SJOGREN'S SYNDROME REVISITED: AUTOIMMUNE EPITHELITIS

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Eponyms have been used in the medical literature either to honour the first person who described the disease or the location where the disorder was first described. In that respect, Sjogren's syndrome (SS) was named after the Swedish ophthalmologist who pointed out that dry eyes and dry mouth constitute local manifestations of a rather systemic syndrome. Clinical and pathogenetic studies suggest that descriptive term for SS should be used.

This is an autoimmune disorder of unknown aetiology characterised by lymphocytic infiltration of the salivary and lacrimal glands leading to xerostomia and keratoconjunctivitis sicca. In some patients sicca symptoms predominate which is called Primary Sjogren's (sicca syndrome), while in others it is associated with another connective tissue disease such as Rheumatoidarthntis (RA), Systemic lupus erythematosis (SLE), Primary and secondary sjogren,s (PSS) or mixed counective time disorder (MCTD) and therefore it is called. Secondary Sjogren's Syndrome. The main features of primary and secondary Sjogren's syndrome are contrasted in the information table-I.

INCIDENCE AND PREVALENCE

The disease predominantly affects women in the third or fourth decades of life. Although precise incidence figures are not known, it has been suggested that sjogren's syndrome is the second most common rheumatologic disorder in the United States. Up to 30 percent of patients with Rheumatoid arthritis, 10 percent of patients with systemic lupus erythematosus, and I percent of patients with scleroderma have been reported as having secondary sjogren's syndrome. Immunogenetic predisposition appears to play an important role in the incidence of sjogren's syndrome. The frequency of the HLA-B8, HLA DRW3 and the MT-2 histocompatibility antigens is significantly increased in patients with primary sjogren's syndrome.

HISTOPATHOLOGY

The major histopathological lesion of this syndrome is a round cell infiltrate which affects the exocrine glands; in the early lesions, it begins around ductal epithelial cells, whereas in advanced lesions the infiltrate extends and replaces the functional tissue.[1] This results in glandular dysfunction and manifests clinically with dry eyes, mouth, nose, airways, atrophic gastritis, subclinical pancreatitis and dry skin. This is called glandular, SS since exocrine glands are primarily affected. However, the lymphocytic infiltrates extends beyond the exocrine glands and affect parenchymal organs such as the thyroid, liver, kidneys and lungs. Thus, this name does not completely describe the syndrome. Careful analysis on clinical and immunopathological

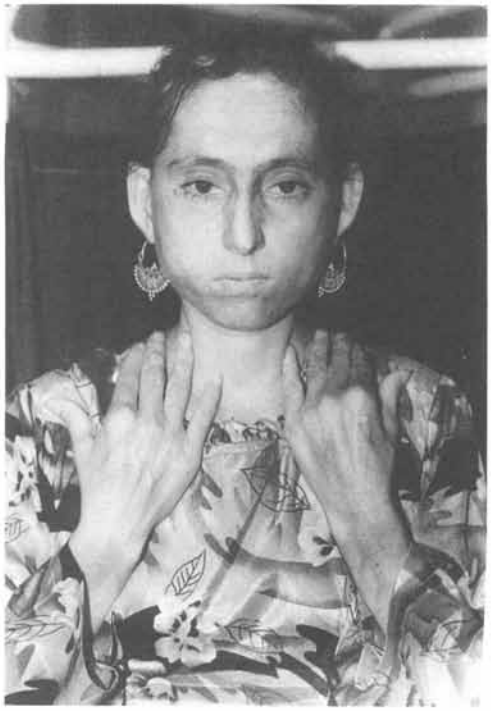
TABLE – I

PRIMARY AND SECONDARY SJOGREN'S SYNDROME

PRIMARY SJOGREN'S (SICCA) SYNDROME	SECONDARY SJOGREN'S SYNDROME
Age of onset 40-60	Age of onset 40-60
HLA-B8 DR3	HLA-B8 DR3 Incidence 10% RA patients
• **Common clinical features** Kerato conjuctivitis sicca Xerostomia Salivary gland enlargement	**Common clinical features** Mild Keratoconjunctivitis sicca Dry Mouth
• **Rarer clinical features** Anaemia, Leucopenia Thrombocytompenia Hepatomegaly Hyperglobulinaemic purpura Vasculitis Neuropathy Myositis Fibrosing Alveolitis Glomerulonephritis Renal tubular acidosis Lymphoreticular malignancy	**Other associated autoimmune disorders** Systemiclupus Erythematosus progressive systemic sclerosis Primary biliary cirrhosis Chronic active hepatitis Myasthenia gravis Polymyositis Throiditis
• **Autoantibodies frequently detected** Rheumatoid factor ANF SS-A (Anti-Ro) SS-B (Anti-La) Salivary duct Gastric parietal cell Thyroid	**Autoantibodies frequently detected** Rheumatoid factor ANF Salivary duct Gastric parietal cell Thyroid

grounds shows that the major cell affected in both glandular and extraglandular syndrome mainly concerns the epithelia.

The histopathological lesion of the kidneys resembles that seen in the exocrine glands (focal infiltrates around tubular epithelium which extend and occupy the interstitium), resulting clinically in a tubular defect with or without acidosis.[3] Lung disease in SS is slowly progressive, affecting mainly the airways and the interstitial space, rarely leading to severe interstitial disease.[4] In a recent study of non-selected and consecutive patients with SS, almost all of the patients presented with expiratory airflow indices compatible with mild small airways obstruction, and this was correlated with a reduced alveoli-arterial oxygen difference. Chest radiography revealed a pattern compatible with minimal to mild interstitial disease. Computerized chest tomography in patients with major radiographic findings showed that the main lesion consisted of thickened bronchial walls, while the mild interestitial pattern was located around bronchi. Transbronchial biopsy performed in patients with follicular bronchiolitis on tomography showed that the



37 years old lady with secondary SS in MCTD

The Schirmer Tear Test in SS

lymphocytic infiltrates were around bronchi adjacent to the bronchial epithelial cells. These findings suggest that initially the round cell infiltrates start in the large airways around exocrine glands and subsequently, as the disease progresses, extend to the peripheral airways. The initial lesion leads to destruction of the large airways exocrine glands which clinically presents as xerotrachea, while in the later stages in a small number of patients spilling of lymphocytes from pheribronical areas to the interstium leads to the subclinical interstitial diseases.[5]

Liver involvement in SS patients is rare, but the co-existence of liver disease and the presence of circulating antimitochondrial antibodies in patient's sera points to the possibility that liver pathology might be autoimmune and similar to that of primary biliary cirrhosis. In fact, the main histopathological finding in the liver biopsies of patients with SS and antibodies to mitochondria and / or elevated liver enzymes is a perichologangial lymphocytic infiltration similar to that found in stage I of primary biliary cirrhosis.[6] The aforementioned observations on kidney, lung and liver in SS patient strongly suggest that the extraglandular autoimmune insult is due to the attraction of lymphocytes by epithelial cells from the renal tubules, the bronchi and the cholangial ducts. The fact all these cells have been shown to share ca common antigen: carbonic anhydrase II.[7] Cellular and humoral responses against this molecule were found in patients with SS and chronic pancreatitis.[8,9] Furthermore, autoimmune sialoadenitis was induced in mice by intradermal immunization with human carbonic anhydase II.[10] These observations are of interest, but further work is needed to evaluate the relationship of this antigen with the autoantigens to which an autoimmune response is known in SS patients.

SS extends from benign lymphoproliferation which, as we have described, concerns glandular and parenchymal organs, to malignant lymphoproliferation which affects B lymphocytes. Recent work has reveled that these cells arise mainly from mucosa-associated lymphoid tissue.[11] This observation further strengthens the hypothesis that chronic activation of lymphosytes by mucosal epithelial cells leads to lymphoid malignancy.

Immunopathological studies suggest that all immunocytes occupying the minor salivary glands of SS patients are activated and most of them are T cells bearing the phenotype of memory cells.[12] B cells constitute the one fourth of the invading lymphocytes, while monocytes-macrophages are very poorly represented in the lesion. Recent preliminary observations revealed that these cells also inappropriately express the nuclear antigen La/SSB on their surface.[13] Furthermore, studies of imprints of conjunctival cells with monoclonal antibodies demonstrated that these cells also inappropriatly express II molecules and La/SSB autoantigen in their membranes.[12] Studies of the proto-oncogene RNA expression of the minor salivary glands of SS patients showed that c-myc was only expressed from the epithelial glandular cells and not from the activated lymphocytes.

Evaluation of cytokines by in situ hybridization in labial salivary glands revealed that the RNA message of proinflammatory cytokines (II-6) comes not only from the infiltrating lymphocytes, but also from the epithelial cells.[14] Finally, insertion of proviral retroviral sequences in the epithelial cells of primary SS patient altered characteristics and these characteristics are selectively expressed by these cells. The significance of the epithelial cells is further attested to in the autoimmune sialoadenitis which develops in tax transgenic mice. The model reveals that the tax gene is epitheliotrophic; after insertion of the gene. The epithelia enlarge and subsequently lymphocytes are attracted which produce the Sjogren's like picture in these animals.[15] On the basis of the summarized clinical and immunopathological studies, the term used for Sjogren's syndrome should reflect both the pathogenetic process and the major cells which probably initiates it. The term autoimmune epithelitis precisely expresses both.

DIAGNOSIS

1. The Schirmer tear test, in which a standard strip of filter paper is placed on the inside of the lower eye-lid; wetting of less than 10 mm in 5 min indicates defective production.[16] If the measurement is low, the schinmer II test is performed by stimulating the nasolacrimal reflex by inserting a Q-tip into the nose.

2. i. Rose Bengal staining of the eyes showing punctate of filamentary keratitis. ii. Slit lamp examination of the eyes after putting a small drop of flourescin inside lower eye lid.

3. Laboratory abnormalities include raised immunoglobulin levels circulating immune complexes and many autoantibodies. Rheumatoid factor is usually positive, antinuclear antibodies are found in 60-70% and antimitochondrial antibodies in 10% of cases. Anti-Ro (SSA) antibodeis are found in 70% of cases compared with 10% of cases of RA and secondary sjogren's syndrome. Th is antibody is of particular interest because it can across the placenta and cause congenital heart block.

4. Lip biopsy: tissue from the minor salivary glands on the inside of the lip is taken. The detailed histology is already discussed earlier.

MANAGEMENT

Although there is no cure but significant symptomatic improvement can be achieved

and many serious complications can be avoided by recognition and early treatment of the glandular and extra glandular manifestations of sjogrens syndrome. The pain due to arthritis is usually controlled with simple analgasic eg aspirine preferably enteric coated. Non steroidal anti inflammatory drugs (NSAIDS) have become very popular during the last decade for the treatment of head aches, joints and muscle pains. Although these madications are considered as a single group (i.e. voltaran, Neproxen, Indocid, Clinoril, Ansaid, Relifax, Faypro and others) individual patients may have good response to one drug and no response to another drug.

Steroids[17] are stronger drugs that work very effectively to decrease the inflammatory response. Unfortunately these drugs have many side effects when taken for prolonged periods including diabetes, hypertension, osteoparosis, catarcts and increased risk of infection. However steroids work rapidly and must be used in certain situations. Attempt to taper the dose of steroids should be persued to avoid the side effects. Disease modifying anti-rheumatic drugs called (DMARDS) were first developed for rheumatoid arthritis and systemic lupus erythomotosis but are also frequently used in sjogrens syndrome. The different DMARDS, used now a days are chloroquine, plaquanil, imuran, mathotrexete and cyclosporin A. The treatment may include different way to relieve other common symptoms such as dry eye, dry mouth and vagina. These measures are briefly discussed below.

For dry mouth:

- Sip fluids throughout the day.
- Use sugar-free gum or candies to stimulate saliva production.
- Try saliva substitutes or mouth coating products. They may be useful in some people, and are available without a prescription.

To prevent dental cavities.

- Have frequent dental checkups.
- Use mouth rinses that contain fluoride.
- Brush and floss your teeth regularly.
- Use sugar free products.

For dry eyes:

- Use artificial tears or eye drops to help relieve the discomfort of dry eyes. Use preservative-free products, if you apply the drops more than four times.
- Try lubricating ointments or small, long acting pellets for overnight or long-lasting relief.
- The ophthalmologist may recommend a simple operation that blocks tear drainage from eyes.

For dry skin:

- Use moisturizing lotions for sensitive skin.
- Avoid draught from air conditioner's heaters, and radiators, when possible.
- Use a humidifier in your house and at work.

For vaginal dryness:

- Use lubricants made specifically to help vaginal dryness. Do not use petroleum jelly.

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