Cytomegalovirus

Cytomegalovirus (CMV) is a common infection with a seroprevalence among adolescents ranging from 47% to 89%.[49] The persistence of CMV with alteration of cell surface expression in certain tissues may initiate the tissue destruction that leads to the clinical manifestations of Sjögren's syndrome. Ductal cells of salivary and lacrimal glands are immunologically attacked due to CMV antigenic expression. The destruction of these ducts leads to xerostomia.[50] However, no relationship between xerostomia and anti-CMV antibodies was noted.[51]

Human T-lymphotropic virus type 1

Human T-lymphotropic virus Type 1 (HTLV-1) is known to cause HTLV-associated myelopathy (HAM)/tropical spastic paraparesis and adult T-cell leukemia.[52] It is estimated that 15-20 million persons are currently infected with HTLV-1 worldwide.[53]

Retroviruses such as HTLV-1 and HIV infect immunocompetent cells, resulting in the destruction or overstimulation of T-cells, and act as potential triggers for autoimmune disease.[54]

Previous studies reported a high prevalence rate of anti-HTLV-1 antibodies in the peripheral blood in 3.8-36.7% of patients with Sjögren's Syndrome.[55-58]

Bacterial infections

Actinomycosis

Actinomycosis is an anaerobic bacterial infection affecting men more frequently between the ages of 30-60 years. Almost half of actinomycosis cases occur in the cervicofacial region, and salivary glands may be involved as well. The organism can colonize inside the ducts of both submandibular and parotid glands and leads to abscess formation in the submandibular and masseter spaces, respectively.[59-61]

Autoimmune diseases

Rheumatoid arthritis

Rheumatoid arthritis is a systemic disease of connective tissue origin, which affects 1% of the world population. Women have a 3-fold higher incidence than do men. RA frequently presents with extra-articular features such as hematologic, neurologic, and cardiovascular involvement concomitant with dysfunction of lacrimal and salivary glands. Zalewska *et al*. showed impairment of salivary immunity system of the oral cavity in xerostomic patients with RA.[62] Secondary Sjögren's syndrome is associated with xerostomia and occurs with autoimmune diseases most frequently with RA.[63]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an inflammatory connective tissue disease with characteristic autoantibodies. SLE is much more common in women than men. It may occur at any age, but appears most often in people between the ages of 10 and 50. More than 75% of patients with SLE are affected with xerostomia. Coexistence of Sjögren's syndrome and SLE has been found in 1/3 of SLE patients. SLE has been shown to be associated with a decreased unstimulated salivary flow rate.[64]

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a cholestatic autoimmune disease predominantly of middle-aged women with progressive destruction of interlobular bile ducts.[65] The most autoimmune disease in PBC patients is Sjögren's syndrome[66] whose symptoms have been observed in 47-73% of patients[67,68] Xerostomia as well as dysphagia seems to be associated with PBC.[69]

Scleroderma

Progressive systemic sclerosis or scleroderma is a chronic sclerotic disease with deposition of extracellular matrix throughout connective tissue and vascular abnormalities, which leads to tissue hypoxia.[70] Fibrosis of capillaries, excretory ducts and acini of salivary and lacrimal glands are associated with xerostomia as oral manifestations of scleroderma.[71] Lymphocytic infiltration has been observed among 15% of patients with systemic sclerosis, which is a sign of secondary Sjögren's syndrome.[72]

Granulomatous diseases

Sarcoidosis

Sarcoidosis is a systemic inflammatory disease with unknown etiology characterized by the presence of noncaseating granulomas that can affect any organ (mostly lungs and lymph nodes).[73] Coexistence of parotid and submandibular gland swelling and xerostomia has been reported in sarcoidosis patients.[74-76] Mansour *et al*., identified five patients representing both clinical and histological features of Sjögren's syndrome and sarcoidosis, suggesting inclusion of sarcoidosis as diagnostic criteria for Sjögren's syndrome.[74]

The salivary glands could be affected by sarcoidosis as well, which was reported in 6% of the cases. Parotid salivary gland enlargement was also detected in 6% of the patients.[74] Parotid gland enlargement in patients presenting with Sicca symptoms is believed to be of clinical significance. Such finding might be more likely associated with sarcoidosis, especially in patients presenting with negative serologic profiles.[74]

Tuberculosis

Tuberculosis (TB) is a chronic bacterial infection, caused by Mycobacterium TB leading to formation of granulomas in infected tissues. The lungs are most commonly affected, but other tissues, including the salivary glands, may be involved. Patients with TB may experience xerostomia and/or salivary gland swelling, with granuloma or cyst formation within the affected glands. Salivary gland enlargement usually presents as part of a characteristic symptom complex, however salivary

gland changes have been reported in the absence of systemic symptoms.[77]

Granulomatous diseases such as sarcoidosis and TB may cause salivary gland hypofunction and lead to xerostomia.[78]

Storage diseases

Hemochromatosis

Hemochromatosis is defined as a pathological condition with iron overload in vital organs with a hereditary/primary cause.[79] Organs commonly affected by hemochromatosis are liver, heart, and endocrine glands. Iron deposition in salivary glands causes hyposalivation. Patients with normal ferritin level had normal salivary flow rate, whereas those with high levels of ferritin showed decreased stimulatory salivary flow rate.[79,80]

Amyloidosis

Amyloidosis is characterized by deposition of an extracellular protein-like material called amyloid. Amyloidosis causes various effects on different organs with a variety of extensions. In addition, amyloidosis may be associated with multiple myeloma or chronic infections. Amyloidosis may be accompanied with oral involvement in the form of macroglossia (10-40%), oral amyloid nodules, and dry mouth due to amyloid infiltration and destruction of salivary glands.[81] A case of pSS manifested as localized cutaneous nodular amyloidosis has been reported.[82] Meanwhile, a relationship between amyloidosis and xerostomia has been documented.[82-84]

Others

End-stage renal disease

End-stage renal disease (ESRD) represents a clinical state or condition with irreversible loss of the endogenous renal function to a degree, which is sufficient to render the patient permanently dependent upon renal replacement therapy in the form of dialysis or kidney transplantation. ESRD leads to accumulation of certain toxic elements, which affects normal functions of the body, and may have significant complications including cardiovascular disease, immune deficiency, anemia, renal function impairment, and bone disease.[85] Xerostomia was found in 28-59% of ESRD patients due to inability of kidneys to reabsorb sodium and the resultant polyuria.[86,87]

Ectodermal dysplasia

Ectodermal dysplasia is a hereditary disease causing anomalies in tissues of ectodermal origin. The significance of this disease lies in severe hypodontia, and an accompanying hypoplasia of the alveolar process. The clinical condition is aggravated by a significant xerostomia as a result of salivary gland aplasia or hypoplasia.[88,89] However, in some patients with ectodermal dysplasia with the presence of salivary glands, hyposalivation have been reported. In a study of 39 patients with ectodermal dysplasia, salivary flow rate was decreased in 13 (33.3%) patients.[90]

Hematopoietic stem cell transplantation and chronic graft-versus-host disease

Chronic graft-versus-host disease (cGVHD) is a multi-organ involvement that occurs post hematopoietic stem cell transplantation (HSCT), with the mouth being one of the most frequently affected sites.[91] The pathogenesis of GVHD is based on donor graft T-lymphocytes that recognize antigenic disparities between donor and recipient and the dysregulation of a broad panel of cytokines. GVHD occurs in 40-70% of patients treated by bone marrow and peripheral blood stem cell transplantation.[92] Oral manifestations are common in patients diagnosed with chronic graft-versus-host-disease.[91] Hull *et al*. mentioned xerostomia as the most common oral symptom in patients with history of HSCT with the majority of patients (53%) having clinical markers of oral cGVHD.[93] Noce *et al*. reported that 59.1% of patients diagnosed with cGVHD had salivary gland dysfunction.[91] Boer *et al*. showed a decrease in salivary flow rate (16% of patients) and a relation between hyposalivation intensity and elapsed time after HSCT.[94] There is similarity in oral clinical manifestations of GVHD and Sjögren's Syndrome because of the same autoimmune nature, but differences have also been found.[95] The suggested pathophysiological mechanisms of xerostomia and hyposalivation observed in GVHD are lymphocytic infiltration, parenchymal destruction, and fibrosis within salivary gland tissue.[95]

Parkinson's disease

Parkinson's disease (PD) is a relatively common, progressive, debilitating, and neurological disorder. Cardinal symptoms are resting tremor, bradykinesia, akinesia, restricted mobility, and postural instability. Levodopa (L-DOPA) has been used as a primary drug for over 30 years. L-DOPA is converted into dopamine in the dopaminergic neurons by DOPA decarboxylase enzyme. Proulx *et al*. have reported that patients with PD produce less saliva than normal. Factors influencing the production of saliva include the use of levodopa and female gender.[96] Hyposialorrhea is an early autonomic manifestation of PD.[97]

Conclusion

Salivary glands are involved due to many systemic diseases with the resultant complication of xerostomia. Autoimmune diseases, diabetes mellitus, ESRD, and GVHD are frequently associated with salivary hypofunction. The underlying mechanism of xerostomia differs in terms of disease. Autoimmunity accounts for xerostomia related to SLE, RA, PBC, thyroid disease, and some viral infections. Some conditions affect salivary glands through infiltration of immunocompetent cells or granuloma formation such as HIV infection, GVHD, sarcoidosis, and TB. Polyuria and dehydration is responsible for dry mouth associated with diabetes and end-stage renal failure, while GVHD and scleroderma cause xerostomia because of fibrosis. Deposition of proteinaceous substances and bacterial infection are also mentioned as alternative mechanisms for xerostomia.

Identification of the main reason of xerostomia helps attain timely diagnosis and more appropriate treatment plan.

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