Sjögren’s Syndrome

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History

- **Mikulicz** - first description of Sjögren’s syndrome

- **Mikulicz’s syndrome** - 1892 described parotid and lacrimal gland enlargement associated with a small round cell infiltrate.

- However, the term Mikulicz’s syndrome could encompass so many different entities including tuberculosis, other infections, sarcoidosis, and lymphoma. Therefore not given credit for discovery.

- The term is still occasionally used to describe the histological appearance of focal lymphocytic infiltrates on salivary gland biopsies.
History

Henrick Sjögren 1899-1987 Sweden

1930-As ophthalmology resident discover women with rheumatism and corneal abrasions who could not produce tears when crying and could not dissolve a lump of sugar in their mouths.

1933-Published his thesis paper on Keratoconjunctivitis Sicca, describing 15 women with lacrimal gland dysfunction leading to ulcerative lesions of the eyes. Was not well received, did not acquire Docenti (Academic PhD).

1951-Sjögren published a series of papers describing 80 patients with the syndrome, in which the majority had arthritis. Sjögren’s syndrome was then recognized in literature.
Sjögren's (show-grin) syndrome - a syndrome describing xerophthalmia (dry eyes) and xerostomia (dry mouth) - (Sicca complex) - due to immune-mediated destruction of exocrine glands, predominately of lacrimal and salivary.
Primary Sjögren’s syndrome - characterized by Sicca complex and extra-glandular symptoms without any additional connective tissue disorder.

Secondary Sjögren’s syndrome occurs in association with another autoimmune disorder such as SLE, RA, or scleroderma.
Incidence

As many as 1-2 million people in the US are affected,

Prevalence of 1-3% of the population
It is in the top three of rheumatic diseases behind systemic lupus erythematosis and rheumatoid arthritis

Approximately 30% of RA pt have SS.
Primary Sjögren’s Syndrome has a ratio 9:1 of women to men. Age range from 40-60, with mean of 52.7 years. However, case reports have been seen in children.
Pathogenesis of Sjögren’s syndrome is believed to be multifactorial.

Known to be autoimmune, but studies suggest that the disease process has genetic, environmental and neuroendocrine components.
Etiology

- There is a genetic predominance of HLA-DR genotype in SS patients. HLA-DR is a major histocompatibility complex, MHC class II cell surface receptor. It is found on antigen presenting cells.

- These genotypes may also produce dysfunctional glands that secrete abnormal amounts of immune-stimulatory chemokines. This is not seen in patients without Sjögren’s disease.
Etiology

- Autoimmunity involved in Sjögren’s disease is still poorly understood. It is believed that genetically defective glandular tissue combined with immunologic, environmental or neuroendocrine factors leads to loss of self antigen awareness.

- Environmental factors may have link to viruses (Epstein–Barr virus, hepatitis C virus, human T-cell leukemia virus-1)

- After the initial trigger, this glandular tissue autoimmune complex then becomes infiltrated with lymphocytes, predominately CD4 T cell (attracted by MHC class II)

- A cascade of events then occur with the CD4 T cell release of cytokine IL-1, TNF, and interferon-gamma, which have destructive effects on the tissue and interfere with acetylcholine release, causing dysfunctional glands.
# Clinical Manifestations

<table>
<thead>
<tr>
<th>Glandular</th>
<th>Sinus/nasal</th>
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<tr>
<td>Ocular</td>
<td>Hepatobiliary and gastrointestinal</td>
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<tr>
<td>Oral</td>
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<tr>
<td>Otological</td>
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<td>Laryngeal</td>
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<td>Thyroid</td>
<td>Neurologic</td>
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<tr>
<td>Pulmonary</td>
<td>Hematologic/lymphatic</td>
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Glandular manifestations

- Decreased lacrimal flow
- Corneal and conjunctiva epithelia damage
- Leads to dry eyes, foreign body sensation, irritation, photosensitivity, thick secretions at inner canthus, and visual impairment.
Sjögren’s syndrome

dry eye
Glandular manifestations

- Involvement of unilateral or bilateral major and minor salivary glands
- Decreased salivary secretions - loss of lubrication, buffering and antimicrobial capacities of saliva.
- Most common complication is increase in dental caries, especially root and incisor caries.
- Frequent fungal infections
- Tongue fissures
- Persistent salivary enlargement.
Tooth decay due to xerostomia
Acute pseudomembranous candidiasis
Parotid Enlargement
occurs in 1/3 of SS patients
Clinical Manifestations

- SS patients typically demonstrate mild to moderate sensorineural hearing loss in high frequencies.
- An association with anti-cardiolipin antibodies has been demonstrated, but no cochlear or vestibular pathology has been found.
- May be caused by immune complexes in the stria vascularis of the basal turn of the cochlea.
Clinical Manifestations

- Granulomatous and non-granulomatous laryngeal nodes have been described.
- Bamboo nodes - whitish or yellowish transverse submucosal lesions localized to middle third of vocal fold.
- However, hoarseness is rare first symptom
Bamboo nodes
Clinical Manifestations

- thyroid abnormalities such as Hashimotos’s thyroiditis are associated with SS
- Antibodies to thyroglobulin can be found in up to 1/2 of SS patients
- 10-15% of Primary SS are clinically hypothyroid
- Therefore, all patients with SS should undergo routine evaluation of thyroid function
Epistaxis and nasal crusting are common findings in SS, with 50% having nasal mucosa hypertrophy and up to 13% have septal perforations.

Xerotrachea (dry cough) and dyspnea are common pulmonary symptoms.

Esophageal spasm and dysmotility are also seen, but may be secondary to absence of saliva.

Atrophic gastritis, celiac disease
Clinical Manifestations

- Lymphoma is a serious complication of SS, occurring late in the disease.
- Risk of lymphoma is 44 times greater than the general population.
- Lymphomas are classified as marginal-zone B-cell lymphomas, caused by chronic stimulation of auto-reactive B cells.
Diffuse large B-cell lymphoma in a 30 year-old woman with Sjögren’s syndrome.
Table 1. Predictors of Lymphoma Development in Sjögren Syndrome*

<table>
<thead>
<tr>
<th>Clinical</th>
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<tbody>
<tr>
<td>Persistent enlargement of parotid glands</td>
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<tr>
<td>Splenomegaly</td>
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<tr>
<td>Lymphadenopathy</td>
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<td>Palpable purpura</td>
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<tr>
<td>Leg ulcers</td>
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<tr>
<td>Serologic</td>
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<td>Low levels of C4</td>
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<td>Mixed monoclonal cryoglobulinemia</td>
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<td>Cross-reactive idiotypes of monoclonal rheumatoid factors</td>
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Clinical Manifestations

- 20-30% of patients have vasculitis, which includes palpable purpura, petechiae, or subcutaneous nodules.

- Renal involvement in 10% of patients - interstitial nephritis.

- Renal tubular acidosis also seen which is secondary to hyper-gammaglobulinemia.

- Myalgias, arthralgias, fatigue, and malaise.
A) Palpable purpura in the lower extremities.
B) Multiple necrotic cutaneous ulcers of the lower extremities in a patient with primary Sjögren's syndrome
C) Annular urticarial lesions of the trunk
Criteria for Sjögren’s syndrome

2002

- US and European diagnosis criteria differed so much that there were ten times as many diagnosis in Europe than in US.
- Caused problems with clinical trials and publication reports
Criteria for Sjögren’s syndrome 2002

- Ocular symptoms
- Oral symptoms
- Objective evidence of dry eyes
- Objective evidence of salivary-gland involvement
- Laboratory abnormality
Criteria for Sjögren’s syndrome

1. Ocular Symptoms (at least one must be present)
   Persistent dry eyes every day for more than 3 months
   Recurrent sensation of sand or gravel in eyes
   Use of tear substitute more than three time a day

2. Oral symptoms (at least one present)
   Feeling of dry mouth every day for 3 months
   Recurrent swollen salivary glands as an adult
   Need to drink liquids to aid in swallowing of dry foods.
xerostomia induced glossitis
Criteria for Sjögren’s syndrome

3. Objective evidence of dry eyes (one must be present)
   Schirmer Test
   Rose-Bengal

4. Lacrimal-gland biopsy
   Focal lymphocytic sialoadenitis in minor salivary glands-containing more than 50 lymphocytes per 4 mm of glandular tissue.
Schirmer’s test

This test consists of placing a small strip of filter paper inside the lower eyelid (conjunctiva sac). The eyes are closed for 5 minutes. The paper is then removed and the amount of moisture is measured. <5 mm in 5 minutes is positive for SS.
Rose Bengal dye

Rose Bengal (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein) is a stain. Its sodium salt is commonly used in eye drops to stain damaged conjunctiva and corneal cells and thereby identify damage to the eye.
Labial gland biopsy
A gold standard of diagnosis
Histopathology of labial gland biopsy
Lymphocytic and plasma cells infiltrate. Two excretory ducts and 3 mucous salivary gland acini are seen.
Criteria for Sjögren’s syndrome

5. Objective evidence of salivary gland involvement (one must be present)

Salivary-gland scintigraphy

Parotid sialography

Unstimulated whole sialometry - < 1.5 ml in 15 min
Scintigraphy

Must show delayed uptake of technetium-99m
Fig 1. Sialography of a 46 year female with SS demonstrating the typical “cherry blossom” appearance. History and photograph contributed by Dr. Lars Hollender, University of Washington.
Criteria for Sjögren’s syndrome

6. Laboratory Abnormality (one must be present)

- Anti-SS-A(Ro) or Anti SS-B(La) (more specific)
- ANA
- IgM rheumatoid factor
Laboratory

**SS patients of both primary and secondary Sjögren’s syndrome** have marked hypergammaglobulinemia (IgG>IgA>IgM), elevated total protein and sedimentation rate, persistent rheumatoid factors, and a decreased WBC count.

**SS-A/Ro and SS-B/La** (anti-RNA antibodies). Antibodies occur in approximately 60% of patients with Sjögren’s syndrome and are associated with early disease onset, longer disease duration, parotid gland enlargement, a higher frequency of extra-glandular manifestations, and more intense lymphocytic infiltration.

**These tests are nonspecific,** also seen in many autoimmune inflammatory conditions.
Indirect immunofluorescein

anti-SSA/Ro autoantibodies
Criteria for Sjögren’s syndrome

- **Primary SS** is defined as the presence of 4 of the 6 diagnostic criteria present.

- **Secondary SS** is defined as presence of connective tissue disease with a positive category 1 or 2 and a positive result in 2 of the remaining 4 criteria.
Exclusion criteria

- Past head and neck radiation treatment
- Hep C infection
- AIDS
- Pre-existing lymphoma or sarcoidosis
- Graft vs host disease
- Anticholinergic drugs
As with all autoimmune disease, there is no cure, and so therapy is aimed at symptomatic relief.

Sjögren’s syndrome is indolent in its course, but one must be aware of the risk of lymphomas in this patient population.
Table 1 Management of glandular manifestations of primary Sjögren's syndrome

<table>
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<tr>
<th>Manifestation</th>
<th>Treatment</th>
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| Ocular involvement<sup>5–8</sup> | Artificial tear substitutes  
Autologous serum drops (experimental)  
Stimulators of tear secretion (cevimeline, pilocarpine)  
Immunosuppressive and/or immunomodulating therapy (cyclosporin drops)  
Surgical procedures (punctal plugs and tear pumps) |
| Oral complications<sup>10,12,15,18–22,24</sup> | Xerostomia  
Saliva substitution  
Stimulation of saliva secretion  
Immunosuppressive and/or immunomodulating therapy |
| Caries                        | Routine dental care, nutrition, fluoride |
| Candidiasis                   | Topical: nystatin 3 times/day for 1 week  
Systemic: ketoconazole 200–400mg/day or fluconazole 50–100mg/day  
or itraconazole 100mg/day, for 2 weeks |
| Upper respiratory involvement<sup>24</sup> | Humidification  
Prevention of infections |
| Gastrointestinal involvement<sup>24</sup> | Atrophic gastritis  
Proton-pump inhibitors, vitamin B<sub>12</sub> supplementation  
Celiac disease  
Gluten-free diet |

Mavragani CP et al. (2006) The management of Sjögren's syndrome  
Medications

- Oral anti-muscarinic therapy proven useful for xerostomia.

- Pilocarpine-first muscarinic receptor antagonist approved by FDA for use in Sjögren syndrome. 
  Dose 5mg qid.

- Evoxac is next generation muscarinic receptor with greater affinity, but less cardiac side effects of anti-muscarinic therapy.
Medications

- Extra-glandular disease such as muscular pains, renal and pulmonary disease may benefit from use of immune modulator such as systemic steroids and anti-malarials.

- However, these therapies have not been proven to provide help with sicca symptoms.
Conclusion

- Sjögren’s syndrome has early ENT manifestations—that include dry mouth and parotid enlargement.

- Otolaryngologist, as part of a multidisciplinary team, may prevent prolong delays in the disease by having a high degree of suspicion.

- Otolaryngologist play key role in diagnostic evaluation, biopsy and treatment.
Dry eyes for >3 mo, recurrent sensation of sand or gravel in the eyes, or use of tear substitutes >3x per day

or

Daily feeling of dry mouth for >3 mo, recurrent or persistent swollen salivary glands, or use of liquids to aid in swallowing dry food

Negative

No SS

Positive

Positive Shirmer’s test (≤ 5 mm in 5 min), or a Rose Bengal score of ≥ 4 according to von Bijsterveld scoring system

Negative

Focus score ≥ 1 in a minor salivary gland biopsy

Positive

Focus score ≥ 1 in a minor salivary gland biopsy

Negative

Positive result in one of the following tests: salivary scintigraphy, parotid sialography, or unstimulated salivary flow (≤ 5 mL in 15 min)

Negative

No SS

Positive

SS

Positive

Antibodies to Ro(SS-A) or La(SS-B), antinuclear antibodies, or rheumatoid factors

Negative

Positive result in one of the following tests: salivary scintigraphy, parotid sialography, or unstimulated salivary flow (≤ 5 mL in 15 min)

Negative

No SS

Positive

SS
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