59)

As of 2016, a global incidence of 36.7 million individuals infected by human immunodeficiency virus (HIV) was reported by the Joint United Nations Programme on HIV/AIDS (UNAIDS, 2017); of these individuals, 2.1 million were children age less than 15 years. Approximately 1.8 million new infections occurred in 2016, with about 1 million deaths resulting from acquired immunodeficiency syndrome (AIDS) globally.[1] During the early AIDS pandemic, head and neck pathology was reported to occur in greater than 50% of HIV-positive patients and in about 80% of patients with AIDS.[2,3] Salivary gland disease specific to HIV infection has existed throughout the highly active antiretroviral therapy (HAART) era,[4] and an increase in HIV salivary gland pathology may be attributed to the persistent increase in HIV infection worldwide.

As of 2017, global HAART coverage reached 60% of all persons living with HIV, compared with 46% as at the end of 2015.[5,6] By June 2016, 18.2 million people were accessing HAART compared with 15.8 and 7.5 million people accessing HAART in 2015 and 2010, respectively. HAART has improved the quality and length of life for individuals with HIV infection. Studies on the enhancement of patient outcome with HAART as well as its effect on HIV-associated salivary gland enlargement, however, have reported inconsistent data.[5,7]

HIV-associated parotid enlargement before the HAART era was observed in 1% to 10% of persons with reported HIV, which correlated with decreased CD4+ counts and advanced stages of HIV and AIDS.[8] Although reports have shown a reduction in the prevalence of oral manifestations of HIV infection and AIDS with the advent of HAART,[5,7] reports from the developed world show an increase in HIV-related salivary gland disease.[7] A significant increase in HIV-associated salivary gland disease (HIV SGD) (1.8%–5%) was reported in North Carolina, USA, by Patton et al.[5] Similarly, Navazesh et al.[7] showed that HAART is a significant risk factor for the development of enlarged salivary glands. However, studies from developing countries, such as Mexico and Greece, report no change in salivary gland enlargement in those with HIV infection on HAART, and yet other reports show a decrease in prevalence of salivary gland disorders unique to HIV-infected persons, such as diffuse infiltrative lymphocytosis syndrome (DILS).[9,10] This disparity across studies from different countries is probably related to variations in sample size (Mexico, $n = 1000$; Greece; $n = 95$; United States, $n = 668$; $n = 570$) rather than to inherent geographic differences.[5,7] Furthermore, the variable findings could be attributed to the type, dosage, and duration of HAART administered and the patient's resultant quality of health. A limitation of these country-based studies may be related to the fact that the results described may represent only one clinical site and trends in patient population in a single site, rather than representing national trends.[11]

Statement of Clinical Relevance

Non-neoplastic salivary gland disease may be related to the initial diagnosis of human immunodeficiency virus infection and the effects of highly active antiretroviral therapy and to its being a part of immune reconstitution inflammatory syndrome. Prompt recognition is invaluable in diagnosis and treatment.

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Most studies concur that HIV SGD linked to the BK polyomavirus (BKPyV) has persisted throughout the HAART era.[4] Not only the global increase in HIV infection but also current advances in HAART and medical management might contribute to any increase in salivary gland pathology because of the patients' prolonged life expectancy.[12]

Salivary gland pathology in HIV and AIDS with and without HAART incorporates both non-neoplastic and neoplastic conditions.[12,13] Neoplastic conditions include Kaposi sarcoma and salivary gland lymphomas, especially of the parotid gland and/or intraparotid lymph nodes. Non-neoplastic changes include benign lymphoepithelial lesions, cystic lymphoid hyperplasia (CLH) or benign lymphoepithelial cysts (BLECs) occurring in HIV, DILS, and parotid lymphadenopathy. Many of these conditions are almost identical in clinical presentation or show considerable overlap,[12,13] and thus, the term *HIV SG* is used to designate HIV infection with salivary hypofunction or xerostomia, diffuse enlargement of one or more major salivary glands, or both.[13] Salivary gland enlargement in HIV and AIDS may also be caused by DILS, hepatitis C virus−associated SGD, and mumps.[14] This review summarizes only cases of non-neoplastic lesions that are pertinent and almost exclusive to salivary glands in the HIV setting.

HIV-ASSOCIATED SALIVARY GLAND DISEASE

HIV SGD is a frequently diagnosed salivary gland−associated complication in HIV-positive persons and is linked to the DNA tumor virus BKPyV.[4] This AIDS-defining condition has persisted throughout the HAART era and includes irreversible salivary gland damage, salivary hypofunction or xerostomia, salivary gland enlargement, benign lymphoepithelial lesions, CLH, and DILS. Its prevalence has increased among patients with HIV infection and AIDS.[4] In the pre-HAART era, HIV SGD was more common in children than in adults, with the prevalence ranging from 11.5% to 25%.[15] Schiødt et al. reported a bimodal age distribution, with HIV SGD being common in children born to mothers with HIV infection and in adults age 20 to 60 years.[13] There is a marked propensity for HIV SGD to occur in males, with Schiødt et al. reporting 94% occurrence in men, as well as an apparent increase in blacks compared with whites and other race groups.[13] These data, however, reflect the epidemiology pre-HAART, with more recent reports showing an increase in the prevalence of HIV SGD with HAART. HIV SGD with parotid enlargement is as common in children as in adults on HAART (16.4%), and the discrepancy between adults and children appears to have diminished in the HAART era.[16] In their study of 30 patients with HIV infection in North Carolina, Burger-Calderon et al.[3] showed 70% with HIV SGD, characterized by salivary gland enlargement and damage, with resultant xerostomia. Of the 21 patients with HIV SGD, 76% were males (age range 29−60 years), and most patients (81%) were on HAART. Even though a significantly greater proportion of females than males on HAART are reported in some countries,[5] males with HIV SGD continue to dominate both in the pre-HAART era and the HAART era. Furthermore, there appeared to be no dramatic difference in HIV SGD presentation among patients on HAART.

However, a significant increase in the prevalence of HIV SGD was noted in patients with HIV infection on HAART by Patton et al.[5] The relationship between HAART and HIV SGD may be attributed to relatively high viral loads in patients in the early stages of disease and in the initial phase of HAART and are thus at increased risk of HIV SGD.[12] HIV SGD occurs in all groups at risk for HIV infection—irrespective of mode of transmission, whether through heterosexual or homosexual acquisition—in people who inject drugs and in recipients of blood and blood products.

Thus, there are conflicting reports regarding the prevalence of HIV SGD, with some studies showing a reduction in HIV SGD with HAART and others showing an overall increase in salivary gland pathology in the HAART era.[17,18] This has been attributed to the size of pre-existing lesions; duration, time, and different regimens of HAART; and the inconsistent availability of HAART in developing countries. Furthermore, the reduction in HIV load and subsequent rise in CD4+ counts seen with the initiation of HAART may possibly result in the reactivation of clinically dormant opportunistic infections (immune reconstitution inflammatory syndrome [IRIS]), with resulting HIV SGD and parotid enlargement.[17] HAART has been reported to be effective in the elimination of parotid swellings as a result of termination of viral replication, as well as viral load reduction and CD4+/CD8+ cell count stabilization, thus obviating the need for parotid gland surgery.[17]

HIV SGD is generally asymptomatic; however, signs include swelling and facial deformity; diffuse soft tissue edema and enlargement of one or more major salivary glands, especially the parotid; dry mouth; and sometimes dry eyes and arthralgia. Swelling may be unilateral (40%) or bilateral (60%).[13] In addition to salivary gland involvement, there may be lymphoid interstitial pneumonitis, gastritis, and hepatitis.[19] HIV SGD often occurs together with persistent generalized lymphadenopathy, which is a persistent or recurrent diffuse acute infection associated with pain and hyperthermia, especially in children.

Histologically, HIV SGD is mainly nonspecific. There may be hyperplastic intraparotid lymph nodes

and/or lymphocytic infiltrates in salivary gland parenchyma, which may simulate other inflammatory salivary gland diseases.[12] Salivary gland enlargement is a result of CD8+ T-lymphocyte infiltration, which results in atypical lymphoid hyperplasia and eventually CLH.[20] BLECs are a local manifestation of longstanding lymphadenopathy and are sometimes associated with DILS. The histologic changes may also be seen in minor salivary glands and may be associated with mucosa-associated lymphoid tissue lymphoma.[12] Radiologic features observed in HIV SGD are essentially similar to those described for CLH.

Salivary flow rate measurement, labial salivary gland biopsy, eye examination for keratoconjunctivitis detection, and serologic tests for antinuclear antibodies, rheumatoid factor, and SS-A and SS-B antibodies may be used as an aid in the diagnosis of HIV SGD and in its differentiation from DILS and Sjögren syndrome (SS). The diagnosis of HIV SGD and DILS should be considered only in the presence of chronic HIV infection. Furthermore, DILS requires evidence of organ infiltration and a blood CD4+/CD8+ ratio less than 1. Other autoimmune diseases need to be excluded, especially in the frequent context of HCV coinfection.[21] Incisional biopsy or fine-needle aspiration of salivary glands may be needed to rule out a tumor, such as a lymphoma or Kaposi sarcoma. Table I highlights the pertinent features observed in HIV SGD, CLH, and DILS.

A link between HIV SGD and BKPyV has been demonstrated.[4] BKPyV is commonly present in most human populations. Its transmission may be via fecal−oral, uro−oral, or vertical transmission. Primary infection is usually asymptomatic, and HIV SGD occurs with reactivation. BKPyV strains preferentially infect salivary gland cells, replicate with viremia, and result in shedding of daughter virions into saliva.[4] The clinical significance of this entity lies in the fact that it may present as a manifestation of HIV infection, with increased expression occurring with HAART and as part of IRIS.[2,22,23] Although some studies have reported HIV SGD to be an early indicator of HIV infection, reports on its exact prevalence in the HAART era and prior period are lacking.[22]

HIV-ASSOCIATED REDUCTION IN SALIVARY FLOW RATE

Patients with HIV infection show clinical reduction in salivary flow rates in the parotid, submandibular, and sublingual glands in both early and advanced stages of infection.[3,23] Although salivary gland hypofunction resulting in decreased salivary flow rates (objective evidence of reduced salivary output) and xerostomia (subjective complaint of dry mouth) may be seen in both adults and children with HIV infection, suggesting that HIV infection may affect salivary gland function,[24] this has not been strongly correlated with HAART, and distinguishing between this being integral to the disease or a side effect of therapy is challenging. However, a study on 293 HIV-positive patients (67.2% on HAART; 32.8% not on HAART) in Mexico showed that salivary flow was greatest in HIV-positive persons not on HAART and in those with the highest average viral load, especially with greater than

Table I. Comparison of HIV SGD, CLH, and DILS

	HIV SGD	*CLH*	*DILS*
Clinical			
Immune status	HIV positive		
Age	Adults and children	Adults and children	Mainly adults
Gender	Mainly males		
Gland involvement	Salivary gland (mainly parotid)		Salivary and lacrimal glands
Extraglandular involvement	Lymphadenopathy		Lung, hepatic, renal, neurologic, muscular, lymphadenopathy
Presentation			
Symptoms	Asymptomatic		
Swelling	Bilateral facial swelling		
Salivary gland enlargement	Mainly bilateral		
Decreased saliva flow	Yes	Yes	Yes
Sicca symptoms	Yes	No	Yes
Histology			
Atypical lymphoid hyperplasia	Yes	Yes	Yes
Cystic change	With/without	Yes	No
Viruses	BKPyV	none	
HLA association	None	HLA-DR11 in blacks	HLA-DRB1
Effect of HAART	Both an increase and a decrease reported with HAART		

BKPyV, BK polyomavirus; *CLH,* cystic lymphoid hyperplasia; DILS, diffuse infiltrative lymphocytosis syndrome; HIV SGD, human immunodeficiency virus−related salivary gland disease; *HAART,* highly active antiretroviral therapy; *HLA,* human leukocyte antigen.

3 years of HAART duration. HAART causes cumulative damage that affects the amount of salivary flow, thus representing an important risk factor for decreased salivary flow and hyposalivation. It is important to establish the reasons for decreased salivation, which may include CLH, DILS, and HAART.[23]

Pre−HAART era studies in Thailand have suggested that changes in salivary gland function may be one of the first presentations of HIV (CD4+ >200 cell/l L); however, the effects of HAART cannot be discounted because an increase in dry mouth has been associated with protease inhibitor−based HAART.[7] With or without protease inhibitor use, low salivary flow levels and other SGD may occur. Reduction in salivary flow has been postulated to result from the chemical structures of drugs altering the structure and composition of saliva as well as from lipodystrophic changes within the salivary glands. The mechanism by which HAART decreases salivary flow remains unclear.[23,25]

Similarly a recent study by Kumar et al.[23] suggested that HIV-positive patients on HAART show a reduced salivary flow rate compared with those not on HAART and that decreased CD4+ cell counts are significantly associated with reduced salivary flow rates in HIV-infected individuals on HAART for greater than 3 years. This is caused not only by the HIV infection itself but may also result from the subsequent immunosuppression or the effect of drugs in HAART.[25] There is lack of strong evidence for reduction in salivary flow rate with long-term use of HAART. In Kumar et al.'s study of 150 persons with HIV infection in India, reduced flow rates were found in all persons with CD4 + counts of less than 200.[23] Furthermore, persons with HIV infection on HAART showed reduced salivary flow rates. The reduction in CD4+ cell counts was significantly associated with reduced salivary flow rate in persons with HIV infection on HAART for 3 years or longer. Even though some earlier studies showed no significant difference in salivary flow rates between persons on HAART and those not on HAART, duration of HAART as a factor affecting salivary flow was not previously considered.[23]

Furthermore, the prevalence of dry mouth is associated with immunosuppression and the presence of systemic disease.[24] Salivary composition may also be altered in these individuals. Oral dryness results in pain, difficulty chewing, adherence of food to oral surfaces, candidiasis, halitosis, chronic burning sensation, altered taste, intolerance to spicy foods, and dental caries.[12,24] There may be accompanying unilateral or bilateral parotid enlargement. Histologically, HIV-associated xerostomia is often nonspecific; however, there may be features similar to those of CLH.[12]

The role of HIV in the pathogenesis of salivary hypofunction and xerostomia is unclear. Although studies have shown a higher prevalence of reduced salivary flow rates with high concentrations of HIV in the salivary glands, low CD4+ counts, viral loads greater than 10,000 copies and protease inhibitor HAART, this correlation was not demonstrated in other studies.[23,25] Destruction of salivary gland elements, such as acinar destruction, remains the most plausible reason for the loss of salivary function and the resulting xerostomia. Further research is required, especially with regard to advanced stage HIV disease and/or a longitudinal evaluation of salivary gland function in patients with HIV, to delineate the beneficial/deleterious effects of HAART on salivary gland function and oral health.

CYSTIC LYMPHOID HYPERPLASIA IN AIDS

CLH, especially of the parotid gland, is a common HIV-associated salivary gland lesion that is often underrecognized.[20] Various terms, such as *Sjögren-like syndrome, BLEL* or *BLEC, cystic lymphoepithelial lesion*, and *HIV SGD*, are used to describe CLH occurring in the salivary glands of HIV-positive individuals.[20] CLH usually precedes AIDS and may be the initial clinical manifestation of HIV infection.[8,14] Even though the reported prevalence of CLH is generally 3% to 10% in Europe and North America, it is still the most common cause of salivary gland enlargement in patients with HIV infection.[17,20,26] Although certain Asian countries, such as Thailand, have reported a prevalence of 1%, the reported prevalence rate in Africa is 19%, as high as 23.3% in South Africa and 47% in Tanzania.[17] The exact reason for this geographic difference in prevalence is unknown, but an association with human leukocyte antigen DR5 (HLA-DR5), untreated advanced-stage AIDS, and malnutrition have been postulated to be important in the pathogenesis of CLH.[17] The prevalence of CLH in HIV-positive patients is still unclear. Various local and symptomatic treatment options for CLH, including repetitive fine-needle aspiration, surgery, radiotherapy, and sclerotherapy, have been used, yet none has addressed its context in, or the progression of, HIV infection.[18] Most reports on the prevalence of CLH are from the pre-HAART era. The introduction of HAART has proven to be of great clinical significance in improving the overall health of patients with HIV infection, indirectly diminishing parotid gland swelling, and improving patient aesthetics, thus eradicating the associated stigma of CLH and the need for its surgical removal. Although the beneficial effect of HAART on CLH in HIV-positive individuals has been recognized, the prevalence of CLH is expected to increase as a result of prolonged life expectancy, together with the combined effects of HAART and overall better management of patients with HIV and AIDS.[18,24] There are other reports, however, that indicate that although the

prevalence of CLH has increased with HIV, it has decreased with HAART.[7,8]

Most studies report predominance in males;[19,27] however, one of the largest series on CLH showed no gender predilection.[20] CLH affects both pediatric and adult populations, with median ages 12 and 38 years, respectively.[28] Pediatric CLH is reported in about 1% to 10% of children with HIV infection.[20,26] CLH was found in several racial or ethnic populations, such as those in Mongolian, Indian, Hispanic, and Caucasian populations, although most cases are reported in black patients.[13,20,29] Studies have reported a genetic association, related to increased expression of the major histocompatibility complex antigen (class II) HLA-DR11 in black patients, which is thought to play a role in the mediation of the immune response to HIV.[20]

Clinically, CLH usually occurs as bilateral, slow-growing, nontender, asymptomatic facial swellings. It most commonly presents as parotid gland enlargement; however, it has been described in other major and minor salivary glands, tonsils, and cervical lymph nodes.[20] CLH usually regresses with HAART.[8,14] The atypical lymphoid hyperplasia and proliferative epithelial changes may be related to viral load, accounting for disease regression with HAART.[14,26]

CT and magnetic resonance imaging are important because even though parotid masses can be detected clinically, often it is difficult to assess their cystic nature. CLH typically presents as single or multiple, well-circumscribed parotid cysts visible on computed tomography (CT) scans. The cystic spaces are usually variably sized radiolucencies present bilaterally within abnormally dense parotid glands.[20] Magnetic resonance imaging provides important information regarding the *location* (intraglandular vs extraglandular), *nature* (solid vs cystic), and *extent* of the lesion (involvement of deep lobes and relationship of adjacent structures). Ultrasonography defines large, hypoechoic areas with septa characteristic of HIV-associated BLECs. However, these findings are sometimes regarded as nonspecific for the diagnosis of CLH, especially in cases of isolated mixed, solid, and cystic nodules.[20]

Histologically, multicystic spaces exist within atypical hyperplastic lymphoid tissue, lined by epithelium that varies from squamous to pseudostratified ciliated respiratory epithelium. The lymphoid proliferation that forms the cyst wall shows florid follicular hyperplasia, demonstrating typical HIV-induced lymphoid changes. Epimyoepithelial islands may be evident. The cyst lumens show mucoid material with acute and chronic inflammatory cells and cholesterol clefts. Positive immunostaining of the follicular dendritic cells with the HIV-1 p24 antigen is often demonstrated. CLH may be present entirely within peri- and intraparotid lymph nodes, in both salivary gland parenchyma and salivary lymph nodes or rarely with salivary gland involvement only.[20]

The pathogenesis of CLH is attributed to ductal compression of striated ducts within entrapped salivary gland inclusions in lymph nodes or in the salivary gland itself by HIV-associated atypical lymphoid hyperplasia.[20] The increase in CLH may be attributed to the spike in HIV incidence.[20] It is imperative to recognize CLH in the differential diagnosis of bilateral parotid enlargement because this lesion shows a profound association with HIV and AIDS.

CLH is thought to be an early (World Health Organization stage I or II) manifestation occurring when immunity is well preserved, and often is the initial presentation of HIV infection. Early detection and treatment is important in reducing mortality, identifying other pathology, and preventing future HIV transmissions. Of further clinical significance is that because parotid enlargement is known within the community to be associated with HIV and is often a stigma of HIV infection, patients are motivated to seek early treatment.[22]

DIFFUSE INFILTRATIVE LYMPHOCYTOSIS SYNDROME

DILS is an uncommon subset of HIV disease that is multisystemic, predominantly affecting the lungs and salivary glands (bilateral parotid swelling). Typically, it displays persistent circulating CD8+ T-cell lymphocytosis and diffuse visceral CD8+ T-lymphocytic infiltration, with cervical lymphadenopathy. Described initially before the advent of HAART, DILS confers a favorable prognosis, resulting in lower HIV disease stage, slower progression to AIDS, and fewer opportunistic complications.[21,27]

It occurs in about 3% to 7.8% of persons with HIV infection and mainly involves the salivary and lacrimal glands; with salivary gland involvement, it falls within the spectrum of HIV SGD.[12,21] The incidence of DILS has progressively decreased since 1994, reflecting the positive impact of HAART.[9] Labial salivary gland biopsy usually confirms periductal CD8+ T-lymphocytic infiltration with acinar atrophy, ductal dilation, and fibrosis indicative of HIV infection.[21] A 4-fold increase in non-Hodgkin lymphoma has been reported.[12]

Not only has HAART been reported to decrease the incidence of DILS, but it has also been proposed that DILS is an antigen-driven response, possibly by a viral antigen, the primary treatment for which is HAART.[18] Furthermore, HAART is associated with an increase in CD4+ cell count and a decrease in the blood viral load, and the combined effect of both these factors possibly correlates with the obstructive physiopathogenesis seen in CLH and a reduction in DILS as a result of

HAART leading to the subsequent reopening of previously obstructed salivary gland ducts.[18]

The diagnostic criteria for DILS includes chronic HIV seropositivity (confirmed with enzyme-linked immunoassay or Western blot test), bilateral salivary gland enlargement, or xerostomia present for greater than 6 months; histologically confirmed salivary or lacrimal gland lymphocytic infiltration without granulomatous inflammation or neoplastic involvement, organ-infiltration and a blood CD4+/CD8+ ratio less than 1 (considering HAART and IRIS), and exclusion of other autoimmune diseases, coinfection (hepatitis C, Epstein-Barr Virus) and immunoglobulin G4 (IgG4)–related disease.[12,21]

DILS is seen in uncontrolled or untreated HIV infection but can arise independently of CD4+ T-cell counts. Bilateral parotiditis, with or without sicca symptoms, is the most common feature characterizing DILS,[9,19,21] with lymphadenopathy and extraglandular organ involvement affecting the lungs, central nervous system, liver, kidneys, and digestive tract.

DILS should be differentiated from SS and IgG4-related disease because they share many glandular and extraglandular features and hypergammaglobulinemia. HIV serology is, thus, indicated when DILS is being considered as a cause of salivary gland enlargement. Although DILS is characterized by CD8+ T-cells, SS shows periductal CD4+ T-cells. IgG4-related disease shows CD4+ T-lymphocytes and lymphoplasmacytic nodules within cellular storiform fibrosis with mild eosinophilia.[21]

DILS displays glandular features with sicca signs and moderate to massive parotiditis, whereas SS shows sicca signs with moderate or no parotiditis. IgG4-related disease has fewer sicca signs with lacrimal and salivary gland enlargement. Prominent extraglandular features in DILS include lung, hepatic, renal, neurologic, and muscular involvement, as well as lymphadenopathy. SS shows skin, lung, neurologic, renal, and gastrointestinal involvement, as well as arthritis, and IgG4-related disease shows lymphadenopathy, pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, and orbital pseudotumor. All 3 entities show hypergammaglobulinemia, with lymphocytosis observed in DILS, lymphopenia in SS, and nonspecific features in IgG4-related disease. The prognosis of this specific immune response to HIV infection continues to be favorable, even though optimal specific therapeutic strategies are lacking.[21]

RANULA

There are differing views as to whether the ranula represents an HIV-associated entity. Although some authors believe that the incidence of ranula in the patient with HIV infection is, per se, not greater,[30] others believe that oral mucoceles and ranulas need to be considered, along with parotid gland enlargement, as part of HIV-related salivary gland diseases and to be considered not only as lesions strongly associated with HIV infection but also as initial signs or early manifestation of HIV infection.[31]

Although involvement of other salivary glands by HIV has been reported, there are very few reports on ranulas being part of HIV SGD. The link between oral mucoceles and ranulas with HIV infection is seen with greater frequency in Southern Africa, where the prevalence of HIV is especially high.[18]

The etiopathogenesis and the reasons for increased prevalence of ranulas in HIV-positive persons, especially in Southern Africa, remain unclear. The fact that ranulas have been reported to occur concurrently with CLH and that they both have a fairly similar presentation point to the possibility of a similar etiology and less invasive therapeutic options. The beneficial effects of HAART on CLH in HIV-positive persons have been reported, but Sybele et al. reported that oral mucoceles and ranulas do not respond to HAART as rapidly as does CLH, which could possibly be attributed to glandular anatomic variations.[31] Furthermore, there is currently no evidence to support treatment of ranulas with HAART.[18]

SIALOLITHIASIS AND SUPPURATIVE SIALADENITIS

Sialolithiasis has very occasionally been associated with HIV infection.[32] The evidence for this association is very weak, with most studies attributing salivary gland calculi to a number of salivary functional changes other than HIV SGD, such as significant reduction in salivary flow rates and altered salivary chemical composition (increased sodium, chloride, lysozyme, peroxidase, lactoferrin, and IgA levels).[33]

HAART with use of agents, such as atazanavir/ritonavir, with a known association to renal and biliary lithiasis is also implicated in sialolithiasis. Among these agents, indinavir has been definitively implicated in lithiasis. This is related to in situ precipitation following pH-dependent solubilization of atazanavir, boosted by high plasma concentrations, saturation or inhibition of efflux transporters, and waning salivary (metabolic) clearances, probably related to bacterial infection increasing salivary pH, dry mouth worsened by HIV infection and HAART.[32] Sialolithiasis as a potential complication should be borne in mind, with the widespread use of HAART in the management of HIV-positive persons.[18]

Rarely, suppurative parotitis, especially that caused by *Streptococcus pneumoniae* should be considered in the differential diagnosis of a unilateral parotid gland swelling in an individual with HIV infection, particularly when the swelling progresses rapidly and is associated with fever. Invasive pneumococcal disease in

HIV infection was 50- to 100-fold more frequent than in the general population in the pre-HAART era, and the rate remains 35 times higher with HAART. This is attributed to defective humoral immunity, impaired interleukin-8 release from alveolar macrophages, and concomitant reduction in neutrophilic recruitment in persons with HIV infection.[34] Bacteria may reach the parotid gland via a hematogenous route, but the absence of significant systemic symptoms often suggests the more typical route of retrograde spread to the parotid gland from the oral cavity.[34,35] Acute suppurative sialadenitis is usually bacterial in nature. The link between acute suppurative sialadenitis and *S. pneumoniae* is, however, reported only in a few isolated cases and warrants further substantiation. Furthermore, it may be secondary to the salivary gland dysfunction in HIV SGD or, indeed, may occur as a result of medications unrelated to HIV treatment.

The incidence of HIV SG disease has persisted in the HAART era, even though the overall rate of oral lesions has decreased.[4] Considering the expansion of HAART, many factors need to be considered when monitoring salivary gland disease in patients with HIV infection. This includes, among other variables, the type, dosage, and duration of HAART administered; time of administration; stage of HIV; clinical and laboratory values during HAART; specific HAART regimens (first-, second-, or third-line); drug resistance; alternative drug use; patient compliance; access to HAART; and the patient's quality of life. Pre-existing disease, age of the patient, concomitant multi-morbidities, viral load and CD4+ count, and reactivation of clinically dormant opportunistic infections are additional factors to consider.[11]

Awareness of the spectrum of salivary gland pathology in HIV and AIDS is important because such manifestations may be an early sign of HIV infection and/or progression, and prompt recognition is invaluable in the diagnosis and treatment of both the salivary gland disease and potential or known HIV infection.

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