Sjögren's Syndrome

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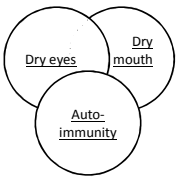
Disclosures

- None

My Biases



- Sjögren's syndrome is a systemic autoimmune disease.
  - Get the diagnosis right---it does matter!
  - Correct diagnosis is the prelude to appropriate management.
  - The promise of biologic therapies will only be realized with application to patients in whom the symptoms are driven by an ongoing autoimmune process.

Outline of Talk

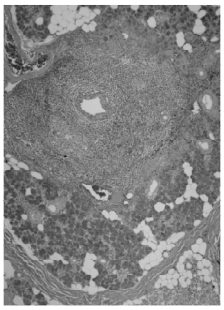
- The Sjögren's phenotype
  - Heterogeneity
  - Differentiation from other forms of sialadenitis
- The diagnosis of Sjögren's
  - Diagnostic methodology
  - Classification criteria: evolution over the past 5 decades
  - Pitfalls in diagnosis
- The treatment of Sjögren's
  - Multidisciplinary
  - Promise of new biologic therapies

Henrik Sjögren-1933

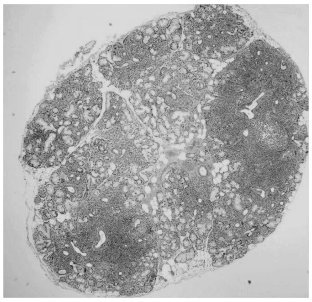
- Described "keratoconjunctivitis sicca" as part of a systemic disease
- Key features
  - Salivary and lacrimal gland dysfunction
  - Lymphocytic infiltration of exocrine glands, especially lacrimal and salivary
  - Association with chronic deforming arthritis (i.e. RA)
  - Remarkable female predisposition

http://cms.revoptom.com/publish/images/2_1611_1.jpg

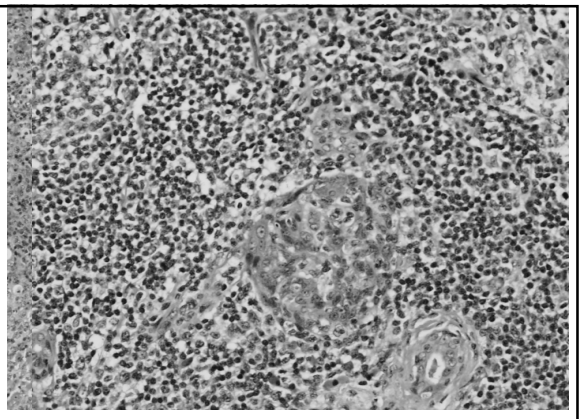
Lymphocytic infiltration of major and minor salivary glands



Parotid gland



Labial minor salivary gland



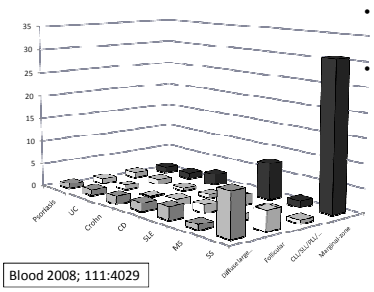
Key Features of Sjögren's Syndrome

- Affects primarily peri- and postmenopausal women
- Prevalence of 0.09-0.6%
- Relatively stable disease course without treatment
- 18-fold increased risk of lymphoma

Sjögren's is a systemic autoimmune disease.

- Characteristic SSA (Ro) and SSB (La) autoantibodies (~60-80%)
- Markers of B-cell overactivity
  - Rheumatoid factor (50-60%)
  - Polyclonal hyperglobulinemia (40%)
  - Monoclonal proteins (15%)
- Extraglandular manifestations (<50%)
  - Systemic: pain, fatigue
  - Organ-specific
- Strong association with other autoimmune diseases

SS stands out among autoimmune diseases: Highest risk of lymphoma



Blood 2008; 111:4029

- 5% lifetime risk of lymphoma (relative risk=18)
- Types
  - Marginal-zone B cell lymphomas, arising from diverse extranodal and nodal sites
  - Diffuse large B cell lymphomas

The Spectrum of Sjögren's Syndrome

- Sjögren's in the young and elderly
- Seronegative Sjögren's
- Overlap with other autoimmune diseases
- High vs. low risk of lymphoma
- Mikulicz syndrome

Sjögren's in the young and old

- Young
  - Higher frequency of autoantibodies and hypergammaglobulinemia
  - More frequent parotitis
  - Less frequent sicca
  - More frequent renal tubular acidosis
  - Overlap with SLE
- Elderly
  - Sicca symptoms common in this age group
  - High prevalence of medications that cause sicca symptoms
  - Age-related histologic changes of acinar atrophy, fibrosis, and ductal dilatation
  - Schirmer's test less reliable

Lupus 1998; 7:202
Scand J Rheumatol 1999; 28:227
J Rheumatol 2008;35;278-284

Arch Intern Med 1999; 159:1359
Age Ageing 1984; 13:159
Ann Rheum Dis 1994; 53:637

Seronegative Sjögren's

- Defined by a positive lip biopsy and the absence of SSA and SSB antibodies
- 20-40% of cohorts
- Older age at diagnosis
- Less systemic/hematologic involvement
- Greater pain severity
- Higher frequency of sensory neuropathy

Arthritis Care and Research 2008;59:1780
Arthritis Care and Research 2013 Jan 17
Clin Exp Rheumatol 2001;19:313
Medicine 2011;90:133
Medicine 2008; 87:210

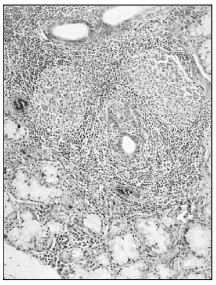
Overlap vs secondary Sjögren's

- Common overlap of Sjögren's with other autoimmune diseases
  - RA (polyarthritis with rheumatoid factor)
  - SLE (leucopenia, hypocomplementemia, arthritis)
  - Primary biliary cirrhosis (SS-A antibodies)
  - Scleroderma (Raynaud's, centromere antibodies)
- Late manifestation of an established CTD
  - Genetic traits may differ from primary Sjögren's
- Shared serologic markers
  - SSA, SSB
  - CCP, DNA, centromere antibodies, rheumatoid factor

Primary vs secondary SS classification is not included in 2012 ACR criteria.

High risk of lymphoma

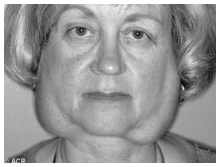
- Predictors at time of diagnosis
  - Germinal center-like structures in labial salivary gland biopsy[1]
  - Parotid gland enlargement[2,3]
  - Palpable purpura[2,3]
  - Cryoglobulinemia
  - Hypocomplementemia[2,3]
  - CD4+ T cell lymphocytopenia[3,4]
- Type I (high risk) vs type II (low risk) populations[2]



[1]Ann Rheum Dis 2011; 70:1363
[2]Arthritis Rheum 2002; 46:741
[3]Semin Arthritis Rheum 2011; 41:415
[4]Ann Rheum Dis 2006; 65:796

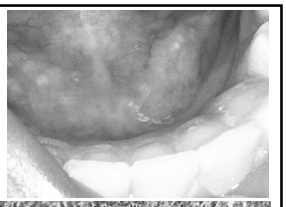
Mikulicz Syndrome

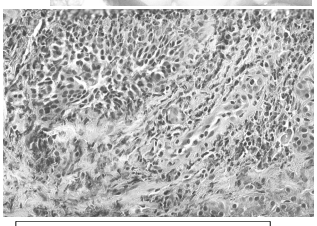
- Chronic enlargement of salivary and lacrimal glands with histologic evidence of chronic inflammation
- Multiple etiologies for this presentation
  - Benign lymphoepithelial sialadenitis
    - Sjögren's syndrome
    - Other systemic rheumatic diseases
  - MALT and other B-cell lymphomas
  - IgG4-related sialadenitis/dacryoadenitis
  - Diffuse infiltrative CD8 lymphocytosis
  - Leukemia, especially ALL
  - Sarcoidosis
  - Tuberculosis



Case 1

- 18 year old woman
  - Long history of asthma
  - Recurrent parotid and submandibular gland swelling since age 8
  - White mucus plugs extrude from her salivary glands
  - WBC 8600 with 29% eosinophils
  - ANA 1:80, negative SSA/B antibodies

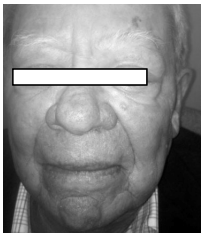


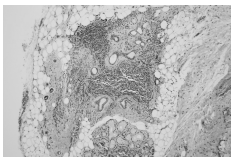


Sialodochitis fibrinosa (allergic parotitis)

Case 2

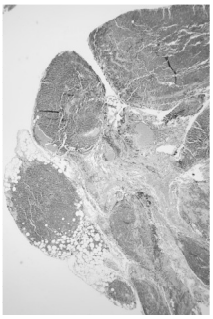
- 81 year old man
  - Early 2011: onset cervical adenopathy, xerostomia, dry eye symptoms
  - October 2011:
    - WBC 7800 (40% lymphs, 32% PMNs, atypical lymphs noted), hemoglobin 12.8 g/dl, platelets 190K
    - SPEP: hypogammaglobulinemia, 0.3 g/dl gamma spike;
    - IgM lambda monoclonal gammopathy
  - November 2011: lip biopsy shows 2 foci in specimen with 6 lobules (c/w Sjogren's)
  - ANA, anti-SSA, anti-SSB negative
  - Treated with prednisone 15 mg qd and methotrexate 15 mg qwk





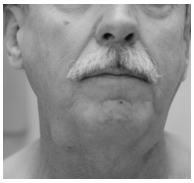
Case 2-cont'd

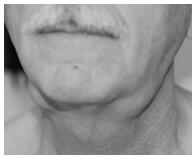
- Left lacrimal gland biopsy:
  - Monomorphic small lymphocytic infiltrate
  - 85% of cells show monoclonal expression of lambda light chain colony with CD5, CD23, and relatively dim CD20
  - Findings indicative of B-cell CLL
- FISH
  - trisomy 12; 13q deletion; trisomy 14 vs translocation of IGH with another locus.



Case 3

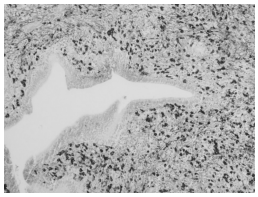
- 69 year old man
  - January 2010: painless jaundice secondary to 2 cm bile duct stricture
  - March 2010: Whipple procedure
    - Autoimmune pancreatitis on path
    - Normal serum IgG4
  - November 2011: rheumatology referral
    - Dry eyes and mouth
    - Abnormal Schirmer's
    - Progressive enlargement of submandibular > parotid glands since 1/2010
    - Weak urinary stream

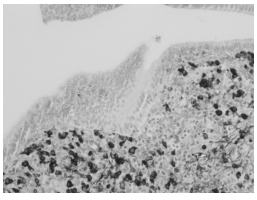




Case 3-cont'd

- Evaluation at JHH-April 2012
  - Induration and enlargement of parotid and submandibular glands
  - WBC 6200 (6% eosinophils)
  - Alkaline phosphatase 254, AST 48, ALT 57
  - IgG 2480, IgG4 36.9 mg/dl
  - ANA 1:40, negative SSA and SSB antibodies
  - Negative rheumatoid factor





Extraglandular Manifestations

- Neurologic (20% of patients)
  - Central nervous system demyelination
  - Sensory neuronopathies
  - Small fiber sensory neuropathy
  - Multiple mononeuropathy

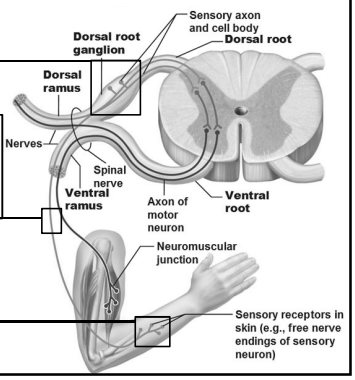
  Often first manifestation of Sjogren's
- Cutaneous
  - Palpable purpura
  - Subacute cutaneous lupus overlap
- Pulmonary
  - Obstructive bronchiolitis
  - Lymphoid interstitial pneumonitis
- Renal
  - Interstitial nephritis with RTA
  - Glomerulonephritis
- Hepatic
  - Primary biliary cirrhosis
  - Autoimmune hepatitis
- Systemic vasculitis
- Lymphoma

Peripheral Neuropathies in Sjögren's

Sensory ataxic neuronopathy
- Absent vibratory sense
- Impaired proprioception
- Positive Romberg
- Absent DTR's

Axonal sensory or sensorimotor neuropathy
- Stocking-glove paresthesias
- Normal or decreased strength
- Decreased or absent DTRs
- Abnormal nerve conduction studies

Small fiber sensory neuropathy
- Mild or no reduction in temperature or pinprick sensation
- Normal proprioception and vibration
- Normal electrodiagnostic studies
- Reduced intraepidermal nerve fiber density

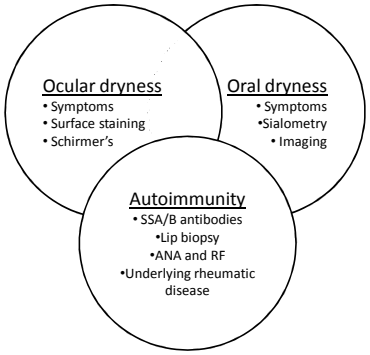


Peripheral neuropathies have varied pathogenesis

- Axonal sensorimotor polyneuropathy
  - Frequent extraglandular disease, associated low C4, cryoglobulinemia, monoclonal protein, lymphoma risk[1]
  - Vasculitis evident on nerve biopsies[2]
- Sensory ataxic neuronopathy
  - Histopathologic evidence of dorsal root ganglionitis
  - Lower frequency of women, SSA/B antibody positivity, and extraglandular disease
- Small fiber sensory neuropathy
  - Non-length dependent pattern suggests dorsal root ganglionitis (confirmed in autopsy of one patient)[3]
  - Lower frequency of B-cell activation markers[1]

[1]Medicine 2011; 90:133; [2]Neurology 1989;39:390; [3]J Neurol Sci 2012; 319:139;

What defines Sjögren's syndrome?



The Mosaic of Different Classification Criteria Sets

□ included
□ not included

	Copenhagen 1986	Greek 1986	Japanese 1986	San Diego 1986	San Francisco 1987	European 1993	Japanese 1999	AECC 2002	ACR 2012
Ocular symptoms									
Oral symptoms									
Schirmer's test									
Rose Bengal test									
Lissamine green staining									
Break up time									
Fluorescein test									
Unstimulated salivary flow									
Stimulated salivary flow									
Parotid sialography									
Salivary scintigraphy									
Minor gland biopsy									
Rheumatoid factor									
Antinuclear antibodies									
Anti-SSA/SSB antibodies									
Obligatory criterion									

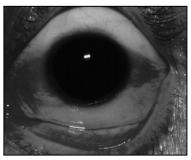
Adapted from C. Vitali

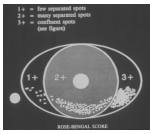
The International Sjögren's Syndrome Registry

- The **S**jögren's **I**nternational **C**ollaborative **C**linical **A**lliance (http://sicca.ucsf.edu)
  - NIH-funded 2003-2013, based at UCSF, 9 global sites-including JHU
- Goals
  - Develop standardized classification criteria for SS
  - Collect, store, and disseminate uniform clinical data and biospecimens for future studies of Sjögren's syndrome (SS)
    - Genome wide association studies
- SICCA cohort includes >3000 individuals with possible early SS to well-established disease
  - >700 underwent a repeat evaluation with second lip biopsy two years after baseline visit

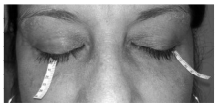
Classic Dry Eye Evaluation

Rose Bengal staining



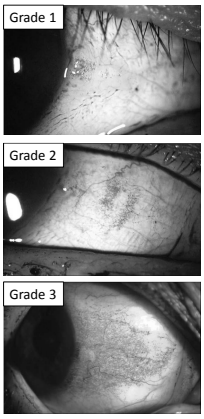


Schirmer strip testing



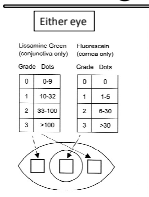
- Schirmer's test strips: filter paper with mm ruling
- Schirmer's test measures tear production
- ≤ 5 mm wetting /5 min is abnormal

SICCA ocular surface staining



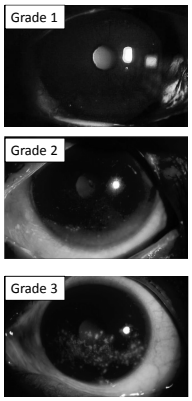
Either eye

Lissamine Green (conjunctiva only)		Fluorescein (cornea only)	
Grade	Dots	Grade	Dots
0	0-9	0	0
1	10-32	1	1-5
2	33-100	2	6-30
3	>100	3	>30



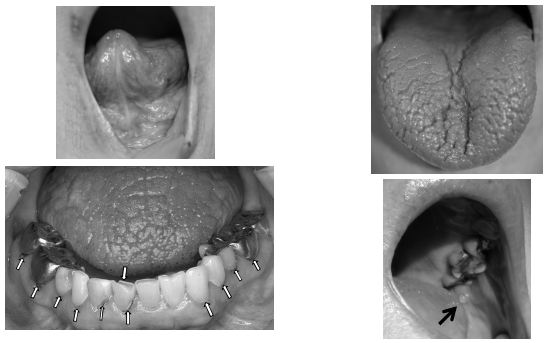
☐ +1 - patches of confluent staining
☐ +1 - staining in pupillary area
☐ +1 - one or more filaments

☐☐ Total score



Am J Ophthal 2010;149:405-415

Salivary Gland Hypofunction: Oral Exam

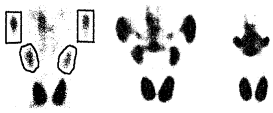


Measurement of Salivary Function

Whole unstimulated sialometry

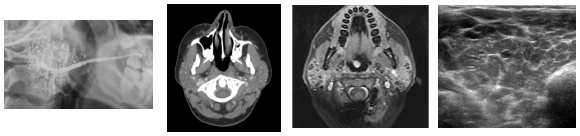
- Best correlate of oral health
- Normal >0.1 ml/min
- Declines with age

Salivary gland scintigraphy



- Not widely available
- High sensitivity but low specificity

Imaging of sialadenitis: Not specific for Sjögren's



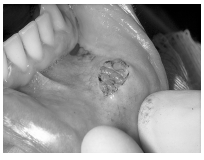
Contrast sialography
- Involves radiation
- Difficult to perform
- May incite inflammation

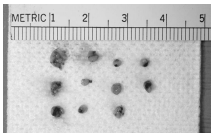
CT
- Involves radiation
- Identifies sialoliths, areas of punctate calcification

MR imaging
- No radiation
- Parenchymal changes
  - T2-hyperintense foci (dilated ducts)
  - T1-hyperintense foci (fatty atrophy)

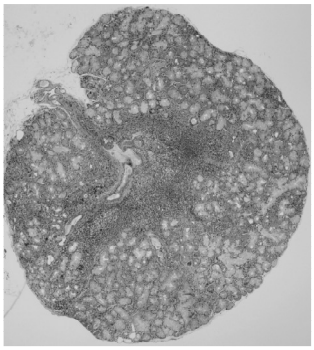
Ultrasound
- No radiation
- Parenchymal heterogeneity, cysts, sialoliths
- Can guide needle aspiration or core biopsy

Minor salivary gland pathology: a key to that of the major salivary glands



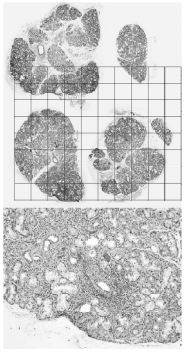


Photos courtesy of Troy Daniels, UCSF



Reading lip biopsies must be protocol-driven.

- Assess adequacy of specimen
  - 4-7 glands
- Assess histopathologic pattern
- If focal lymphocytic sialadenitis:
  - Calculate total surface area
  - Count number of foci adjacent to normal acini
  - Calculate focus score
    - Number of lymphocytic foci per 4 mm^2 of glandular tissue
  - Assess for germinal centers



Protocol available at: http://sicca.ucsf.edu/Labial_Salivary_Gland_Assessment.doc

Daniels TE et al, Arthritis Rheum, 63:2021, 2011

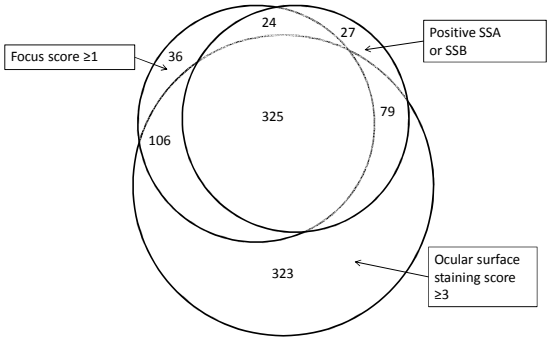
Correlates of Labial Gland Histopathology in the SICCA Cohort

Phenotypic feature	FLS FS≥1 N=730 N (%)	FLS FS<1 N=328 N (%)	NS/SCS No FS N=668 N (%)	P (chi²)
Positive anti-SS-A/-B	487 (76)	63 (10)	91 (14)	<.0001
Rheumatoid factor	458 (72)	64 (10)	113 (18)	<.0001
Ocular surface staining ≥ 3	630 (50)	206 (16)	415 (33)	<.0001
ANA ≥ 1:320	477 (72)	68 (10)	115 (17)	<.0001
IgG >1445 mg/dl	424 (73)	54 (9)	104 (18)	.0001
UWS flow <0.1 ml/min	502 (53)	148 (15)	306 (32)	<.0001
Dry mouth symptoms	669 (43)	292 (19)	595 (38)	0.3
Dry eye symptoms	624 (43)	292 (20)	549 (37)	0.01

FLS=focal lymphocytic sialadenitis; NS/SCS-non-specific/sclerosing chronic sialadenitis; UWS=unstimulated whole saliva

Daniels TE et al, Arthritis Rheum, 63:2021, 2011

SICCA Cohort (1156 participants)



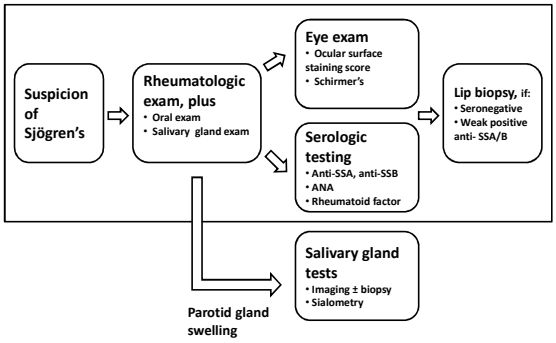
Arthritis Care and Research 61:711, 2009

ACR Preliminary Classification Criteria for Sjögren's Syndrome

- The classification of Sjögren's syndrome will be met in patients who have at least two of the following three objective features:
  - [Positive serum anti-SSA and/or anti-SSB] or [positive rheumatoid factor and ANA ≥ 1:320]
  - Labial salivary gland exhibiting focal lymphocytic sialoadenitis ≥ 1 focus/4 mm²
  - Keratoconjunctivitis sicca with SICCA staining score ≥ 3
- *The same criteria apply to patients with other autoimmune connective tissue diseases, such as rheumatoid arthritis, systemic lupus, etc.*

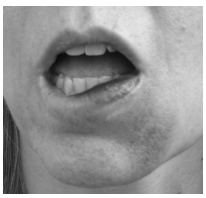
Arthritis Care Res 2012; 64:475

Diagnostic Steps



Lip Biopsies: Pros and Cons

- Pros
  - Important criterion for disease classification
  - Provides prognostic information regarding the risk of lymphoma
  - May reveal an alternative diagnosis
- Cons
  - Need for invasive procedure
  - Risk of persistent lip numbness averages 3-5% in reported series[1,2]
  - Inadequate tissue sampling
  - Misinterpretation of biopsies is common.[3]



[1]Arthritis Rheum 2008; 59:714
[2]Eur Arch Otorhinolaryngol 2006; 263: 233
[3]J Rheumatol 2002; 29:938

Pitfalls in Sjögren's Diagnosis

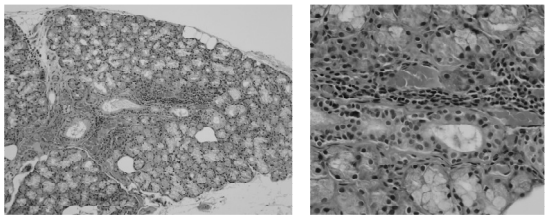
- Overinterpretation of sicca symptoms
- Ocular component
  - Failure to perform/score ocular surface staining
  - Age-related decline in tear production
- Oral component
  - Failure to account for anti-cholinergic drug effects
  - Poor specificity of abnormal testing
- Labial gland biopsy
  - Inadequate tissue
  - Failure to interpret according to established protocols
- Serologies
  - Low titer SSA or SSB antibodies
- 2012 ACR criteria are not clinician-friendly!

My Name is [ ] and I have Sjogrens. I have been suffering from Sjogrens side effects for 16+ years. I was finally diagnosed last year via lip biopsy as I am serum negative. [ ]

DIAGNOSIS:

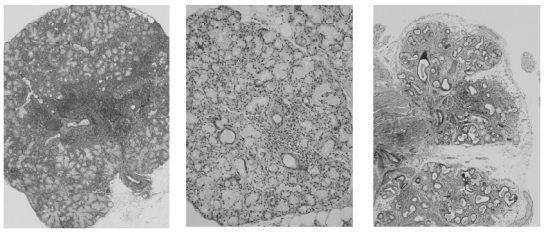
Salivary gland, minor, biopsy
- Benign minor salivary gland tissue with mild to moderate chronic sialadenitis, Daniel's focus score = 1.25 (see comment).

COMMENT:
A Daniel's focus score of greater than 1.0 supports a diagnosis of Sjögren's syndrome in the appropriate clinical context. Clinical correlation is recommended.



Total surface area=22.5 mm^2

Three Common Types of Labial Gland Histopathology: SICCA Cohort (n=1787)



Focal lymphocytic sialoadenitis 61%

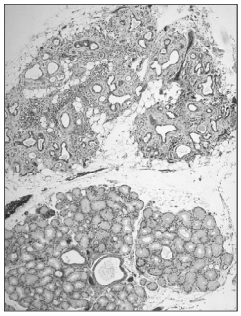
Non-specific chronic sialoadenitis 21%

Sclerosing chronic sialoadenitis 17%

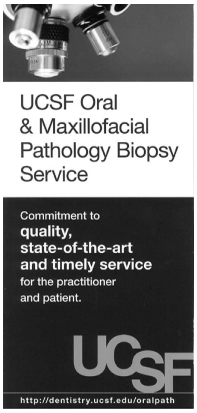
Daniels TE et al, Arthritis Rheum, 63:2021, 2011

Sclerosing Chronic Sialadenitis

- Glandular fibrosis, acinar atrophy, and ductal dilatation/hyperplasia increase with age.[1,2]
- Sclerosing chronic sialadenitis correlated with increased age in SICCA.[3]
- Does not correlate with the autoimmune abnormalities of primary SS.[3]



[1]J Clin Pathol 1986;39:406
[2]Age Ageing 1984;13:159
[3]Arthritis Rheum, 63:2021, 2011



Reference laboratory for labial gland biopsies

http://dentistry.ucsf.edu/oralpath

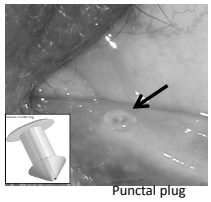
Correlates of SSA and SSB Reactivity in the SICCA Cohort

Phenotypic feature	Positive SSA & SSB (N= 447) (18.1%)	Positive SSA only (N= 357) (14.4%)	Positive SSB only (N=61) (2.5%)	Negative SSA & SSB (N=1612) (65.1%)
ANA≥1:320 (%)	311 (77)	127 (43)	3 (9)	207 (16)
Rheumatoid factor ≥44 IU/ml	353 (79)	132 (37)	9 (15)	282 (18)
IgG>1445 mg/dl	319 (72)	135 (38)	5 (8)	196 (12)
C4<16 mg/dl	105 (24)	69 (19)	5 (8)	164 (10)
WBC ≤ 4000	117 (27)	69 (20)	2 (3)	96 (6)
Anemia	120 (27)	57 (16)	9 (15)	192 (12)
Ocular surface stain ≥ 3	427 (96)	292 (82)	37 (61)	1093 (68)
Schirmer's ≤5 mm/5 min	216 (48)	122 (34)	10 (16)	387 (24)
UWS ≤0.1 ml/min	304 (68)	192 (54)	22 (37)	755 (47)
Focus score ≥ 1	343 (79)	169 (49)	15 (25)	307 (19)
Germinal centers	125 (28%)	39 (11%)	4 (7%)	72 (4%)

Baer et al, manuscript in preparation

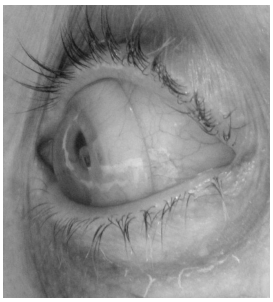
Treatment of Dry Eyes

- Artificial tear substitutes/gel/ointments
  - Preservative-free if >4/day
- Anti-inflammatory therapy
  - Topical corticosteroids for flares only
  - Topical cyclosporine
  - Systemic: tetracycline
- Dietary omega-3 fatty acids (fish or flaxseed oil)
- Punctal occlusion
- Secretagogues
- Autologous serum tears
- Bandage contact lenses, ocular surface prosthesis



Punctal plug

Scleral Prosthesis



http://www.bostonsight.org/PROSE-treatment/Conditions-PROSE-Treats/Dry-Eye-Syndrome

Treatment of Dry Mouth

- Discontinue medications with anti-cholinergic effects
- Moisture replacement
  - Small sips of water, ice chips
  - Saliva substitutes, gels, patches, lozenges
- Stimulation of glandular secretions
  - Gustatory and mechanical (sugarless chewing gum and hard candies containing xylitol, fruits rich in malic acid)
  - Systemic (pilocarpine and cevimeline)

Prevention of Dental Caries

- Targeted dental care: early detection of caries, prevention measures
- Diet assessment: sugar, fermentable carbohydrates, exogenous acid
- Promote remineralization
  - Supplemental fluoride
  - Calcium/phosphate products
- Anti-bacterial rinses
- Secretagogues
- Treat oral mucosal infections

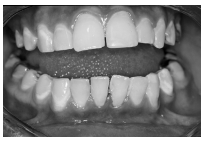
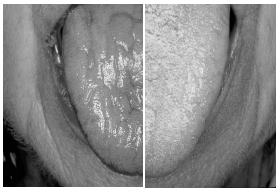


Photo from http://emedicine.medscape.com/article/1008536-overview

Chronic Erythematous Candidiasis

- In setting of poor saliva production, topical treatment required.
- Topical oral anti-fungal agents typically have high sugar content.
- Choices:
  - Compounded troches with nystatin and artificial sweetener
  - Vaginal nystatin tablets
  - Miconazole buccal tablets



Erythematous candidiasis: before (left) and after 4 weeks treatment. **Note** restoration of filiform papillae and resolution of ***angular cheilitis***

Photos courtesy of Troy Daniels, UCSF

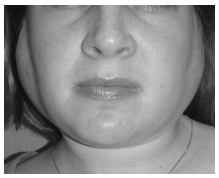
Vaginal Dryness

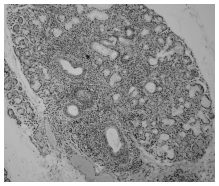
- Over-the-counter vaginal lubricants and moisturizers
- Vitamin E oil
- Local vaginal estrogen: cream, tablets, hormone-releasing rings
- Hormone replacement therapy

Menopause 2012; 19:109

Case 4

- 33 year old woman, school teacher
  - 2 year history of parotid gland swelling
  - Dryness of mouth and eyes
  - Evaluation
    - Schirmer's 3 mm OD and 4 mm OS (wetting over 5 min; nl > 10 mm)
    - Ocular surface staining score 11 OU (normal <3)
    - Whole unstimulated saliva flow 0.259 cc/5 min (normal >0.5 ml/5 min)
    - IgG 1901 mg/dl
    - Rheumatoid factor 78 IU
    - High titer SSA and SSB antibodies

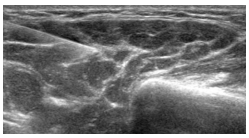


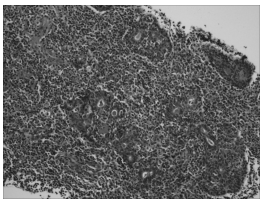


How should I monitor for lymphoma?

- No established guidelines.
- Causes for concern:
  - Persistent or new onset salivary/lacrimal gland swelling or masses
  - Lymphadenopathy
  - Splenomegaly
  - Several autoimmune diseases in same patient
  - B symptoms
  - New onset serious extraglandular disease

Case 4-cont'd





- 10% monoclonal B cell population
- Admixture of T and B cells
- Benign lymphoepithelial sialadenitis

What therapy would you offer this patient?

Controlled Trials of Systemic Immunomodulatory Therapy in SS

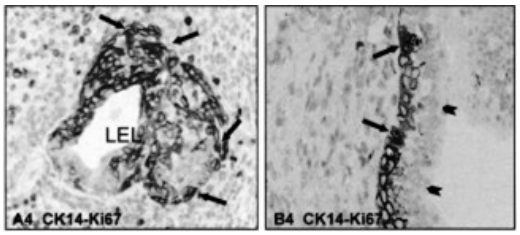
Agent	Subjective improvement	Objective improvement
Alternate-day prednisone	Yes	No
Hydroxychloroquine	No	No
Cyclosporine	Yes	No
Azathioprine	No	No
Thalidomide	Intolerable SEs	
Infliximab	No	No
Etanercept	No	No
Interferon-gamma (lozenges)	No	No
Anakinra	Primary outcome not met: reduced fatigue at 4 weeks	

Placebo-controlled Trials of Rituximab for Sjögren's Syndrome

Study	No. of pts	Duration of F/U	1° outcome measure	1° outcome met?	Significant effect seen
Meijer et al, 2010	20 RTX 10 Placebo	48 weeks	Increase in stimulated whole saliva at week 48	No	↑ stimulated saliva @ 5, 12 wks
Dass et al, 2008	8 RTX 9 placebo	6 months	>20% improvement in fatigue VAS at 6 months	No	↓ fatigue VAS relative to baseline
Mariette et al 2012	60 RTX 60 placebo	24 weeks	≥30 mm improvement in 2 of 4 VAS	No	Δ salivary flow, Δ sicca and fatigue VAS

Open label experience: benefit for extraglandular disease, parotid gland swelling, cryoglobulinemia

Clinical and histologic evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjögren's syndrome



Pijpe J, Meijer JM, Bootsma H, et al **Arthritis & Rheumatism**, 2009; 60:3251-3256

Effect of Belimumab on Parotid Gland Swelling in Sjögren's Syndrome

- Glandular domain activity: 15/30 at baseline, 7/29 at wk 28
- In 13 pts with parotid swelling (non-malignant):
  - Glandular domain improved in 10 (77%) at wk 28
  - Persistent disappearance of swelling in 4/5 at wk 52
  - Relapse of swelling in 2/5 after cessation of belimumab

Arthritis Rheum 2012; 34:S926

Therapeutic choices for patient

- Hydroxychloroquine
- Low-dose prednisone
- A decision to do more is controversial.
  - Rituximab
  - Belimumab
  - Low-dose irradiation
- Participate in a clinical trial
  - Baminercept

Summary

- It does matter…..
- Only a minority of patients with dry eyes and/or mouth have Sjögren's syndrome.
- Diagnostic testing for Sjögren's must now be protocol-driven.
- SS is a heterogeneous disorder and definition of phenotypic subsets is crucial for elucidating diverse pathogenetic pathways.

The Jerome L. Greene Sjögren's Syndrome Center

- **Rheumatology**
  - Alan Baer, MD; Julius Birnbaum, MD, MHS; Thomas Grader-Beck, MD, PhD
- **Ophthalmology**
  - Esen Akpek, MD; Monica Schaeffer, OD
- **Otolaryngology**
  - Jean Kim, MD, PhD; Roni Dinkes, Au.D
- **Gynecology**
  - Anne Burke, MD
- **Neurology**
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Funding support
- Jerome L. Greene Foundation
- NIDCR
- NIAMS