



Sjögren's Syndrome and Viral Infections

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ABSTRACT

Sjögren's syndrome (SS) is a systemic autoimmune disease, characterized by lymphocytic infiltration of the secretory glands. This leads to dryness of the main mucosal surfaces such as the mouth, eyes, nose, larynx, pharynx, and vagina. Although there is little morbidity data at the initial diagnosis, SS may be a serious disease, with extra mortality caused by hematological cancer. The cause of SS is unknown, but factors postulated to play a role include genetic and environmental factors, hormonal abnormality, and viral infection. Under the influence of these factors, the immune system becomes abnormal and the tissue is damaged. In this study, we summarize recent developments in our understanding of the relationship between SS and viral infections, including Epstein–Barr virus (EBV), hepatitis C virus (HCV), human T cell lymphotropic virus type 1 (HTLV-1), cytomegalovirus (CMV), and human immunodeficiency virus (HIV).

Keywords: Sjögren's syndrome; Epstein–Barr virus; Hepatitis C virus; Human T cell

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lymphotropic virus type 1; Cytomegalovirus; Human immunodeficiency virus

Key Summary Points

Sjögren's syndrome is a multifactorial disease.

The pathogenesis of Sjögren's syndrome is obscure.

All kinds of viruses are linked with pathogenesis of Sjögren's syndrome.

Viruses are promising potential targets in curing Sjögren's syndrome.

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INTRODUCTION

Sjögren's syndrome (SS) is a common and chronic autoimmune disease that is

characterized by lymphocyte infiltration and inflammation in the exocrine glands, especially in salivary and lacrimal glands, resulting in secretory gland dysfunction [1]. SS mainly causes dry surfaces of oral cavity, eyes, nose, pharynx, throat, and vagina [2]. Notably, SS may be a serious disease with high mortality caused by hematological tumors [3]. SS was previously divided into primary Sjögren's syndrome (pSS) that occurs alone and secondary Sjögren's syndrome (sSS) that is associated with other diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) [4]. The new ACR/EULAR criteria no longer distinguish between primary and secondary SS. It may be more accurate to refer to SS as 'overlapping' with other rheumatic diseases [5, 6]. A serious complication of SS associated with increased mortality is the increased risk of lymphoma.

Although sicca symptoms, consisting of dry mouth and dry eyes, are some of the symptoms most commonly presented in general medicine practice, SS is often underestimated or misdiagnosed [7]. There are few incidence data in primary care, but preliminary reports show that the annual incidence rate is about 2/1000 [8]. A serious complication of SS associated with increased mortality is the increased risk of lymphoma. It has been reported that patients with SS have a non-Hodgkin's lymphoma risk increased by 6.5–16%, and a 1000-fold increase in the risk of parotid marginal zone lymphoma [9]. Patients with SS need to spend twice as much on health care as primary care patients, similar to those with RA [10].

The pathophysiology of SS is considered to be multifactorial, involving the interaction between genetic factors and exogenous and endogenous factors that can trigger abnormal autoimmune responses, especially mediated by T and B lymphocytes [11]. Inflammation increases tissue damage, leading to functional damage of affected organs and a chronic inflammatory environment. There are three recurrent events generally associated with SS: (1) a triggering period induced by environmental factors under specific epigenetic factors, genetic susceptibility, and hormone regulation; (2) dysfunction of normal salivary gland

epithelial cells; (3) chronic inflammation characterized by hyperactivity of lymphocyte B and autoantibodies [12, 13].

Currently, the pathogenesis of SS is not clear. It is considered to be due to the influence of multiple factors such as genetic defects, immune mechanism, and virus infection [14]. The genetic susceptibility to SS plays a role in the triggering stage of the disease. A strong correlation between HLA-DR and HLA-DQ alleles (belonging to MHC class II genome) and SS has been observed in different populations, including Caucasians, Japanese, and Chinese [15]. Moreover, some research has analyzed the contribution of epigenetics to SS and auto-antibodies production. The epigenetic processes more closely related to the disease are DNA methylation, as well as functions of circular mRNA, miRNA, and long non-coding RNA [16].

In this review, we summarize studies that focus on the relationship between SS and virus infection, including Epstein–Barr virus (EBV), hepatitis C virus (HCV), human T cell lymphotropic virus type 1 (HTLV-1), cytomegalovirus (CMV), and human immunodeficiency virus (HIV).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EBV and SS

Epstein–Barr virus (EBV), a γ -herpesvirus, widely exists in all populations and continues to exist in most individuals as a lifelong and asymptomatic infection of the B-lymphocyte pool [17]. EBV selectively infects B lymphocytes by binding to CD21 receptor on the surface of B-cells through the major viral envelope glycoprotein gp350 [18], and the second glycoprotein gp42 binds to human leukocyte antigen as a co-receptor [19]. EBV is a human cancer-related virus, infecting more than 90% of the world's population [20]. EBV infection has been linked to a series of lymphoid and epithelial malignancies, such as Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal cancer, and EBV-associated gastric cancer. In the past two

decades, there has been a growing interest in EBV-related epithelial tumors, which accounts for 80% of EBV-related malignant tumors [21].

Based on observations of primary SS following acute EBV infection, it becomes necessary to explore the relationship between EBV and SS, and whether target DNA of EBV exists in tissue samples from patients with SS is essential and first to confirm. Saito et al. used polymerase chain reaction (PCR) to detect EBV DNA in peripheral blood mononuclear cell (PBMC) and tissue biopsies of patients with SS. Their results show that EBV DNA is increased in the salivary gland of these patients [22]. Pufelder et al. found that EBV DNA sequences were detected in 50% of PBMC samples and 80% of lacrimal gland and tear specimens from SS patients [23]. Meanwhile, EBV-DNA has also been detected in parotid biopsy specimens of SS by Southern blotting and by slot-blot hybridization in parotid saliva of SS [24–26]. Tateishi et al. demonstrated that B cell lines of SS patients produce EBV at a higher frequency and in prominently larger amounts, than B cell lines from patients with systemic lupus erythematosus or RA [27], whereas Merne et al. found that EBV latent membrane protein- and DNA-positive staining in SS patients was comparable to control subjects'. The low frequency of EBV protein and DNA detected in biopsy specimens of SS does not indicate that the virus itself is the cause of SS [28]. Patrick et al. showed that a low occurrence of EBV DNA in biopsies and the normal levels of EBV antibodies in SS does not demonstrate that the virus itself is the causative agent [29]. Meanwhile, Sanosyan et al. indicated that EBV infection remains efficiently controlled in the blood of SS patients [30]. However, the possibility of EBV as a cofactor cannot be ruled out. Furthermore, EBV infection can develop diverse autoreactivities, including SS in genetically susceptible individuals, with different clinical features depending on the genetic make-up and the site of reactivation [31].

Three roles have been proposed for EBV in the pathogenesis of SS: (a) EBV exists in normal salivary gland epithelial cells, and the exaggerated immune response to EBV may play a role in the destruction of salivary glands in SS patients; (b) compared with normal salivary glands, SS

salivary gland biopsy contains more EBV DNA, suggesting that the virus activation and lymphatic infiltration of SS patients cannot govern the replication of EBV; (c) the salivary gland epithelial cells of SS patients express high levels of HLA-DR antigen, and may provide EBV-related antigens to immune T-cells of SS patients [32]. Whittingham et al. briefly described two cases of primary SS as a direct consequence of EBV infection. The inflammatory process of exocrine glands eventually leads to SS due to the combined effects of chronic EBV infection and autoimmunity [33]. Yamaoka et al. found that spontaneous transformation of B-cell lines can produce a large number of transformed EBV, which is preferentially established in SS patients, and EBV-specific regulatory mechanisms is impaired in these patients.

There are many mechanisms and theories about the effect of EBV on the autoimmune process of SS, including the similarity (molecular mimicry) between viral EBNA-2 protein and Ro-60 antigen or viral EBER-1 and EBER-2 proteins and La antigen. EBV infection increases the risk of EBV-related malignancies, and SS also increases the risk of some of them, which may result in risk compounding [34]. Moreover, Gallo et al. have demonstrated that a functional EBV microRNA, *ebv-miR-BART13*, can be transferred from B cells to salivary epithelial cells, where it downregulates STIM1 protein, thereby affecting the activation of key Ca²⁺ entry mechanisms required for fluid secretion. These results show a functional relationship between *ebv-miR-BART13-3p* and decreased salivary secretion in the salivary gland, and suggests that *ebv-miR-BART13-3p* may be a therapeutic target for refining xerostomia in SS patients [35].

EBV produces viral interleukin-10 (vIL-10), a product of EBV replication gene *bcrf1*, and its structure and function are similar to human cytokine IL-10. Importantly, vIL-10 inhibits cytokine production and B cell proliferation and differentiation of CD4 + T lymphocytes. As such, it affects the initial steps of the immune response, suppressing T cells of macrophages, dendritic cells, and lymphocytes, and the antiviral activity of interferon. This down-regulation of T-cell-dependent host response is one

of the strategies by which the virus avoids virus clearance by the host. All of these confirm the immunomodulatory and immunosuppressive effects of EBV [36].

T cells play an important role in the regulation and polarization of local autoimmune response infiltrated by exocrine lymphocytes. The overexpression of T cell co-stimulatory gene CD70 on CD4 + cells is caused by hypomethylation of CD70 promoter. It may contribute to pSS and self-reactivity to EBV infection [37, 38]. In EBV-related malignancies, CD70 is also expressed by B cells [38]. Meanwhile, in some individuals, due to EBV infection, autoimmune diseases are prone to occur. It is related to the increased absorption of virus by B cells (expression of CD21 receptor) or epithelial cells. Autoimmune EBV-infected B cells (maintained in the target organ) send co-stimulatory signals to auto-reactive T cells, but this signal leads to the activation of T cell apoptosis [39].

The theory of impaired EBV-specific T cell response in autoimmune diseases is based on the genetic susceptibility to CD8 + deficiency and the imbalance between CD4 + and CD8 + T cells (increased of CD4 + /CD8 + ratio). This mechanism leads to the development of autoimmune diseases such as RA, SLE, and pSS [40]. However, it is still controversial whether this defect may be caused by the accumulation of CD8 + T cells in target organs of autoimmune diseases.

Pender et al. have suggested that CD8 + deficiency, increased CD4 + /CD8 + ratio, combined with lack of sunlight and vitamin D deficiency, weaken host control of EBV infection [41]. EBV is also associated with increased susceptibility to EBV-related autoimmune diseases. Vitamin D reduces the CD4 + /CD8 + ratio, which is due to increase in the number of CD8 + T cells, and may play an important role in the CD8 + T cell response [42].

HCV and SS

Hepatitis C virus (HCV) is a linear single-stranded RNA virus discovered in 1989 [43].

Infection with HCV can lead to acute or chronic hepatitis, liver fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma [44]. Disease progression after HCV infection depends on factors including gender, coinfection with HIV, duration of chronic infection, and alcohol consumption [45]. Incidence of HCV infection is unevenly distributed in different countries, and is prevalent in the world, ranging from 0.5 to 6.5%. In Western countries and Australia, the rate ranges from 0.5 to 1.5%, reaching 2.3% in Southeast Asia and Eastern Mediterranean countries, 3.2% in China, 0.9% in India, 2.2% in Indonesia, and 6.5% in Pakistan; in sub-Saharan Africa, the prevalence of HCV infection ranges from 4 to 9% [46].

HCV is considered one of the viruses most frequently associated with autoimmunity. Extrahepatic lesions in patients with chronic HCV infection [47], whether clinical or immunological, may cause some systemic autoimmune diseases to meet the current classification criteria [48]. In 1992, Haddad and his colleagues found histological evidence of SS (Chisholm Mason grade 3 or 4) in 16 cases of breast cancer and 28 cases of chronic HCV infection. Since then, more than 400 cases of HCV-induced SS have been reported, making SS one of the most closely related systemic autoimmune diseases associated with hepatitis C [49]. Also, Dinescu et al. reported the cases of two female patients diagnosed with HCV chronic infection who were later diagnosed with HCV-induced SS [50].

By meta-analysis, results reported by Wang et al. suggest that HCV infection is associated with SS [51]. Arrieta et al. showed that HCV infects and replicates in the epithelial cells from salivary glands of patients with SS or chronic sialadenitis [52]. Manuel et al. revealed Th1/Th2 cytokine imbalance in patients with SS secondary to HCV infection. Furthermore, they found that the SS observed in some HCV patients could be explained as one of the extrahepatic manifestations of chronic HCV infection [53]. However, some extrahepatic manifestations in patients with chronic HCV infection may mimic the clinical, immunological, and histological manifestations of pSS. Therefore, HCV patients with sicca symptoms

and positive autoantibodies may be misdiagnosed as pSS [54].

HTLV-1 and SS

Human T-cell lymphotropic virus type 1 (HTLV-1), a member of the Delta retrovirus genus, was discovered in 1980 in T-cells of a patient with cutaneous T-cell lymphoma [55, 56]. Infection with the HTLV-1 is related to the development of an aggressive form of T-cell leukemia known as adult T-cell leukemia/lymphoma (ATLL) [57]. Globally, HTLV-1 infects about 5 to 10 million people, with the highest prevalence in southern Japan, the Caribbean, South America, Africa, northeast Iran, Melanesia, Romania, and Australia [58].

Terada et al. found that HTLV-1 seroprevalence rate among the SS patients (17/74, 23%) is significantly higher than that among blood donors (916/27284, 3%). These findings strongly suggest that HTLV-1 is involved in the pathogenesis of the disease in a subset of patients with SS in endemic areas [59]. Nakamura et al. analyzed HTLV-1 virological and histopathological in two cases of anti-centromere-antibody-seropositive SS, and found that a high HTLV-I viral load in situ is supposed to promote the production of cytokines, especially TGF- β , leading to the fibrous change of labial salivary glands in anti-centromere-antibody-seropositive SS patients [60]. Meanwhile, Lee et al. observed that SS can be distinguished based on the expression of HTLV-1, and showed that HTLV-1 in the salivary glands is involved in the pathogenesis of a subpopulation of patients with SS, and that HTLV-1-related SS may have different immunological patterns than idiopathic SS [61].

CMV and SS

Cytomegalovirus (CMV) is human herpesvirus type 5 and an agent of a global infection, although there are differences in seroprevalence among countries [62]. The seroprevalence of CMV is about 40–50% in highly developed countries, 95% in developing countries, 30% in children, 50% in women of childbearing age,

and 60–70% in adults [63, 64]. On the other hand, the incidence rate has been decreasing slowly over the years. In industrialized countries, CMV infection rate is 1–7% per year [65, 66].

To explore the possible relationship between SS and CMV, Scully et al. examined serum antibodies to CMV in patients with SS, using enzyme linked immunosorbent assay (ELISA). The result demonstrates that patients with SS do not have significantly different CMV antibodies compared with healthy controls [67]. Meanwhile, Venables et al. showed false-positive IgM anti-CMV antibodies detected in serum from one patient with SS [68]. Furthermore, CMV has been detected in a patient with RA, and none detected in biopsies of minor salivary glands [69].

HIV and SS

Human immunodeficiency virus (HIV), a lentivirus, causes HIV infection and, over time, acquired immunodeficiency syndrome (AIDS) [70]. It infects vital cells in the human immune system such as helper T cells (specifically CD4 + T cells), macrophages, and dendritic cells [71]. HIV infection leads to low levels of CD4 + T cells through a number of mechanisms [72]. The virion enters macrophages and CD4 + T cells by the adsorption of glycoproteins on its surface to receptors on the target cell followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell [73, 74].

Coll et al. explored the relationship between HIV and autoimmune diseases. Their results show that the presence of antibodies to p55 or p68 proteins of HIV in patients with SS or SLE proved to be the only statistically significant difference between the other autoimmune diseases studied and the control group. Importantly, PCR assay was performed to rule out the presence of HIV [75]. Furthermore, Yamano et al. showed that target genes for HIV are not detected in any of the salivary gland tissues or peripheral blood mononuclear cells from SS patients [76].

CONCLUSIONS

Sjögren's syndrome is a multifaceted disease that combines pleiomorphic systemic autoimmune manifestations, glandular manifestations, common psychosomatic factors, and the possible progression to non-Hodgkin lymphoma. SS management has two complementary aspects: improving the quality of life of patients by symptomatic treatment of dryness, fatigue, and chronic pain through multidisciplinary approaches; and treating systemic symptoms to prevent injury, which could otherwise worsen life and functional outcomes. Although we know more and more about the pathophysiology of SS, there are still many questions to be answered. SS is characterized by lymphoplasmacytic infiltration of exocrine glands. The etiology of SS is complex, which is affected by genetic, epigenetic, hormone, and environmental factors.

Target genes and/or proteins of EBV, HCV, and HTLV-1 are detected in patients with SS, and the antibody of CMV and proteins of HIV do not significantly exist in SS group compared with control group. Recent reports provide evidence that EBV is involved in SS patients. Furthermore, there are many mechanisms and theories about the effect of EBV on the autoimmune process of SS, and there are few reports on the relationship between other viruses and SS. Although SS may be associated with viral infection, the most common antiviral drugs do not seem to show real benefits in the treatment of SS [47]. In fact, since viral infection may trigger the disease, subsequent antiviral therapy can control persistent infection, but it has no effect on persistent diseases that may no longer depend on the initial viral infection.

The pathogenesis of SS, as caused by viral infection, is not fully understood. As is well known, animal models are powerful study tools for clarifying the pathogenesis of human diseases. So far, many mouse models of SS, including induced models and genetic models, in which mice spontaneously develop SS-like disease, have been established [77, 78]. We look forward to more thorough exposition of the

relationship between SS and viral infection based on animal models.

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Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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