Sjogren’s Syndrome
Key Concepts for internists

Update in Internal Medicine
University of Pittsburgh Medical Center

October 19, 2017

Ghaith Noaiseh, MD
Director. UPMC Sjogren’s Syndrome Clinic

Assistant Professor of Medicine
Division of Rheumatology and clinical Immunology
University of Pittsburgh Medical Center
Financial disclosures

• No consulting fees

• Study site Co-Investigator:
  - HGS
  - BMS
  - Medimmune
  - Astra Zeneca
  - Ablynx
  - Pfizer
Henrik Sjögren

19 cases of keratoconjunctivitis sicca including two cases with swelling of the major salivary glands

As of August 14th 2013
Challenges in Diagnosis

• Diagnosis frequently delayed
• Diagnosis often preceded by Dx of other AIRD
• Misdiagnosis / under-diagnosis
• Lack of understanding of disease spectrum
• Certain subsets of disease more challenging to diagnose
Epidemiology

• Prevalence: 0.01% and 0.72%


• Peak incidence: 5th – 6th decades of life

• F : M ratio 10-20 : 1

Pathophysiology
Autoimmune epithelitis

• Glandular epithelial cells (EC) as a key player

• **Activated** EC act as a non-professional APC

• Other organs: Kidney, liver, lungs, thyroid may be involved with ECs as primary target

The pathogenesis of autoimmune epitelitis as a potential explanation for SS

The pathogenesis of autoimmune epitelitis as a potential explanation for SS

Pathogenesis models of salivary gland inflammation in SS

A. Glandular hypofunction explained by tissue loss secondary to immune attack, resulting in cytotoxic cell death and apoptosis

B. Glandular hypofunction results from downregulation of receptor-mediated secretion of salivary fluid into the ductal lumen.

St. Clair. W. in Kelley’s textbook of Rheumatology 9th ed
Clinical manifestations
The spectrum of Sjogren’s syndrome

- Sicca
- Fatigue
- Pain (Most patients)

Extraglandular manifestations (30-40%)
- ILD
- Interstitial nephritis

Vasculitic features
- Glomerulonephritis
- Mononeuritis multiplex
- LCV

Lymphoma (5%)
Dry eyes

- Grittiness
- Foreign body sensation
- Burning
- Photophobia
- Corneal perforation in severe cases
Air

Lipid layer

Aqueous layer

Mucus layer

Ocular surface epithelium
Dry mouth

- Difficulty chewing, swallowing dry food
- Altered taste (metallic, salty, bitter)
- Problems wearing dentures
- Dysphagia (confused with pharyngeal dysphagia)
- **Rampant dental caries**, loose fillings

- **Atrophic oral candidiasis**
Other exocrine gland dysfunction

• Upper airways:
  - Nasal obstruction, dryness
  - Hoarseness
  - Cough
• Vagina:
  - Dyspareunia
  - Recurrent candidiasis
• Skin:
  - Xerosis cutis
Salivary gland enlargement

- Parotid or submandibular: in 25-35 %
- Usually painless
- Unilateral or bilateral

- Asymmetric enlargement *may indicate a neoplasm* (lymphoma)
### Parotid Gland Enlargement Differential diagnosis

<table>
<thead>
<tr>
<th>Sialadenitis</th>
<th>Sialadenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sarcoidosis</td>
<td>• Alcoholism</td>
</tr>
<tr>
<td>• IgG4-related diseases</td>
<td>• Chronic liver disease</td>
</tr>
<tr>
<td>• Viral infections (Mumps, HIV)</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Bacterial</td>
<td>• Bulemia Nervosa</td>
</tr>
<tr>
<td>• Primary B and T cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>• Multicentric Castleman's disease</td>
<td></td>
</tr>
<tr>
<td>• Malignant carcinoma</td>
<td></td>
</tr>
<tr>
<td>• Benign tumors</td>
<td></td>
</tr>
<tr>
<td>• Calculus duct obstruction</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Hallmarks - The triad

1. Sicca syndrome
2. Fatigue
3. MSK Pain

- One or more is present in **almost all** patients
- Main drivers of morbidity
- May be confused with fibromyalgia
Systemic Manifestations

- 25-40% of patients
- More likely in anti SSA


- Predictor of extraglandular manifestation and poor outcome
Joint involvement

- Inflammatory arthralgia
- True arthritis: Resembles RA
  - Usually non-erosive
  - Can be Relapsing-remitting
- Subclinical synovitis in 30% on ultrasound

Pulmonary involvement
Neurological manifestations

Sjogren’s syndrome patients may develop which of the following complications:

1. Sensory peripheral neuropathy
2. Mononeuritis multiplex
3. CIDP
4. Autonomic neuropathy
5. All of the above
Neurological manifestations

Sjogren’s syndrome patients may develop which of the following complications:

1. Sensory peripheral neuropathy
2. Mononeuritis multiplex
3. CIDP
4. Autonomic neuropathy
5. All of the above
Skin Manifestations

Erythema Annulare (similar to subacute cutaneous lupus rash)
Leucocytoclastic vasculitis
Renal Manifestations

The most common renal involvement in Sjogren’s syndrome is:

1. Pauci-immune crescentic glomerulonephritis
2. FSGS
3. IN leading to Renal tubular acidosis Type I
4. IN leading to Renal tubular acidosis Type 2
5. Non of the above
Renal Manifestations

The most common renal involvement in Sjogren’s syndrome is:

1. Pauci-immune crescentic glomerulonephritis
2. FSGS
3. IN leading to Renal tubular acidosis Type I
4. IN leading to Renal tubular acidosis Type 2
5. Non of the above
Associated non-Rheumatic Diseases

• Autoimmune thyroid disease: most common
• Autoimmune hepatitis - Primary Biliary Cirrhosis
• Celiac disease
• Autoimmune adrenal gland disease
• Autoimmune hypophysitis
• Pernicious anemia
Lymphoma in Sjogren’s syndrome
Histological types

• Mostly low-grade B cell NHL → marginal zone → mucosa-associated lymphoid tissue (MALT) lymphomas

• Often develops in organs where SS is active

• Germinal center-like structures is a risk factor

### Risk indicators for lymphoma development

**Clinical features:**
- Persistent parotid gland enlargement
- Purpura
- European League Against Rheumatism Sjögren syndrome Disease Activity Index (ESSDAI) score of ≥5

**Genetic polymorphisms:**
- TNFSF13B
- TNFRSF13C
- TNFAIP3

**Histopathological features:**
- Presence of germinal centers in the MSGB
- Focus score of >3

**Laboratory abnormalities:**
- CD4+ lymphopaenia

**Immunological findings:**
- Low complement C3 or C4 levels
- Mixed cryoglobulinaemia
- MGUS
- Increased lymphocyte-related cytokine levels (including BAFF, FMS-like tyrosine kinase 3 ligand, CXCL 13 and CXCL 11)
- Increased β2-microglobulin levels
- Presence of rheumatoid factor

---

Risk indicators for lymphoma development

**Clinical features:**
- Persistent parotid gland enlargement
- Purpura
- European League Against Rheumatism Sjögren syndrome Disease Activity Index (ESSDAI) score of ≥5

**Genetic polymorphisms:**
- TNFSF13B
- TNFRSF13C
- TNFAIP3

**Histopathological features:**
- Presence of germinal centers in the MSGB
- Focus score of >3

**Laboratory abnormalities:**
- CD4+ lymphopaenia

**Immunological findings:**
- Low complement C3 or C4 levels
- Mixed cryoglobulinaemia
- MGUS
- Increased lymphocyte-related cytokine levels (including BAFF, FMS-like tyrosine kinase 3 ligand, CXCL 13 and CXCL 11)
- Increased β2-microglobulin levels
- Presence of rheumatoid factor

## Risk indicators for lymphoma development

### Clinical features:
- Persistent parotid gland enlargement
- Purpura
- European League Against Rheumatism Sjögren syndrome Disease Activity Index (ESSDAI) score of ≥5

### Genetic polymorphisms:
- TNFSF13B
- TNFRSF13C
- TNFAIP3

### Histopathological features:
- Presence of germinal centers in the MSGB
- Focus score of >3

### Laboratory abnormalities:
- CD4+ lymphopaenia

### Immunological findings:
- Low complement C3 or C4 levels
- Mixed cryoglobulinaemia
- MGUS
- Increased lymphocyte-related cytokine levels (including BAFF, FMS-like tyrosine kinase 3 ligand, CXCL 13 and CXCL 11)
- Increased β2-microglobulin levels
- Presence of rheumatoid factor

---

Diagnostic modalities
Lissamine staining as shown by slit-lamp examination

A. Punctate staining of the cornea.

B. Punctate staining of the conjunctival epithelium.

Kelley's Textbook of Rheumatology, 9th ed
Sialometry (USFR)

- 5 or 15 minute whole saliva collection
- Expectorate in pre-weighed container
- Measure Pre and post- weight ⇒ saliva weight

Cutoff: USFR < 0.1 ml/min

Autoantibodies in SS

- ANA: most common Ab: up to 85%

- SSA: 60-70%. **Most specific.** Predicts systemic involvement

- SSB: usually follows SSA. **Caution if isolated**

- Rheumatoid factor: 50% → risk of lymphoma

Minor Salivary Glands Biopsy (MSGB)

- Salivary glands contain secretory acini and ducts
- Two types of secretions: serous and mucous
- Acini are serous, mucous, or both
  - Serous acini secrete **proteins in watery fluid**.
  - Mucous acini secrete **mucin**
Minor Salivary Gland Biopsy (MSGB)

- **At least three** salivary gland lobules
- Examined area should be $\geq 4 \, \text{mm}^2$

- Distinct pattern: Focal Lymphocytic Sialadenitis (FLS)

- A focus is $\geq 50$ lymphocytes in a cluster surrounding normal tissue

- If FLS present $\rightarrow$ Focus score (FS) is calculated:
  - FS is number of foci in $4 \, \text{mm}^2$

- **Positive** if FS $\geq 1$
Normal salivary gland
Normal salivary gland

www.dartmouth.edu
Focal Lymphocytic Sialadenitis

Other lab tests

- SPEP: **Hyper** or **hypo**gammaglobulinemia. M-spike
Other lab tests

• SPEP: **Hyper** or **hypo**gammaglobulinemia. M-spike
• Complement C3 and C4. Predictor of poor outcome
Other lab tests

- SPEP: **Hyper** or **hypo**gammaglobulinemia. M-spike
- Complement C3 and C4. Predictor of poor outcome
- Cryoglobulins: Predictor of poor outcome
Other lab tests

- SPEP: **Hyper** or **hypo**gammaglobulinemia. M-spike
- Complement C3 and C4. Predictor of poor outcome
- Cryoglobulins: Predictor of poor outcome
- ESR and CRP
- CBC: Neutropenia, Lymphopenia
  - Hemolytic anemia (rare)
- Consider Hepatitis C screen in all patients
Classification Criteria and diagnosis
Classification Criteria

2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren’s syndrome

A consensus and data-driven methodology involving three international patient cohorts

Caroline H Shiboski,1 Stephen C Shiboski,1 Raphaële Seror,2 Lindsey A Criswell,1 Marc Labetouille,2 Thomas M Lietman,1 Astrid Rasmussen,3 Hal Scolfield,4 Claudio Vitali,5,6 Simon J Bowman,2 Xavier Mariette,2 the International Sjögren’s Syndrome Criteria Working Group

Table 3 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren’s syndrome: The classification of primary Sjögren’s syndrome (SS) applies to any individual who meets the inclusion criteria,* does not have any of the conditions listed as exclusion criteria,† and has a score of ≥4 when the weights from the five criteria items below are summed

<table>
<thead>
<tr>
<th>Item</th>
<th>Weight/score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm²†</td>
<td>3</td>
</tr>
<tr>
<td>Anti-SSA/Ro-positive</td>
<td>3</td>
</tr>
<tr>
<td>Ocular Staining Score ≥5 (or van Bijsterveld score ≥4) in at least one eye§</td>
<td>1</td>
</tr>
<tr>
<td>Schirmer’s test ≤5 mm/5 min in at least one eye§</td>
<td>1</td>
</tr>
<tr>
<td>Unstimulated whole saliva flow rate ≤0.1 mL/min§**</td>
<td>1</td>
</tr>
</tbody>
</table>

*These inclusion criteria are applicable to any patient with at least one symptom of ocular or oral dryness, defined as a positive response to at least one of the following questions: (1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (2) Do you have a recurrent sensation of sand or gravel in the eyes? (3) Do you use tear substitutes more than three times a day? (4) Have you had a daily feeling of dry mouth for more than 3 months? (5) Do you frequently drink liquids to aid in swallowing dry food? or in whom there is suspicion of Sjögren’s syndrome (SS) from the European League Against Rheumatism SS Disease Activity Index questionnaire (at least one domain with a positive item).
†Exclusion criteria include prior diagnosis of any of the following conditions, which would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: (1) history of head and neck radiation treatment, (2) active hepatitis C infection (with confirmation by PCR), (3) AIDS, (4) sarcoidosis, (5) amyloidosis, (6) graft-versus-host disease, (7) IgG4-related disease.

Shiboski C et al. ARD and A&R (2017)
Applies to any individual who meets the inclusion criteria, * does not have any of the conditions listed as exclusion criteria, † and has a score of ≥4 when the weights from the five criteria items below are summed.

<table>
<thead>
<tr>
<th>Item</th>
<th>Weight/score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm²‡</td>
<td>3</td>
</tr>
<tr>
<td>Anti-SSA/Ro-positive</td>
<td>3</td>
</tr>
<tr>
<td>Ocular Staining Score ≥5 (or van Bijsterveld score ≥4) in at least one eye§¶</td>
<td>1</td>
</tr>
<tr>
<td>Schirmer’s test ≤5 mm/5 min in at least one eye§</td>
<td>1</td>
</tr>
<tr>
<td>Unstimulated whole saliva flow rate ≤0.1 mL/min§**</td>
<td>1</td>
</tr>
</tbody>
</table>

2016 ACR/EULAR criteria
Prognosis

Main causes of death:

• Lymphoma
• Severe manifestations (ILD, renal failure, severe cryoglobulinemic vasculitis)
• infections and cardiovascular disease

Management
Management of Sicca syndrome
Management of dry mouth

○ Prevention:
  • Dental visits
  • Avoid toxins (alcohol, smoking)
  • Avoid anticholinergics
  • Treat associated sinusitis/rhinitis
  • Fluoride compounds

○ Replacement:
  • Mechanical stimulation of saliva
  • Saliva substitutes
  • Secretagogues
Secretagogues

• For **both** dry mouth and eyes

• Consider in:
  - Excessive dental caries
  - Significant symptoms
  - Corneal damage

1. Pilocarpine 5-7.5 mg up to QID
2. Cevimeline 30 mg TID

• **Side effects**: Sweating, flushing, urinary frequency, GI

• **Caution** if severe asthma / angle-closure glaucoma

• Cevimeline has a better side effect profile

Secretagogues

• For **both** dry mouth and eyes
• Consider in:
  - Excessive dental caries
  - Significant symptoms
  - Corneal damage

1. Pilocarpine 5-7.5 mg up to QID
2. Cevimeline 30 mg TID

• **Side effects**: Sweating, flushing, urinary frequency, GI
• **Caution** if severe asthma / angle-closure glaucoma
• Cevimeline has a better side effect profile


**Consider for any case of dry mouth**
Management of dry eyes

• Mild, episodic symptoms:
  - Environmental modification may be enough
• Volume replacement and lubrication
  - Artificial tears and ointments/gels
• **Topical** anti-inflammatory therapy:
  - Steroids - Cyclosporine - Lifitegrast - Autologous serum
• Secretagogues
• Punctal occlusion/cauterization
Management of systemic manifestations
Hydroxychloroquine

• Commonly used for:
  - Fatigue
  - Arthralgia/Arthritis
  - Purpura

• Not useful in managing sicca symptoms

• Conflicting data in prospective studies
• Support of use in retrospective studies
**DMARDs in SS**

**Azathioprine:**
- *Price et al:* placebo-controlled RCT, 25 pts, 6 months
  - No significant change in disease activity variables
  

**Cyclosporine:**
- *Drosos et al:* placebo-controlled RCT, 20 pts, 6 months, 5mg/kg
  - Improvement of subjective dry mouth
  - No difference in objective dry mouth, parotid gland enlargement, Schirmer’s and parotid flow rate


**Methotrexate, Leflunomide, mycophenolate mofetil:**
- One prospective study for each agent
  - Limited improvement in Sicca symptoms
  - High rate of adverse effects

Biologic therapy

• TNF inhibitors: No role
• Rituximab:
  - Negative studies
  - ?Helpful for vasculitic features

• Ongoing trials for Belimumab and Abatacept

• Other novel therapies
Conclusions

• SS is the most common ANA-positive AID
Conclusions

• SS is the most common ANA-positive AIRD
• SS is not just the “disease of dry eyes and mouth”
Conclusions

• SS is the most common ANA-positive AID
• SS is not just the “disease of dry eyes and mouth”
• Over 50% of SS patients have a benign course but high-burden symptoms
Conclusions

• SS is the most common ANA-positive AID
• SS is not just the “disease of dry eyes and mouth”
• Over 50% of SS patients have a benign course but high-burden symptoms
• Many SS patients develop systemic manifestations, some are severe
Conclusions

• Among AI diseases, SS has the highest OR for lymphoma development
Conclusions

• Among AI diseases, SS has the highest OR for lymphoma development
• Patients with high disease activity need close monitoring
Conclusions

• Among AI diseases, SS has the highest OR for lymphoma development
• Patients with high disease activity need close monitoring
• Clinical/serological risk factors for Lymphoma should be clarified/performed during evaluation
Questions?