Viruses and Salivary Gland Disease (SGD): Lessons from HIV SGD

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ABSTRACT

Viral infections are often associated with salivary gland pathology. Here we review the pathogenesis of HIV-associated salivary gland disease (HIV-SGD), a hallmark of diffuse infiltrative lymphocytosis syndrome. We investigate the presence and contributions of viral diseases to the pathogenesis of salivary gland diseases, particularly HIV-SGD. We have detected BK viral shedding in the saliva of HIV-SGD patients consistent with viral infection and replication, suggesting a role for oral transmission. For further investigation of BKV pathogenesis in salivary glands, an *in vitro* model of BKV infection is described. Submandibular (HSG) and parotid (HSY) gland salivary cell lines were capable of permissive BKV infection, as determined by BKV gene expression and replication. Analysis of these data collectively suggests the potential for a BKV oral route of transmission and salivary gland pathogenesis within HIV-SGD.

HIV-ASSOCIATED SALIVARY GLAND DISEASE (HIV-SGD)

HIV-SGD is AIDS defining in pediatric HIV infection and has increased in the adult HIV population. The term ‘HIV-SGD’ was first coined by Schiødt *et al.* (1989) to describe an enlargement of major salivary glands and/or a complaint of xerostomia in the absence of xerogenic agents, medications, and diseases known to cause xerostomia in HIV patients (Schiødt *et al.*, 1989, 1992). In HIV-SGD, quantitative changes occur in the saliva—such as lower secretory rates of sodium, calcium chloride, cystatin, lysozyme, and total anti-oxidant capacity—which affect the homeostasis of the oral cavity and

account for significant morbidity during the progression of HIV disease (Lin *et al.*, 2003). Typically, HIV-SGD presents a unilateral or bilateral diffuse soft swelling resulting in facial disfigurement, and may be associated with pain. Histologically, HIV-SGD is characterized by hyperplastic, intraparotid lymph nodes and/or lymphatic infiltrates within the salivary gland tissue. This lymphocytic infiltrate consists predominantly of CD8 T-cells that are also CD29+, indicative of a memory cell phenotype. Recent histochemical analysis has revealed the location of the infiltrate as periductal with acinar atrophy, ductal dilation, and mild to moderate fibrosis with collagen deposition (McArthur *et al.*, 2003; Rivera *et al.*, 2003). HIV-SGD also affects the minor salivary glands, with labial salivary glands demonstrating features of sialadenitis.

HIV-SGD has been universally established as among the most important AIDS-associated oral lesions. Oral lesions are important clinical indicators of HIV/AIDS by suggesting HIV infection in the undiagnosed individual, indicating clinical disease progression, and predicting development of AIDS (Patton and van der Horst, 1999). Specific common oral lesions are strongly associated with immune suppression, as measured by CD4 cell counts, and are modestly associated with high viral burden, thus serving as potential clinical markers of HIV viremia and the consequent destruction of the immune system with progressive HIV disease. Since the introduction of highly active anti-retroviral therapy (HAART) in the mid-1990s, the prevalence of types of oral cavity infections of HIV-infected patients has changed over time, with hairy leukoplakia (HLP), oral candidiasis (OC), and oral Kaposi’s sarcoma (KS) decreasing and the incidence of HIV-SGD increasing (Patton *et al.*, 2000; Greenspan and Greenspan, 2002). For example, in an HIV-infected North Carolina population, HIV-SGD has gone from 1.8% in an early cohort to 5.0% in a late cohort (Patton *et al.*, 2000).

This increase in HIV-SGD after the induction of a HAART drug regimen is reminiscent of previously described cases of immune reconstitution disease (IRD). IRD among HIV-infected patients is an adverse consequence of restoration of immune responses during the initial months of anti-retroviral treatment (ART) (Lawn *et al.*, 2005). Rizos *et al.* (2003) described a patient on triple anti-retroviral therapy with excellent immunological and virological responses and parotid gland enlargement that may have reflected immune reconstitution. IRD typically occurs as a result of a pre-existing opportunistic infection or a subclinical infection becoming “unmasked” upon the

Key Words

Virus, salivary gland, HIV, DILS.

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Fig. HIV-associated salivary gland disease. **(A)** Detection of elevated BKV salivary levels in HIV SGD as compared with HIV individuals without the disease or with HIV-negative individuals. **(B)** Detection of labeled BKV virions. White arrows point to BKV virions (green) infecting salivary gland cells. Virions are detected throughout the cytoplasm. Nuclei are stained red. (Reprinted with authors' consent.)

introduction of HAART treatment, when HIV viral load decreases and CD4 count increases. Therefore, HIV-SGD presenting as an IRD implies that an infectious agent may play a role in its etiology.

In a prospective study, the association of a Sjögren's-like syndrome (SLS) with the progression of HIV-related disease in a cohort of HIV patients treated with HAART was evaluated (Mastroianni, 2004). The study identified four cases of SLS in a cohort of 150 HIV-positive patients treated with HAART, whereas none of the HIV-positive patients not treated with HAART fulfilled the diagnostic criteria for SLS. In conclusion, the study suggested that HAART treatment may play an important role in the etiology of SLS, and that SLS may be a new and important complication of long-term HAART regimens (Mastroianni, 2004). Interestingly, 75% of these patients did not express the autoantibodies typical of SS, and thus probably had HIV-SGD. This study highlights the clinically identical nature of the two diseases and provides further evidence that HIV-SGD increases with HAART therapy. As more people receive HAART therapy, the potential for increasing incidence of HIV-SGD grows.

In developing countries, the incidence of HIV-SGD has been reported to be as high as 48% of HIV-1-infected patients (McArthur *et al.*, 2000). Parotid gland lesions are generally much larger and more disfiguring in pediatric patients than in adults, and in most children xerostomia is not usually associated with parotid swelling, although in adult patients it is a fairly common complaint. In both adults and children, the lesion often occurs in conjunction with generalized lymphadenopathy. Reasons for the differences between the adult and pediatric manifestations are not yet understood (Leggott, 1992). In children with HIV infection, it

has been shown that the presence of salivary gland enlargement is associated with less rapid progression to death than is found in those with OC or herpes simplex. The time to death averages 5.4 years, compared with 3.4 years in those with OC (Katz *et al.*, 1993). This may be due to a protective effect of the CD8 T-cells that predominate in the lymphocytic infiltrate in the salivary glands in that condition and are part of diffuse infiltrative lymphocytic syndrome (DILS) (Itescu *et al.*, 1989, 1990). This is perhaps a marker of the ability of the host to respond to viral infection. The HIV-SGD disease process is of particular interest, because in 1-2% of patients, malignant lymphomas have been described in association with these glandular lesions, making this disease a pre-malignant lesion (Ioachim and Ryan, 1988; DiGiuseppe *et al.*, 1996).

DIFFUSE INFILTRATIVE LYMPHOCYTIC SYNDROME (DILS)

HIV-SGD reflects a localized manifestation of DILS that occurs in the parotid gland of HIV-positive persons. DILS is characterized by salivary and lacrimal glandular swelling and sicca symptoms of various degrees of intensity, accompanied by persistent circulating and visceral CD8+ lymphocytic infiltration of parotid glands, lacrimal glands, kidneys, muscles, nerves, lungs, and lymph nodes, in association with HIV infection (Itescu *et al.*, 1989). DILS has also been designated as a cystic lymphoid hyperplasia of AIDS and is a close phenotypic mimic of Sjögren's syndrome in terms of sicca symptoms, salivary glandular enlargement, histology, and predisposition to develop non-Hodgkin's lymphoma. The difference between DILS and Sjögren's syndrome (Table 1), however, lies in the frequent occurrence of

extraglandular sites of lymphocytic infiltration in DILS, the nature of the infiltrating lymphocytes—that is, CD8 in DILS vs. CD4 in Sjögren's syndrome—and the scarcity of serum autoantibodies in DILS (Itescu *et al.*, 1993). Other conditions that may mimic DILS include salivary gland tumors, especially papillary cystadenoma lymphomatosum, viral conditions such as parotitis, bacterial infections such as tuberculosis, or systemic diseases, for instance, sarcoidosis. Sialadenosis, related to endocrine and nutritional conditions or neurogenic medications, may also be included in the differential diagnosis (Ramos-Gomez, 2002). As in HIV-SGD, patients with DILS appear to be at a significantly increased risk of malignant lymphomas (Mandel *et al.*, 1998).

SGDs: INFECTIOUS ETIOLOGIC AGENTS?

In HIV-SGD, epidemiologic data point to an antigen-driven process. A prospective study that recognized that the epidemiology, clinical presentation, and certain extraglandular manifestations of HIV-SGD/DILS have changed concomitant with the introduction of HAART suggests that DILS is an antigen (viral)-driven response, and that the primary treatment for it is anti-HIV therapy (Basu *et al.*, 2006). Further evidence alluding to an infectious etiologic agent is in the form of data showing different rates of HIV-SGD in children (20–47%) vs. adults (3–7.8%) (DiGiuseppe *et al.*, 1996). We postulate that this may indicate primary viral infection in children vs. residual immunity in adults. Further, the infiltrating lymphoid cells present during HIV-SGD point to an antigen-driven MHC-determined host immune response (Itescu *et al.*, 1989). That the lymphocytosis within HIV-SGD is phenotypically an antigenically driven response may also implicate an infectious agent present during HIV immunosuppression.

It has been postulated that SS autoimmune disease is primed by viral infection. There is evidence that the type 1 interferon pathway is highly stimulated locally and systemically in SS (Ronnblom *et al.*, 2003). It has been suggested that viruses may initially infect the gland, leading to production of type 1 interferon by plasma dendritic cells. Interferon would then activate the adaptive immune system. Activation of the adaptive immune response would then result in auto-antibody immune response, even in the absence of virus.

VIRUSES AND SALIVARY GLAND DISORDERS

There is a long association between viral infections and diseases of the salivary gland. In general, viral infections of the salivary gland may result in reduced saliva production and/or swelling. Mumps is the most common salivary gland infection caused by paramyxovirus (Fields *et al.*, 1996). Paramyxovirus is transmitted by droplet infections carried in the saliva. There is a primary viral infection of the oral cavity and a multiplication of the virus in the upper respiratory tract and the regional lymph nodes. Paramyxoviral infection causes bilateral swelling of the parotids, although the other salivary glands may also be affected. However, subsequent to vaccine development, the incidence of mumps has been drastically reduced.

Several viruses, including DNA, RNA, and retroviruses, have been considered important co-factors in the development

Table 1. Comparison of Salivary Gland Disorders: HIV-associated Salivary Gland Disease vs. Sjögren's Syndrome

HIV-SGD/DILS	SS
<ul style="list-style-type: none"> • An AIDS-defining illness in pediatric HIV infection, affecting up to 60% of children worldwide • Incidence is increasing in the adult HIV population and post-HAART has become a hallmark of HIV-associated immune reconstitution syndrome • Infiltration of CD8+ T-cells 	<ul style="list-style-type: none"> • The second most common autoimmune rheumatic disease, affecting ~1 to 2 million Americans, with women affected 9x more frequently than men • EBV, KSHV, Coxsackie, and HTLV have been investigated as potential etiologic agents • Infiltration of CD4+ T-cells

of SS. The two DNA viruses that have been studied in association with pSS are cytomegalovirus (CMV) and Epstein-Barr virus (EBV) (Saito *et al.*, 1989; Mariette *et al.*, 1991; Maitland *et al.*, 1995). Overall, the data regarding CMV and EBV as causative agents for SS are contradictory, and, because pSS does not occur in most cases of viral reactivation *in vivo*, the link between reactivation and autoimmunity induction remains to be established. Two RNA viruses have been detected within the salivary glands of SS patients: hepatitis C and Coxsackie virus, both of which require more investigation before they are classified as being the etiologic agent of SS (Triantafyllou *et al.*, 2004; Carrozzo, 2008). Interestingly, four different retroviruses have been associated with pSS: human T-lymphotropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV), intracisternal A-type particles, and human retrovirus 5 (Garry *et al.*, 1990; Shattles *et al.*, 1992; Griffiths *et al.*, 1997; Yamano *et al.*, 1997). However, only HTLV-1 and HIV produce a Sjögren's-like syndrome with significant pathologic and clinical differences from pSS.

In HIV-positive patients, HIV p24 protein was detected in the salivary glands by an immunohistochemistry technique (Rivera *et al.*, 2003). Rivera's group was also able to identify Epstein-Barr virus (EBV) protein, but not cytomegalovirus (CMV), by immunohistochemistry in the salivary glands of HIV patients (Rivera *et al.*, 2003). Yen *et al.* (2004), however, concluded that CMV and KSHV were not associated with Benign Lymphoepithelial Cysts (BLC) of the parotid gland, although EBV was found more frequently in the disease than in normal parotid controls (Yen *et al.*, 2004). Human herpes virus 6 (HHV-6) and HHV-7 were also demonstrated in the salivary glands and in the saliva in HIV-positive persons (Di Luca *et al.*, 1995). However, their presence has not been attributed to etiological importance for salivary gland lesions. The lymphocytic infiltration observed in HIV-SGD/DILS may be an antigen-driven event, due to the presence of infection of the salivary gland. Papovaviruses have also long been associated with salivary gland disease development in experimental animals. Murine infection with polyomaviruses is associated with parotid gland tumorigenesis and has been implicated in human carcinogenesis (Imperiale, 2000). As

Table 2. Viruses Detected in the Salivary Gland

Virus	Associated Disease(s)
BK virus	HIV-SGD
Paramyxovirus	Mumps
Human immunodeficiency virus (HIV)	HIV-SGD, SS
Epstein-Barr virus (EBV)	BLC, salivary gland tumors, SS
Cytomegalovirus (CMV)	Sialadenitis
Coxsackie virus	SS
Human T-lymphotropic virus (HTLV)	SS
Human herpes virus 6 (HHV-6)	Parotitis
Human herpes virus 7 (HHV-7)	Parotitis
Kaposi sarcoma virus (KSHV)	Warthin's tumor, SS-associated parotid MALT lymphomas
Influenza	Parotitis
Parainfluenza virus (PIV)	Parotitis
Guinea pig CMV	Guinea pig CMV infection
Hepatitis C	SS
Mouse CMV (MCMV)	Acute and chronic SGD
Mouse polyomavirus (PyV)	Mouse parotid tumor
Encephalomyocarditis (EMC)	Sialodacryoadenitis

suggested by the body of work reviewed above, viral infection is tightly associated with salivary gland pathology (Table 2). With the exception of mumps virus and PIV, the majority of these human studies detected only viral nucleic acid, but did not determine whether salivary gland tissues are actually permissive for these agents.

VIRAL INFECTION AND HIV-SGD

The potential for a viral etiologic agent in HIV-SGD is highly feasible. We have detected BKV in the saliva of patients with HIV-associated salivary gland pathology and in healthy individuals (Jeffers *et al.*, 2009). Primary infections with BKV are typically subclinical or linked to mild respiratory illness (Fields *et al.*, 1996), followed by viral dissemination to the sites of lifelong persistent infection. The major site of persistence for BKV is the kidney and urinary tracts, with epithelial cells of the kidney, ureter, and bladder as the predominant cell types that are persistently infected (Fields *et al.*, 1996; Imperiale, 2000). Interestingly, with quantitative real-time PCR analysis, BKV DNA was detected in saliva samples from HIV-positive patients and healthy control individuals (Fig.). Like most opportunistic pathogens, BKV DNA was detected in the saliva at higher levels in immunocompromised patients compared with healthy individuals. BKV DNA levels were highest in persons with HIV-SGD.

To begin to decipher BKV pathogenesis within the salivary gland cell, it was essential to develop an *in vitro* model system. BKV infection was characterized in submandibular (HSG) and parotid (HSY) gland cell lines. These cells were able to support viral entry, transcription, translation, and virion production, and BKV infection could be inhibited by saturation of the capsid protein with its ganglioside receptor (Jeffers *et al.*, 2009). BKV entry into salivary gland cells was inhibited by the blocking of VP1 *via* ganglioside saturation, as had previously been shown in Vero cells (Sinibaldi *et al.*, 1990). As expected, viral transcription was more significantly diminished in the presence of

100 µg/mL ganglioside compared with 60 µg/mL in the salivary gland cells. Similar trends were observed in the Vero cell line upon ganglioside treatment. Likewise, a consistent decrease in viral protein expression was detected with ganglioside treatment in both salivary gland and Vero cells. The detection of labeled BKV virions within the cytoplasm of salivary gland cells confirmed BKV entry (Fig., C). In salivary gland cells, labeled virus was still detected at 48 hpi, while labeled virus was no longer detected in Vero cells at the same time-point, perhaps due to viral uncoating and entry into the nucleus. Viral gene products were first observed at 24 hpi for both T Ag and VP1 with real time RT-PCR, with viral transcription peaking at about 3 dpi for both submandibular and parotid gland cell infection. Protein expression was first detected at 4 dpi by immunoblot and immunofluorescence. While BKV transcripts were detected in abundance, the expression of viral-encoded proteins was more modest. The difference in mRNA *vs.* protein levels may reflect the decreased stability of the BKV T Ag protein. Productive infection was further substantiated by the detection of virions by EM at 5 days post-infection, as well as the presence of DNase-resistant virus in the supernatant. These virions increased over time and were used to infect naïve Vero cells. Interestingly, the kinetics of infection appeared to be slower in salivary gland cells than in kidney cells (Jeffers *et al.*, 2009).

We thus demonstrated that BKV was detected in oral fluids, and that BK infection and replication occur *in vitro* in salivary gland cells. Analysis of these collective data suggests the potential for the BKV oral route of transmission and oral pathogenesis.

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