Difficult Sjögren's Disease

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Disclosures

- Consultant
  - Bristol-Myers Squibb
- Royalties
  - UpToDate

Difficulties in Sjogren's diagnosis and management

- Establishing the diagnosis, especially in the absence of anti-SSA antibodies
- Unrelenting symptoms of oral and ocular dryness
- "I am tired all the time and hurt all over. Is it my Sjogren's?"
- Salivary gland enlargement and pain
- The risk of lymphoma

Can I just settle for a diagnosis of "likely Sjogren's"?

- The arguments for this viewpoint include:
  - In the absence of disease-modifying therapy, a definitive diagnosis of Sjögren's is not essential.
  - It is hard to get ophthalmologists to do the tests included in the ACR/EULAR classification criteria.
  - There are few oral medicine specialists.
  - The lip biopsy is invasive, not done in a uniform fashion, and often vague in its interpretation.

“Difficult” Sjogren’s is easier with more complete data

- Avoidance of immunosuppressive/immunomodulatory treatment if not a definite diagnosis (e.g. SFN, POTS, etc)
- Recognition of alternative diagnoses for salivary gland enlargement
- Prognostic information

Two patients with ocular and oral dryness for <5 years

51 year old woman

- Diminished sublingual salivary pool; no glossitis
- Schirmer 5 OD, 8 OS
- Saliva flow: 1.38 cc/5 min
- WBC 3510
- IgG 3010 mg/dl, polyclonal
- Antibodies to SSA and SSB
- Rheumatoid factor negative

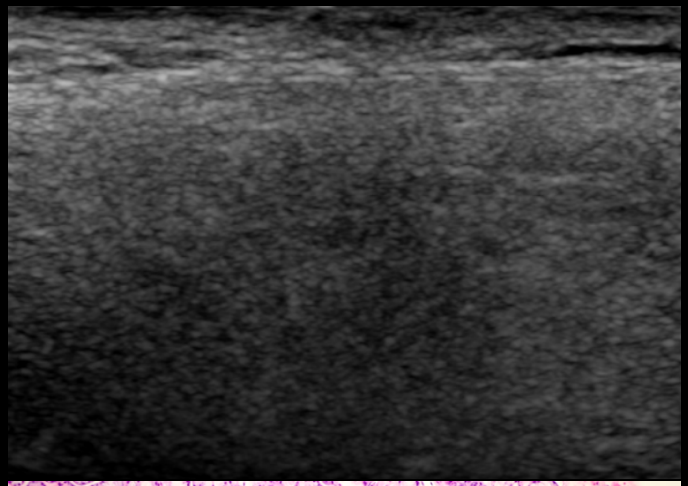
44 year old woman

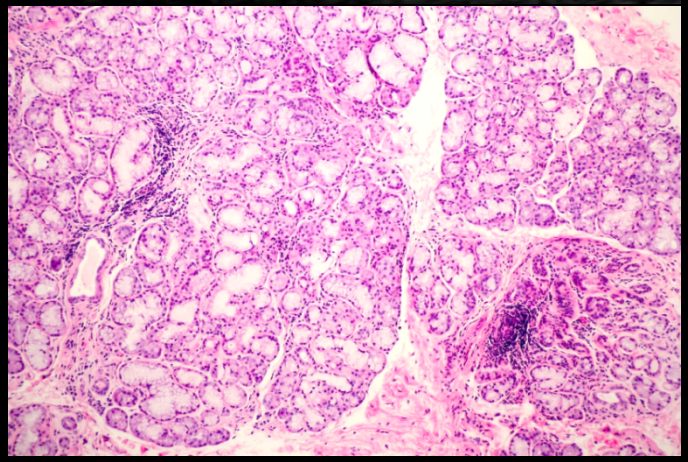
- Atrophic glossitis; absent sublingual salivary pooling
- Schirmer 5 OD, 4 OS
- Saliva flow: 0.276 cc/5 min
- WBC 3080
- IgG 2005 mg/dl, polyclonal
- Antibodies to SSA and SSB
- Rheumatoid factor 128 IU/ml

Both patients meet classification criteria for Sjögren's syndrome.

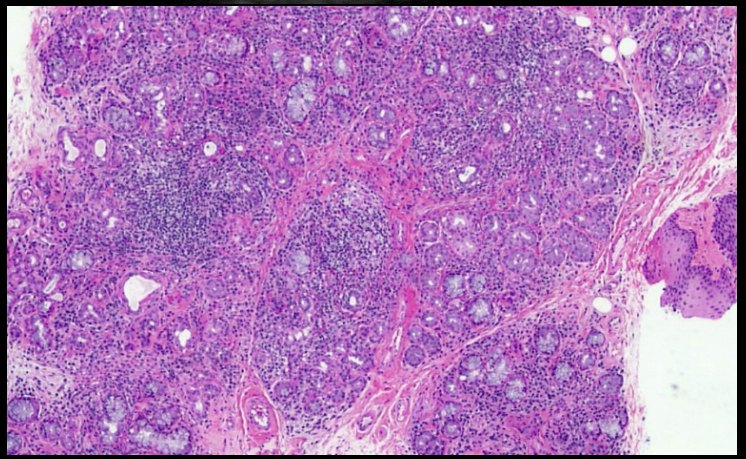
Parotid ultrasonography and minor salivary gland biopsy

Patient 1

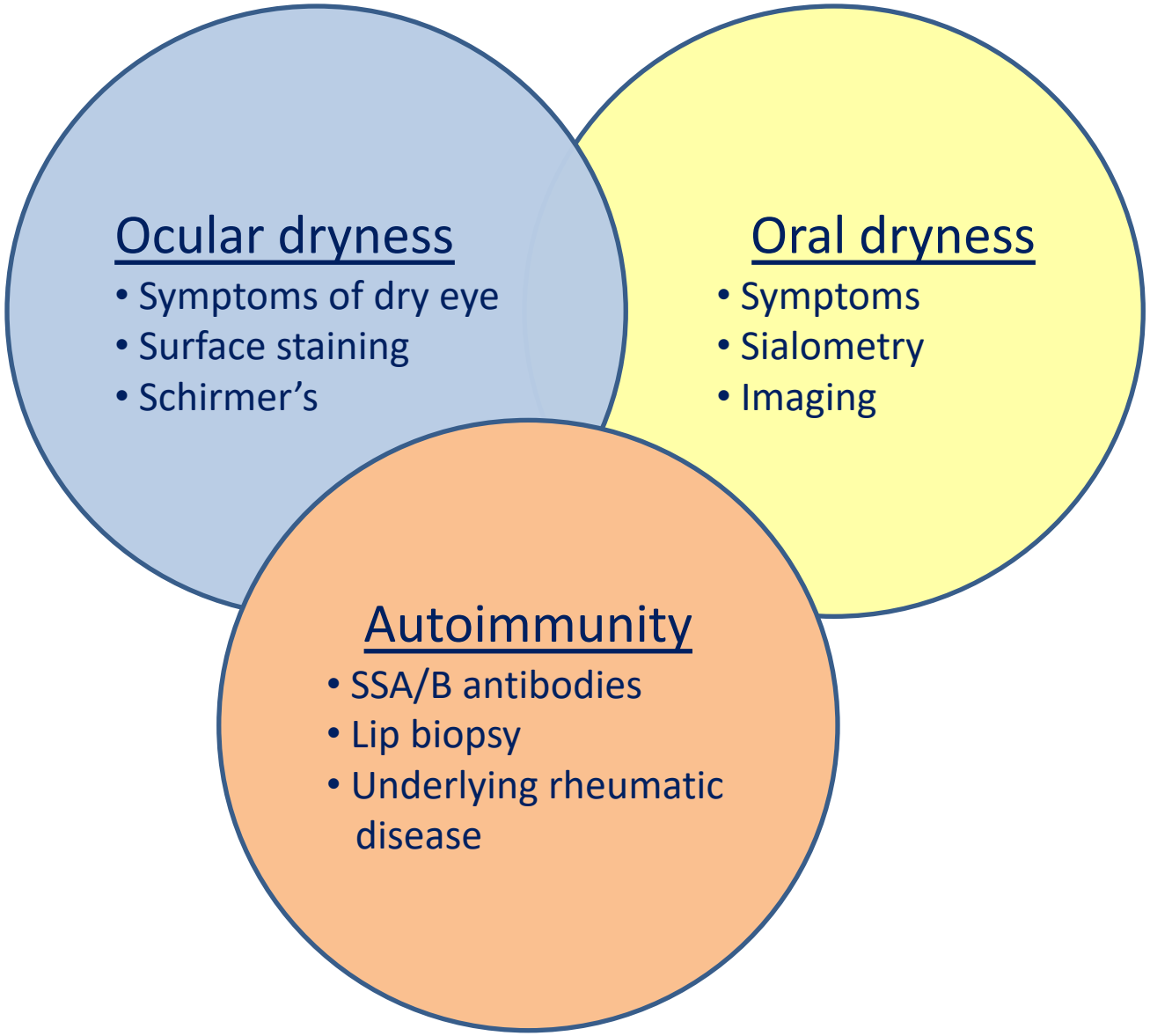




Patient 2



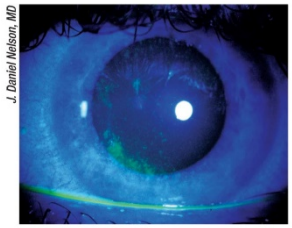
Diagnosing Sjögren's disease



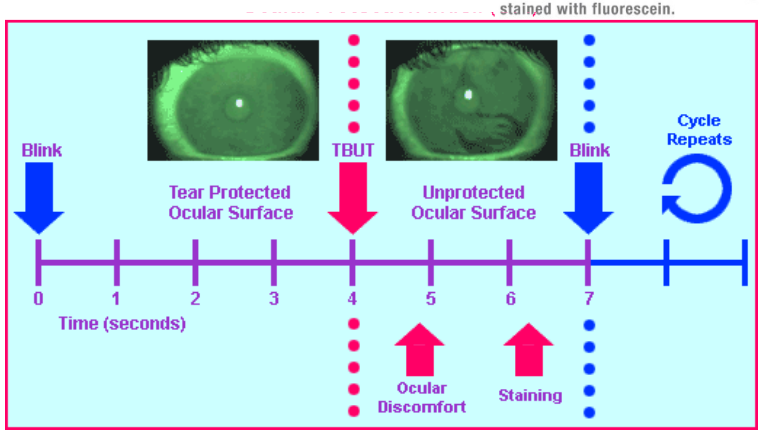
Assessment of dry eye

The usual eye exam includes:

- Tear film assessment (tear meniscus, debris)
- Tear break up time
- Corneal staining with fluorescein

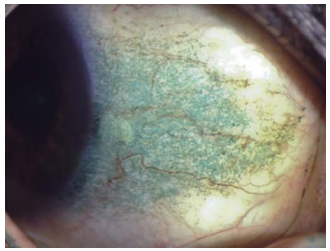


Punctate epithelial erosions in an eye stained with fluorescein.



The Sjogren's eye exam requires:

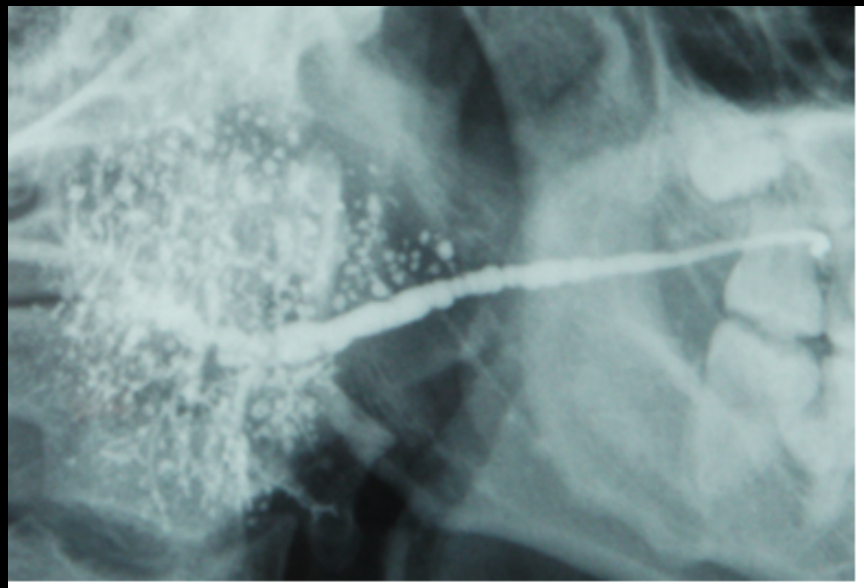
- Conjunctival staining with lissamine green
- Corneal staining with fluorescein
- Schirmer's test

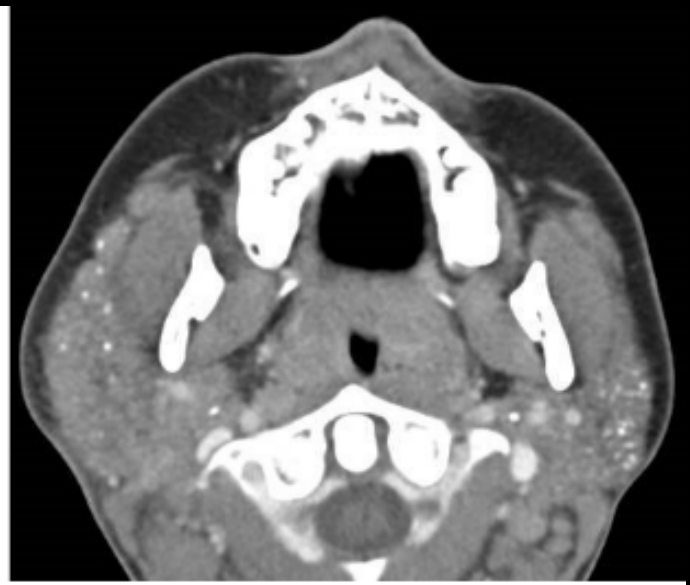


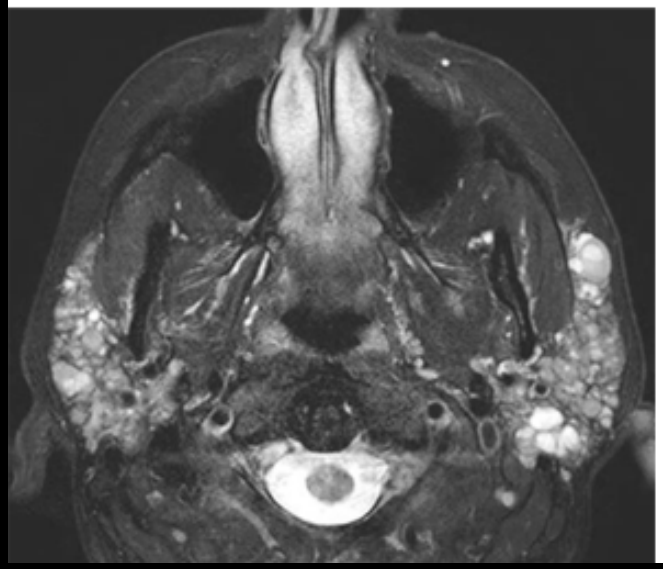
Saliva flow can be measured (sialometry).

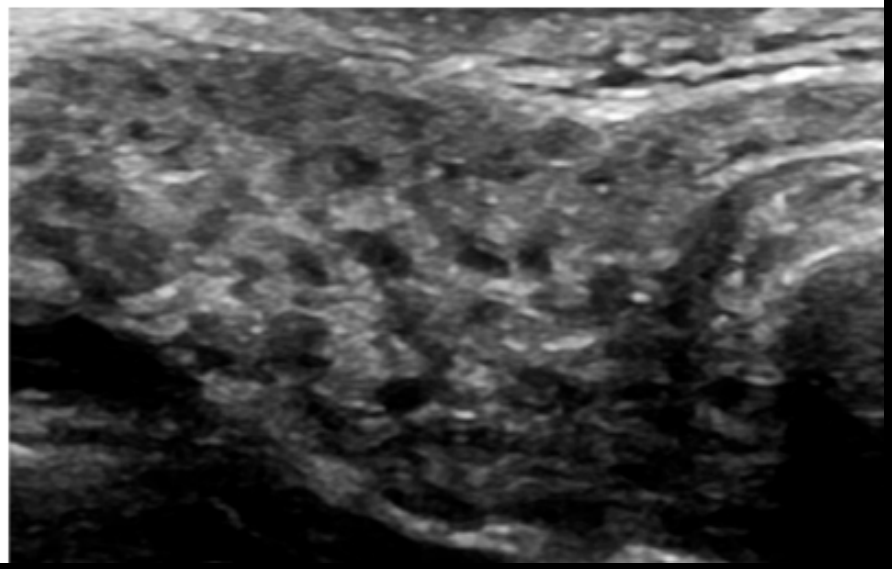
- Whole unstimulated sialometry
  - Easy to perform in clinical setting
  - Best correlate of dry mouth complaint and oral health
  - <0.5 ml/5 min is abnormal

Can structural imaging be an alternative to a salivary gland biopsy?

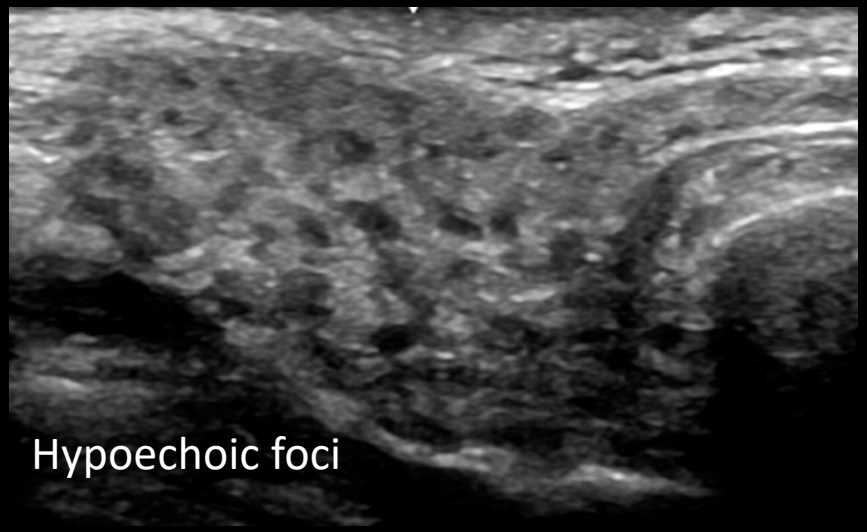




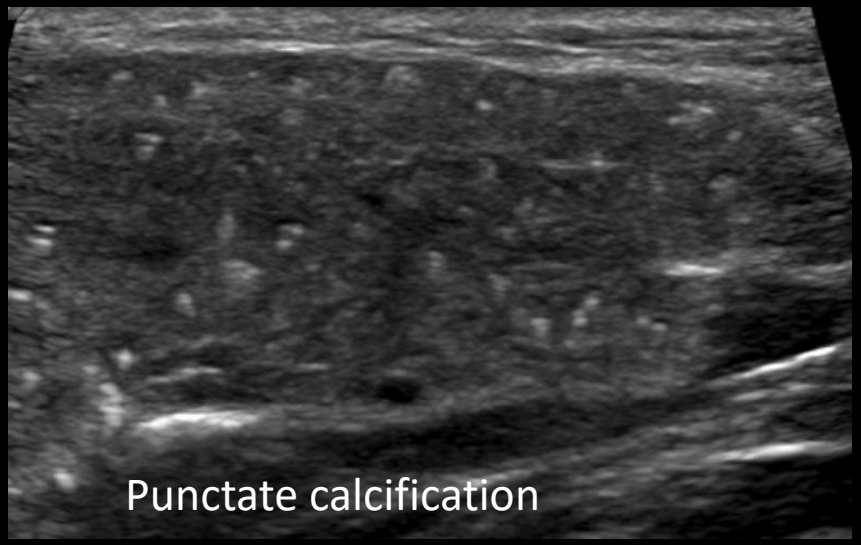




Salivary gland ultrasound scoring items

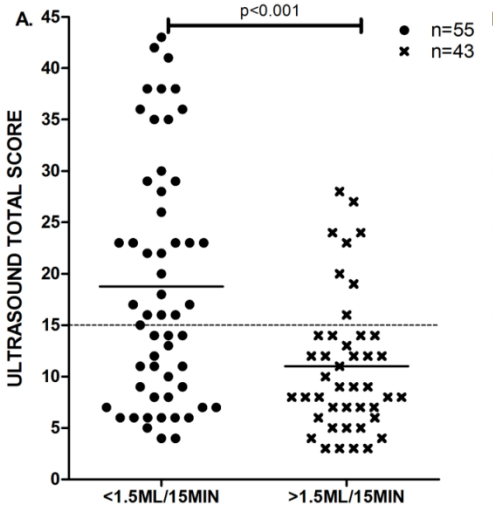


Clarity of posterior border

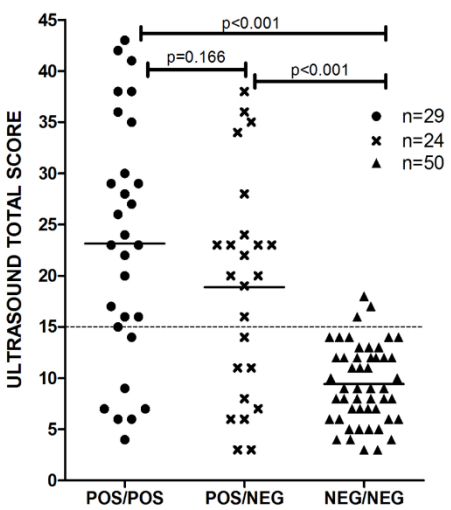


Ultrasound score correlates with key phenotypic features

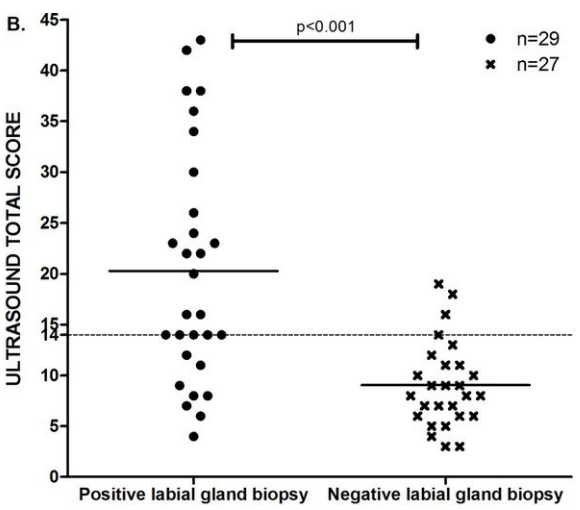
Unstimulated whole saliva flow



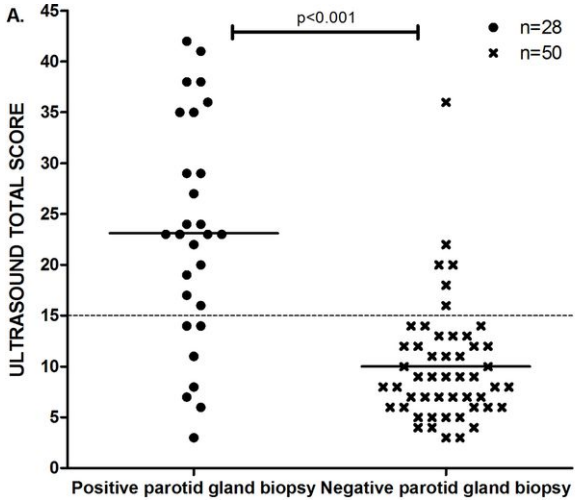
Anti-SSA and –SSB antibodies



Labial gland biopsy



Parotid gland biopsy

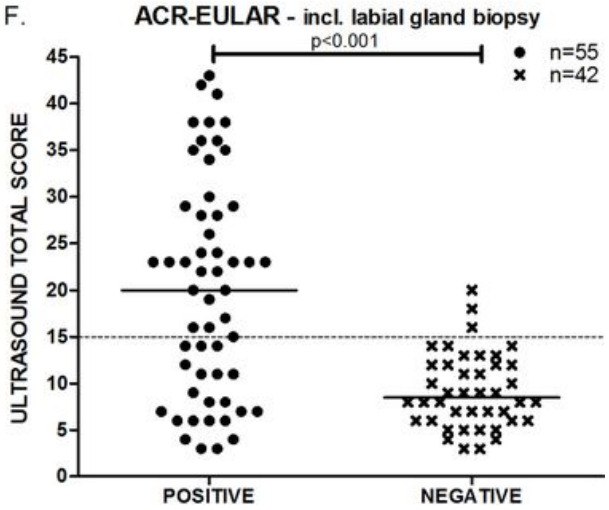


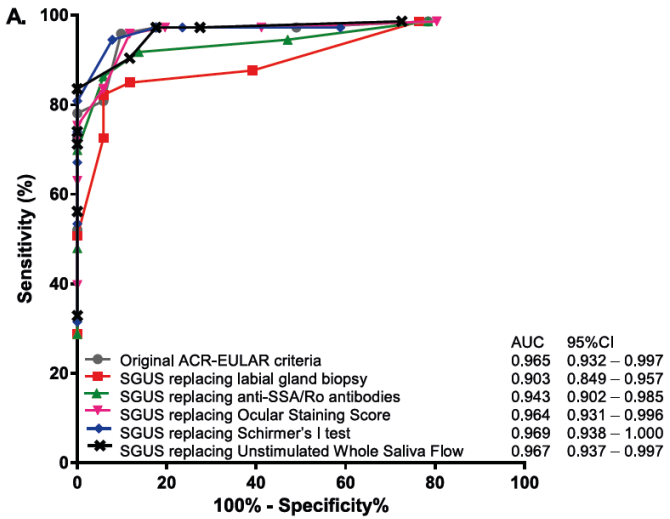
Score based on:

- parenchymal echogenicity
- homogeneity
- presence of hypoechogenic areas
- hyperechogenic reflections
- clarity of the posterior gland border

Mossel et al. Ann Rheum Dis 2017 Nov;76(11):1883-1889

Can salivary gland ultrasonography (SGUS) be a substitute for lip biopsy?





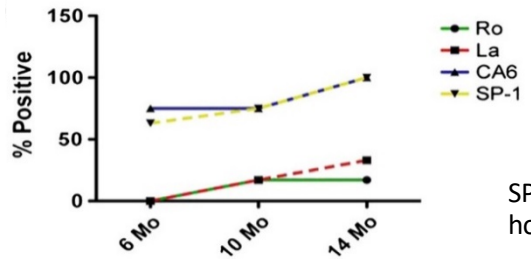
- SGUS primarily identifies seropositive patients with positive lip biopsy
- May not differentiate Sjögren's from other forms of sialadenitis
- Anti-SSA and abnormal SGUS may suffice to define SS.

Ann Rheum Dis 2017;76:1883-1889
Arthritis Care Res 2020;72:583-590

Seronegative Sjogren's

- 20-25% of Sjogren's cohorts
  - Some will have centromere, RNP, CCP
  - Evolution to a positive SSA is rare, but does occur
  - Early Sjogren's antibodies have no diagnostic value
- Diagnosis requires a lip biopsy

The Sjo™ panel: murine tissue-specific antibodies marketed as a test for early SS



SP-1: no human homologue

Analysis of 80 SICCA registrants with Sjögren's (ACR criteria)

	Sjögren's with novel antibody positive	Sjögren's with novel antibody negative
Ro positive	31	35
Ro negative	10	4

Overall sensitivity: Ro 82.5%; novel antibody 51.3%
Specificity not assessed in absence of non-SS pts

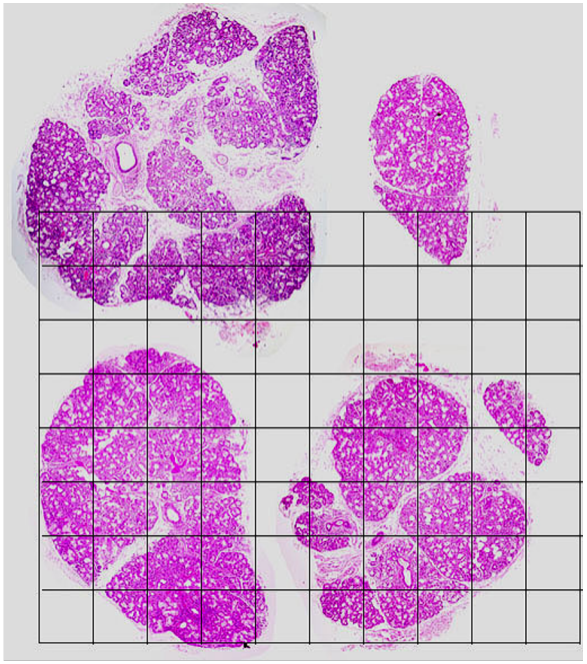
- Salivary protein 1 has no human homologue
- At U Penn Rheum clinic
  - At least one TSA in:
    - 43% SS pts (n=145)
    - 59% non-autoimmune controls (n=32)
    - 40% chronic sialadenitis (n=15)
    - 33% other CTD (n=36)
- NIDCR study with LIPS assay
  - No reactivity in 20 SS patients to 22 human proteins with enriched expression in salivary gland, including CA6, PSP

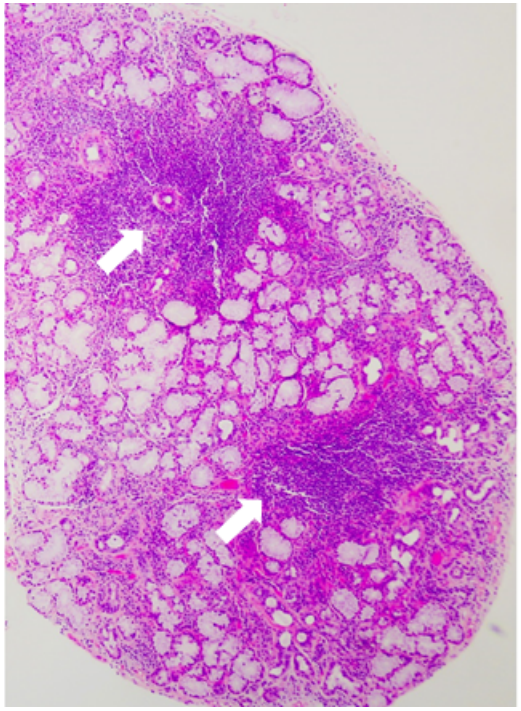
Clin Immunol 2012;145:251; Clin Exp Rheumatol. 2018; 36(Suppl 112):S256; J Dent Res 2019;98:772;

The focus score

- A semi-quantitative assessment of severity of focal lymphocytic sialadenitis
- Calculate total glandular surface area
  - Count number of foci adjacent to normal-appearing acini
  - Calculate number of lymphocytic foci per 4 mm^2 of glandular tissue
- Focus score = number of lymphocytic foci per 4 mm^2 of glandular tissue
- Focus score ≥1 is a diagnostic criterion for Sjögren's syndrome

Ann Rheum Dis. 2015 Sep;74(9):1645-50



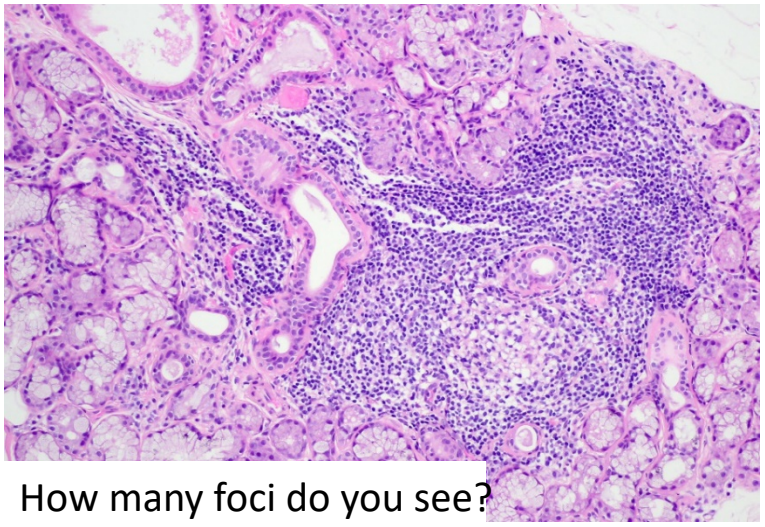


Who needs a lip biopsy?

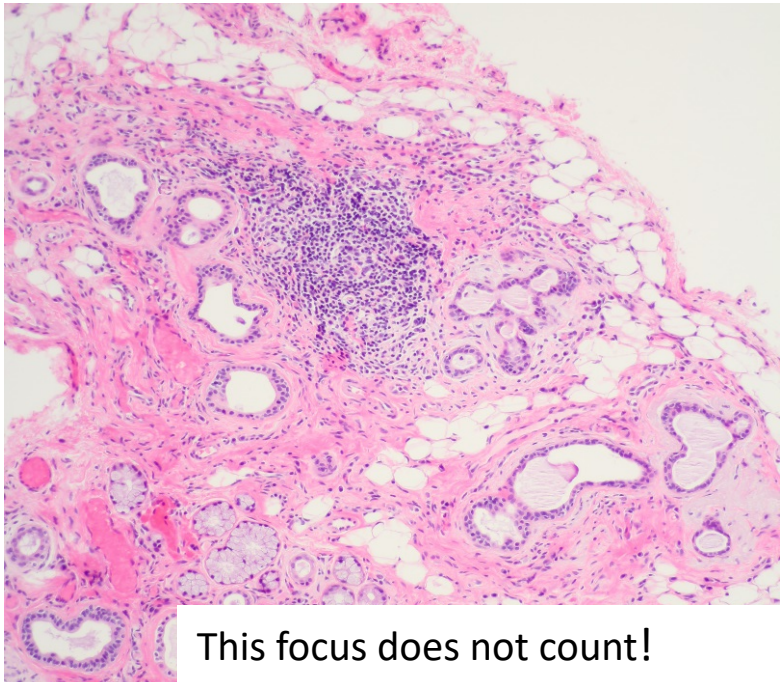
- Those lacking SSA and centromere antibodies
- Those with SSB antibodies alone
- Those with low titer SSA
- Concern for lymphoma or alternative diagnosis

Pitfalls in reading lip biopsies

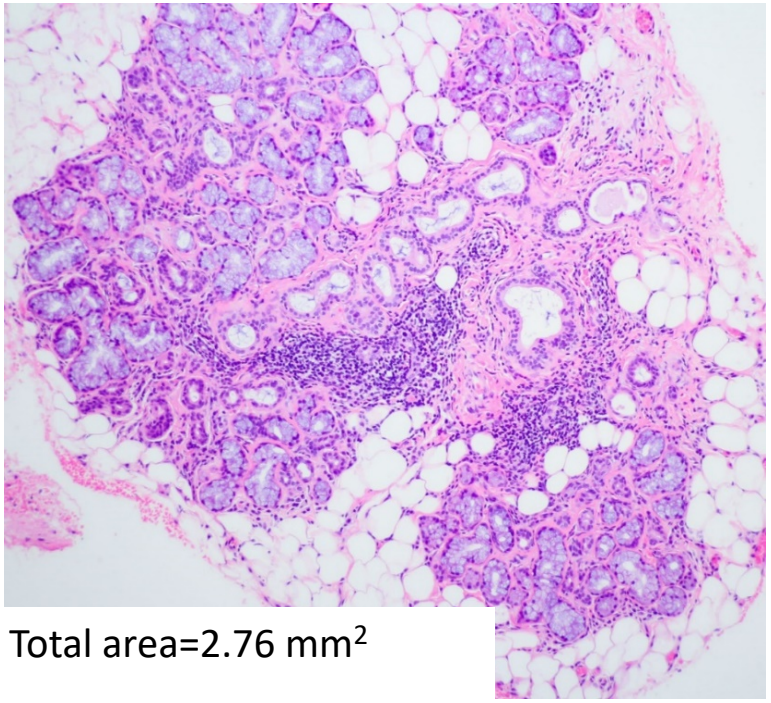
- "Eyeballing the surface area"
- Counting foci in areas of ductal dilatation
- Defining foci
- Sample too small



How many foci do you see?



This focus does not count!



Total area=2.76 mm^2

Unrelenting sicca

- Are medications leading to worse symptoms?
- Are the ocular symptoms related to a deficiency of tears?
  - Meibomian gland dysfunction
- Are the oral symptoms related to a deficiency of saliva?
  - Chronic erythematous candidiasis
- Is there a blockage of saliva flow?
- Can DMARDs improve gland function?

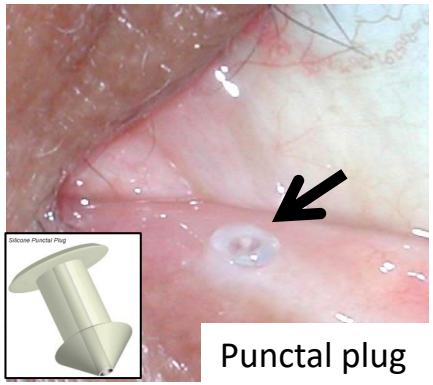
Dry eye management

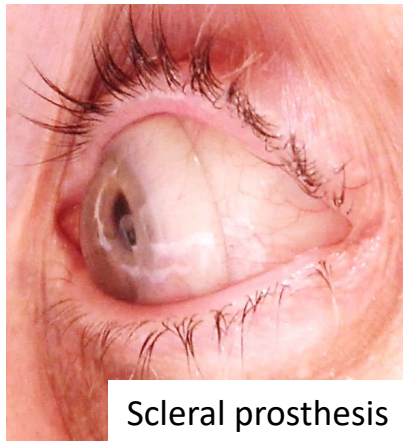
Stage 1
- Environmental modification
- Ocular lubricants
- Lid hygiene and warm compresses

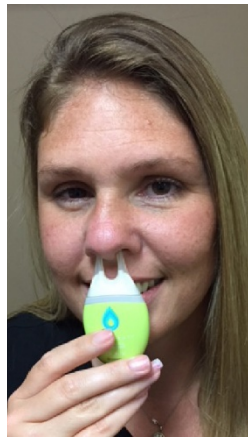
Stage 2
- Preservative-free ocular lubricants
- Punctal occlusion
- Moisture chamber spectacles/goggles
- In-office treatments for Meibomian gland dysfunction
- Prescription drugs
  - Topical cyclosporine or lifitegrast
  - Topical corticosteroids (limited duration)
  - Topical or oral antibiotics for blepharitis

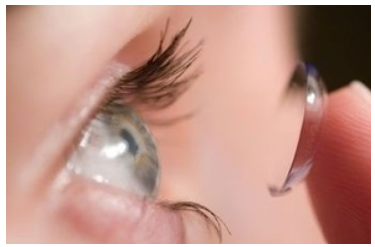
Stage 3
- Oral secretagogues
- Electrical stimulator
- Autologous serum tears
- Therapeutic contact lenses
  - Soft bandage lenses
  - Rigid scleral lenses

Stage 4
- Amniotic membrane grafts
- Punctal cautery
- Tarsorraphy

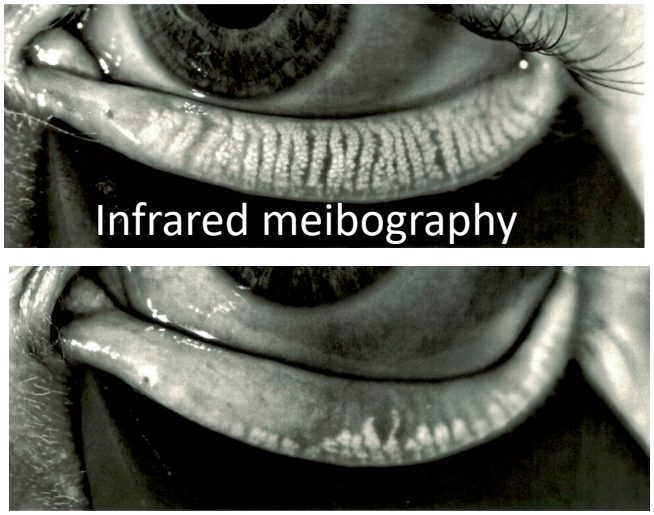

Punctal plug


Scleral prosthesis


TrueTear



Meibomian gland dysfunction (MGD) frequently accompanies aqueous tear deficiency of Sjögren's



- Amenable to therapy with eyelid hygiene, antibiotics
- Advanced modalities: intense pulsed light, thermal pulsation (Lipiflow), intraductal gland probing

Invest Ophthalmol Vis Sci. 2011 Mar; 52(4): 1938–1978.

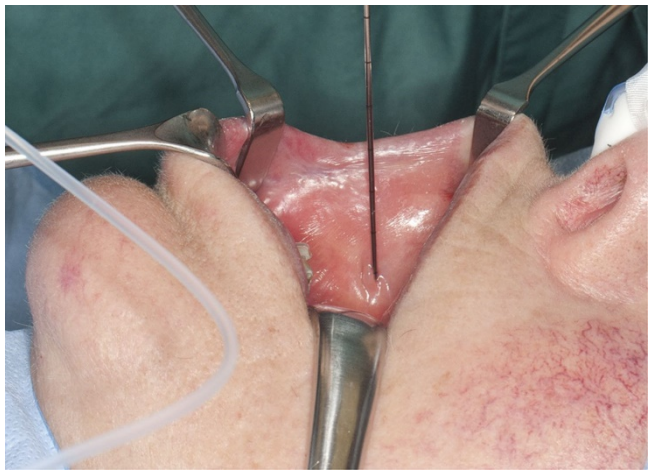
Using secretagogues

- Use limited by side effects
  - sweating, flushing, nausea, vomiting, and diarrhea
  - Can be decreased by taking after meals
- Cevimeline generally better tolerated
- Intolerance to one does not reliably predict intolerance to the other.
  - 25% users were able to continue long-term treatment after switching to the alternative
- Titration of dose can reduce incidence of side effects
  - Cevimeline can be easily dissolved to make a solution

Management of oral candidiasis in salivary hypofunction

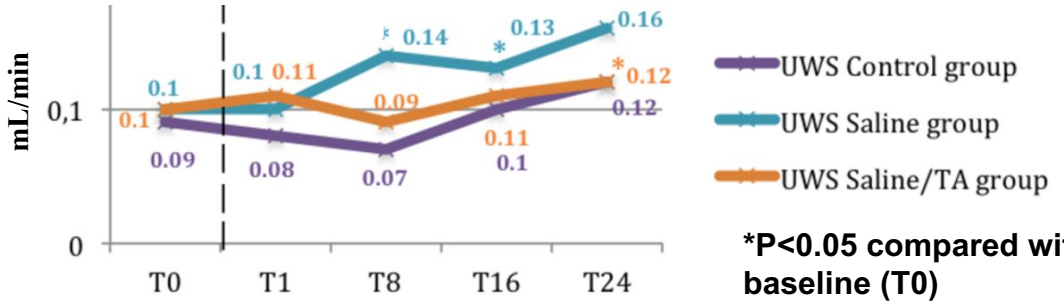
- Mild disease
  - Clotrimazole troches, miconazole buccal tablets for 7-14 d
  - Avoid nystatin suspension due to its high sugar content
- Moderate to severe disease
  - Fluconazole 100-200 mg qd for 7-14 d
  - Chronic suppression: fluconazole 100 mg 3x/week
  - Topical therapies for resistant cases
- Dentures or mouthguards: treat overnight in nystatin suspension or chlorhexidine 0.12% solution

Sialendoscopy in Sjögren's



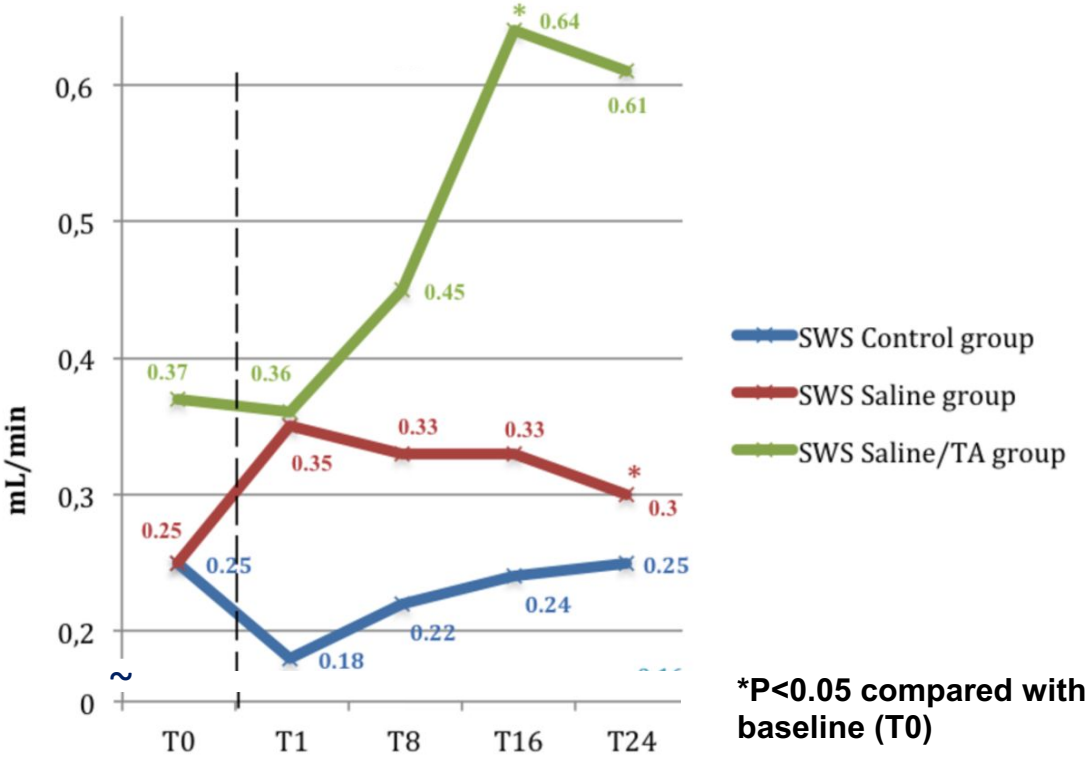
- 49 SS patients
- Sialoendoscopy in 2 groups: saline rinse with and without steroids; control group without any intervention
- Strictures present and removed in all treated glands
- Improved saliva flow in both intervention groups

Unstimulated whole saliva flow



*P<0.05 compared with baseline (T0)

Stimulated whole saliva flow



*P<0.05 compared with baseline (T0)

Ann Rheum Dis 2018;77:1025-1031

Placebo-controlled drug trials in Sjögren's disease that have failed

Oral medications

- Alternate-day prednisone
- Hydroxychloroquine
- Cyclosporine
- Azathioprine
- Thalidomide
- DHEA*
- Omega-6 fatty acids
- Petesicatib (cathepsin S inhibitor)
- Leniolisib (PI3Kδ inhibitor)

Biologic medications

- Etanercept*
- Infliximab
- Anakinra
- Baminercept (lymphotoxin inhibitor)
- Rituximab
- Abatacept
- Tocilizumab
- Anti-ICOS-L mAB

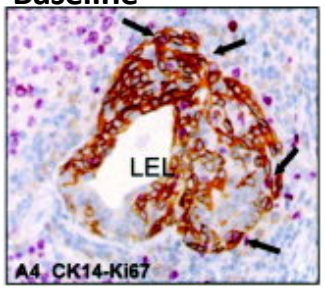
*Studies conducted at NIH

Can rituximab ameliorate glandular disease? (Lessons from RCTs)

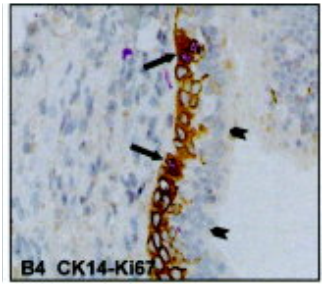
- Tear/salivary flow
  - At early time points (5,12 weeks) in small RCT[1]
  - Not at trial end (24, 48 wks) in two large RCTs[2,3]
- Parotid gland enlargement
  - No benefit in TEARS trial (large RCT) [2]
- Histopathology
  - Improved parotid gland histopathology[4]
  - Transient decrease in salivary gland B cells[5]
- Imaging:
  - Improved parotid parenchyma echostructure in 50% RTX vs 7% PBO in TEARS[6]
  - Improved total ultrasound score in TRACTISS, but not in size or number of hypoechogenic foci[7]

LEL histopathology

Baseline

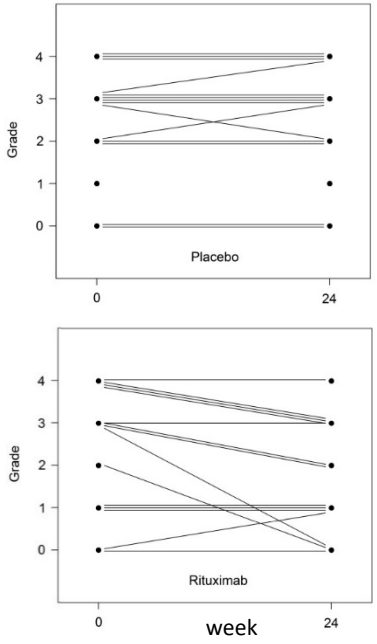


Post-rituximab



Arthritis Rheum, 2009; 60:3251

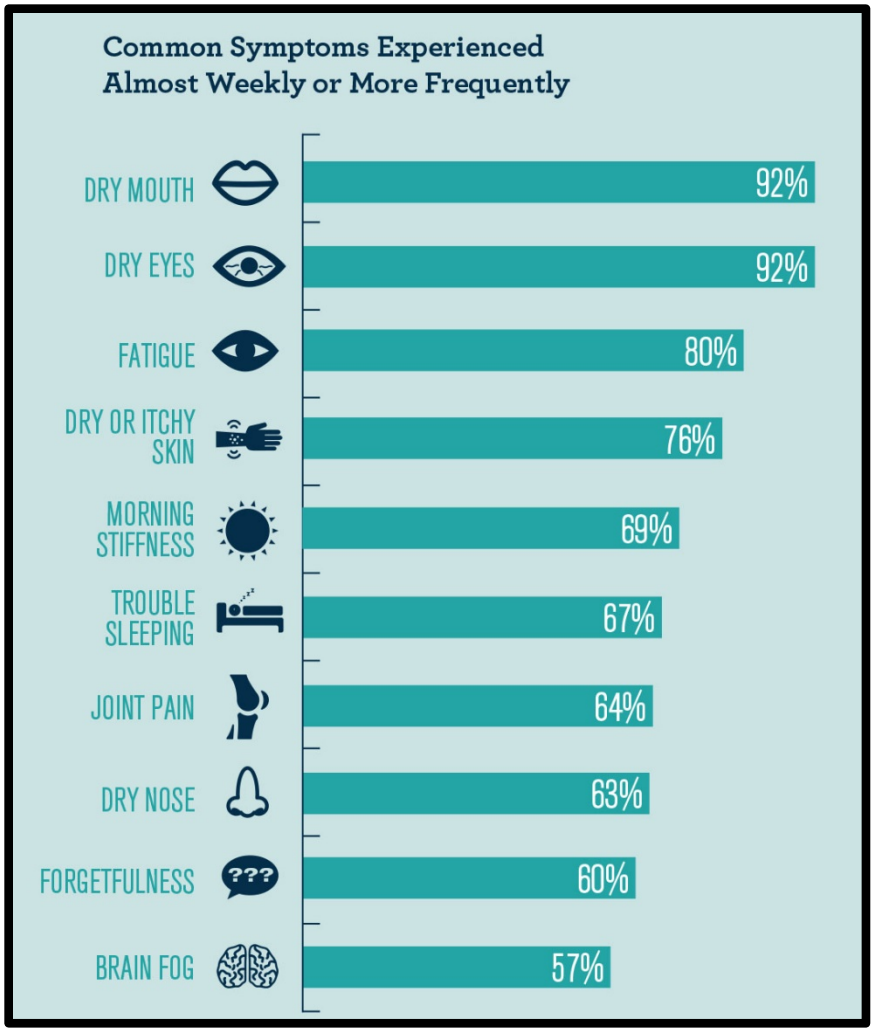
Ultrasound echotexture



Arthritis Rheum 2015;67:1623

[1]Arthritis Rheum. 2010;62:960-8; [2]Ann Intern Med. 2014;160:233-42; [3]Arthritis Rheumatol. 2015; 67 (suppl 10), Abstract 3203; [4]Ann Rheum Dis 2016;75:1933-1938; [5]J Autoimmunity 2016;67:102; [6]Arthritis Rheum 2015;67:1623; [7]Ann Rheum Dis 2018;77:412

Pain and fatigue: is it my Sjögren's?

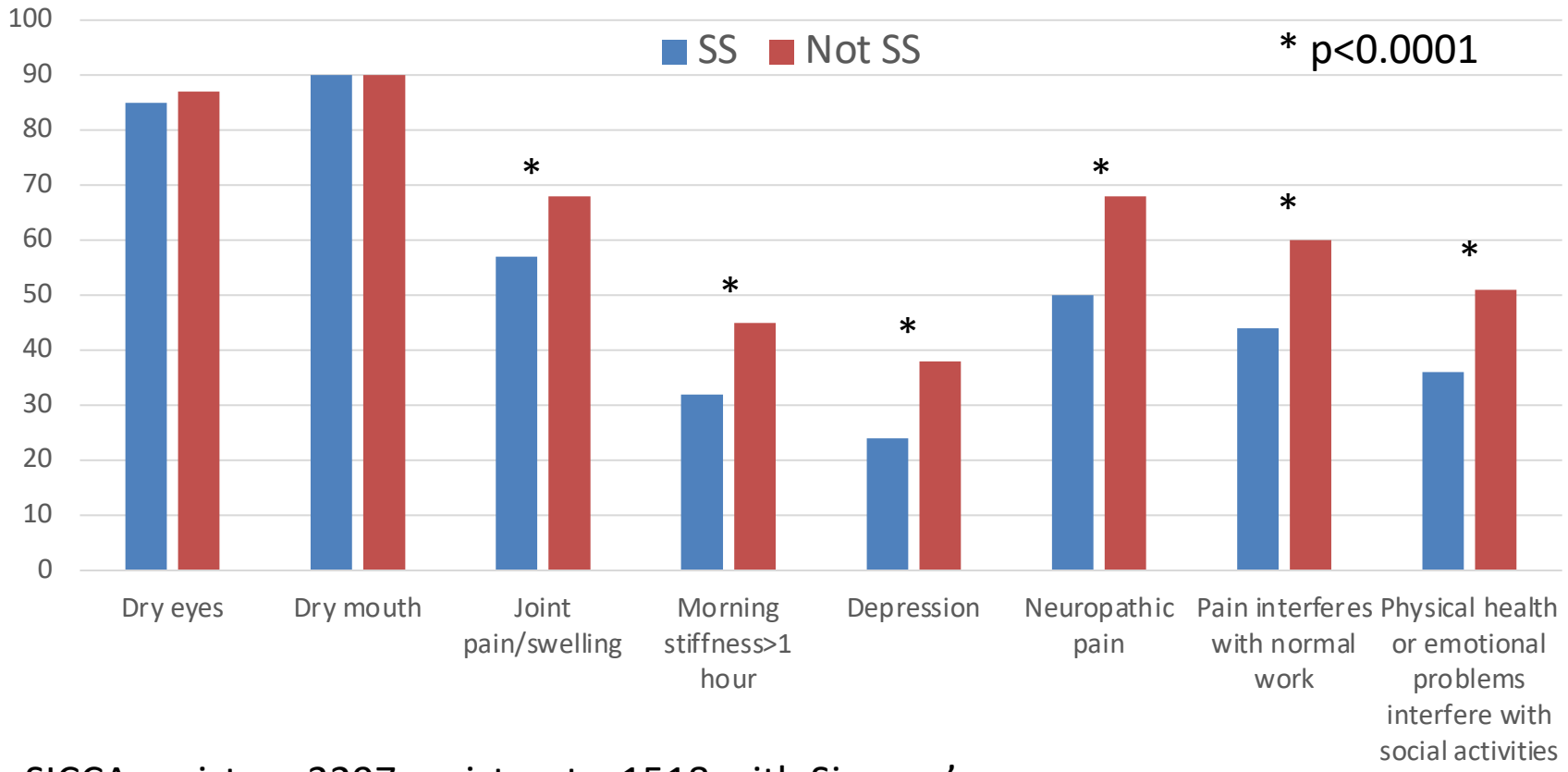


Harris Survey conducted by Sjögren's Foundation, 2016

2,962 adults aged 18 or over

All reporting physician-diagnosis of Sjögren's

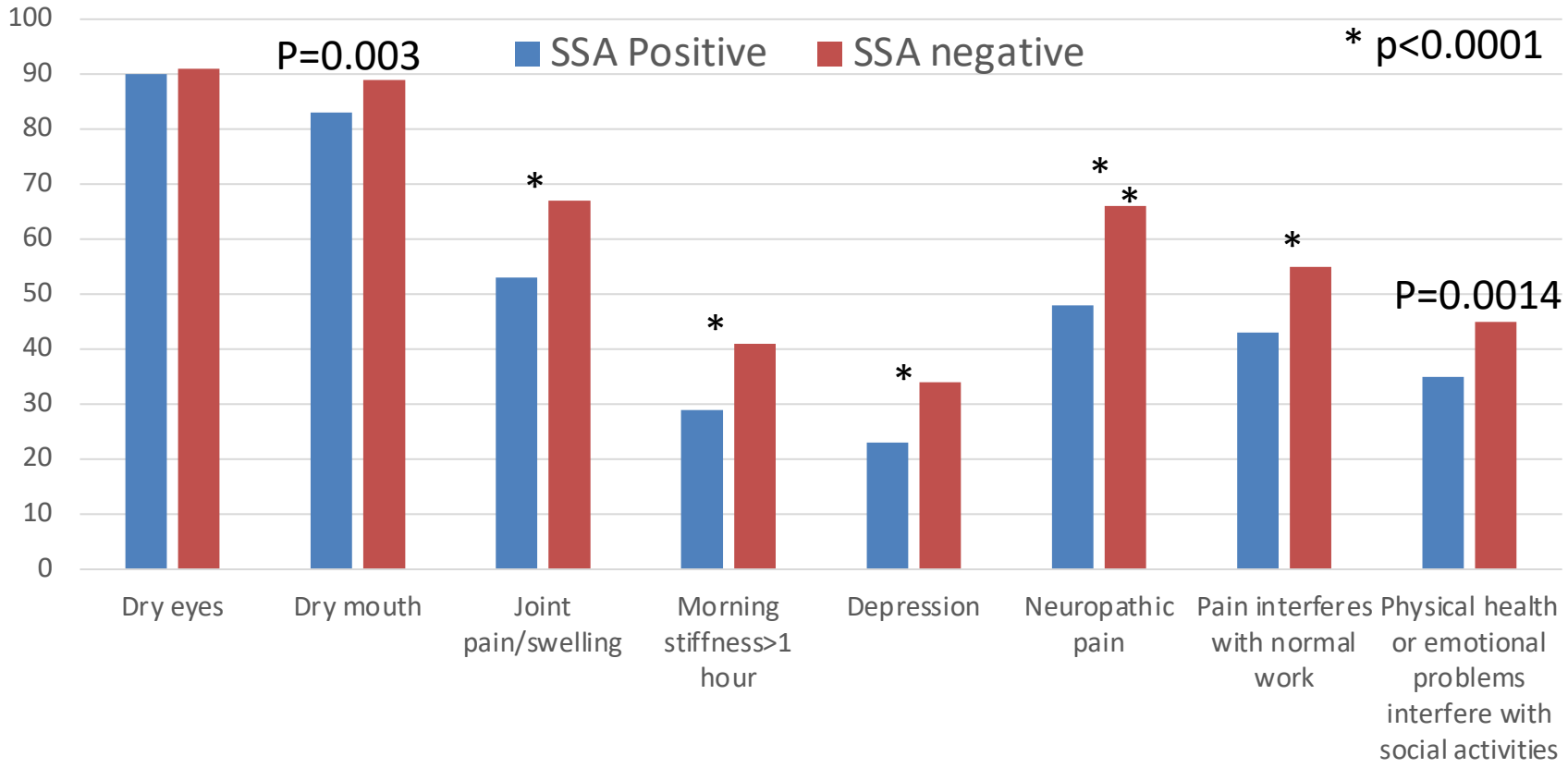
Symptom burden in people with suspected or established Sjögren's



SICCA registry: 3297 registrants; 1518 with Sjogren's

Neuropathic pain=positive response to persistent burning, sharp jabbing pain, or prickling or tingling

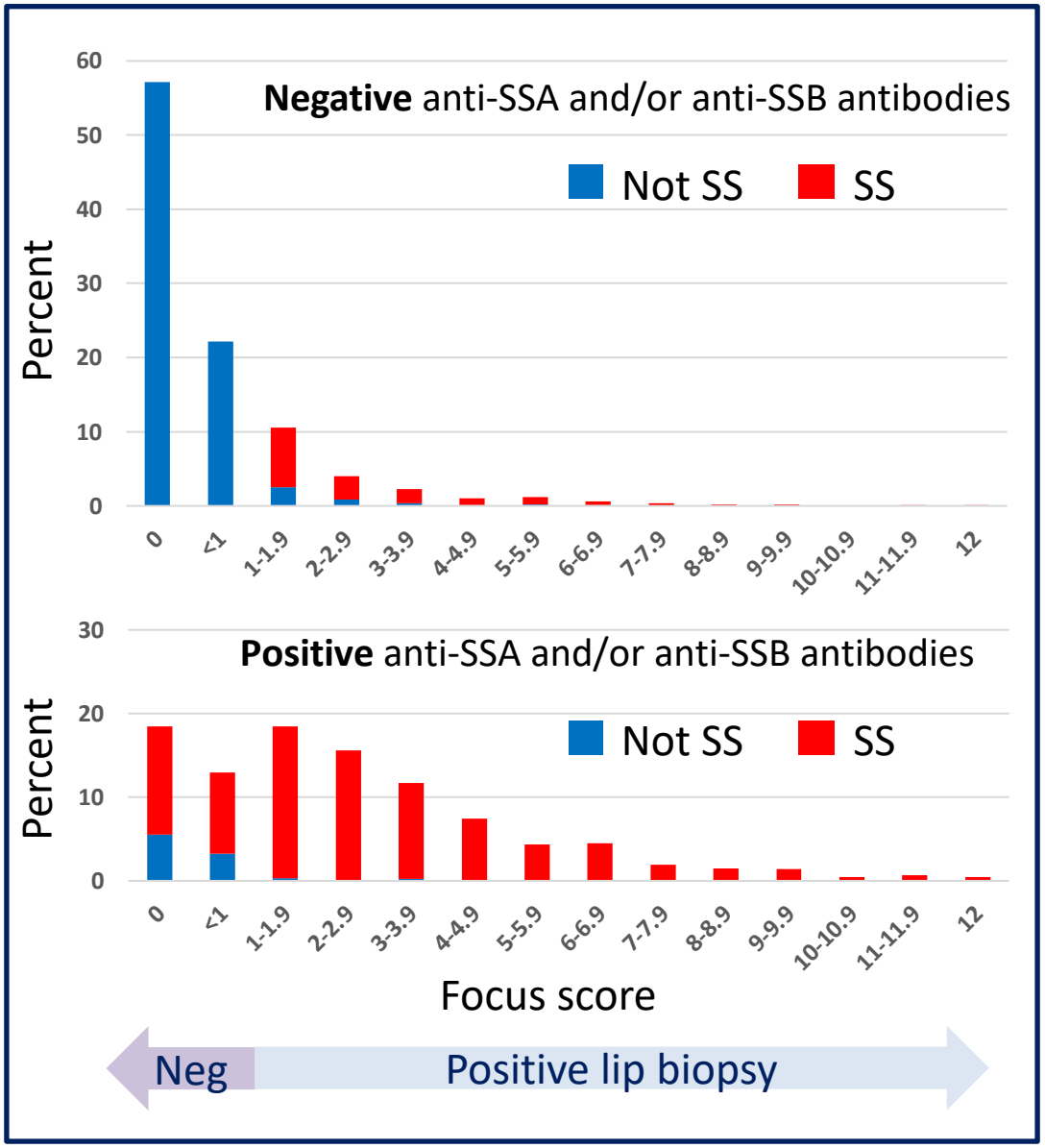
Symptom burden in Sjögren's: Anti-SSA positive vs anti-SSA negative



SICCA registry: 3297 registrants; 1518 with Sjogren's

Neuropathic pain=positive response to persistent burning discomfort, sharp/ jabbing pain, or prickling/tingling sensation

Seronegative Sjögren's has low focus scores.



Seronegative (20-40%)

- + lip biopsy in all (by definition)
- Older age at diagnosis
- Unexpected phenotypic correlates:
  - Greater pain severity[1]
  - More prevalent widespread pain[2]
  - Pure sensory small fiber neuropathy[3]

[1]Arthritis Care Res 2013; 65:1291
[2]Clin Exp Rheumatol. 2014 32:349
[3]Brain. 2005 128:2518

Seropositive (60-80%)

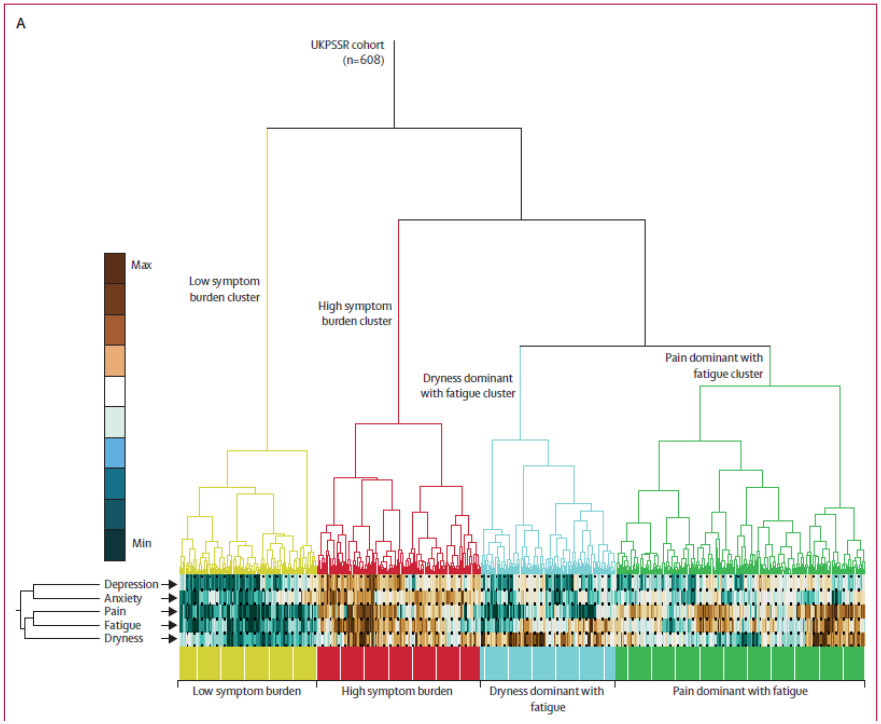
- + lip biopsy in ~70%
- Phenotypic correlates
  - Higher focus score
  - More severe glandular dysfunction
  - Hypergammaglobulinemia
  - Rheumatoid factor
  - Vasculitis
  - Leucopenia

SICCA registry; 3297 registrants

Seronegative sicca syndrome

- Sicca as a manifestation of dysautonomia, anxiety/depression, medications with anti-cholinergic side effects
- At risk for misdiagnosis as Sjögren's due to
  - Imprecision of lip biopsy interpretation
  - Low titer, inconsistent SSA and/or SSB testing
  - Minor changes in epidermal nerve fiber density
- But often, compelling stories for a trigger and nagging questions about an autoimmune etiology

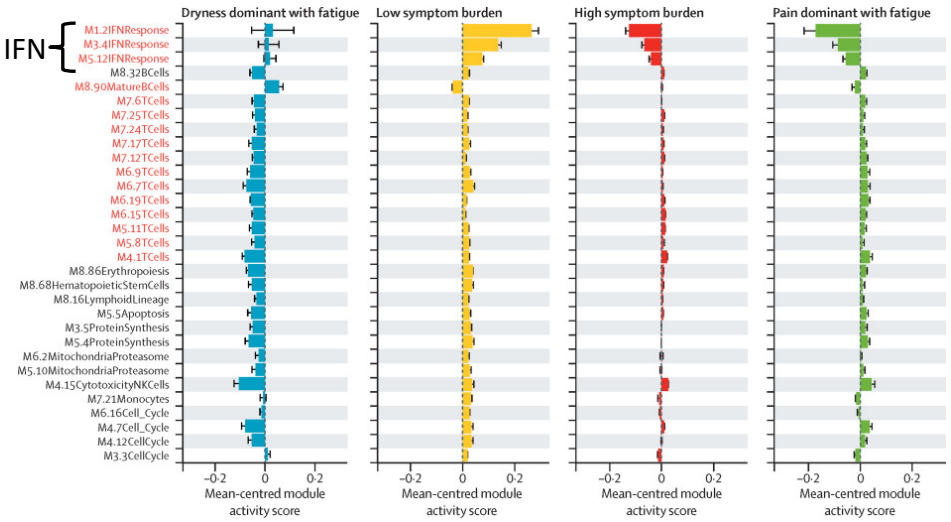
Symptom-based stratification



Objective parameters between groups

	LSB	HSB	DDF	PDF	P-value
UWS (ml/15 min)	0.4	0.2	0.1	0.3	0.03
Schirmer (mm/5 min)	3.0	3.0	2.0	4.0	0.03
Lymphs (x10^9/L)	1.2	1.5	1.3	1.3	0.0009
IgG (mg/dl)	18	14.1	16.6	14.4	0.0009
SSA/SSB positive (%)	93	87	94	85	0.048
Lymphoma (%)	2	6	11	3	0.0113

Transcriptomic module activity between groups



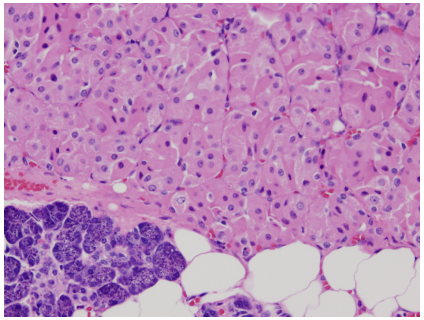
LSB: low symptom burden
HSB: high symptom burden
DDF: Dryness dominant with fatigue
PDF: Pain dominant with fatigue

Lancet Rheumatology 2019; 1:e85-e94

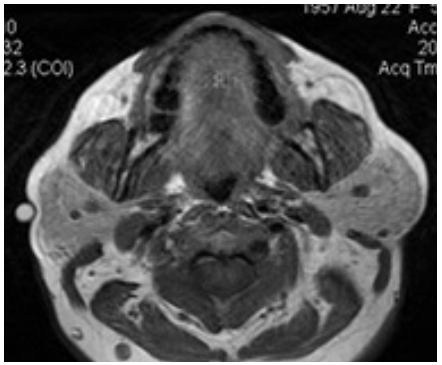
My approach to fatigue and pain

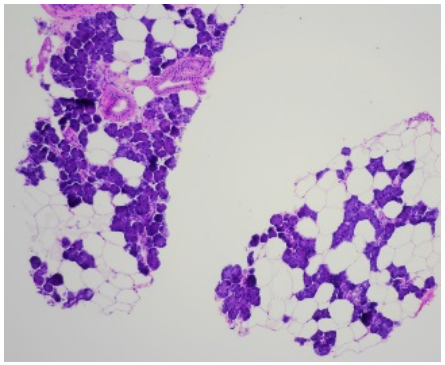
- If the diagnosis of SjD is unequivocal
  - Rule out associated conditions
  - Evaluate for small fiber neuropathy if symptoms are suggestive
  - Empiric trial of steroids
  - For fatigue, rituximab, belimumab
- If the data supporting the diagnosis are not robust
  - Labial gland biopsy: review, repeat or secure de novo
  - Repeat serology if originally low titer
- Be comfortable saying “It’s not (your) Sjögren’s”

Persistent bilateral salivary gland enlargement: not all Sjogren's

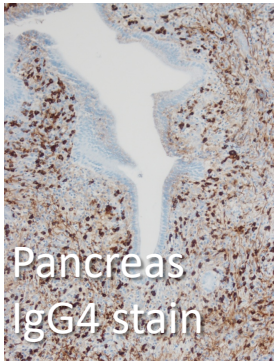


Multifocal nodular oncocytic hyperplasia (benign neoplasm)

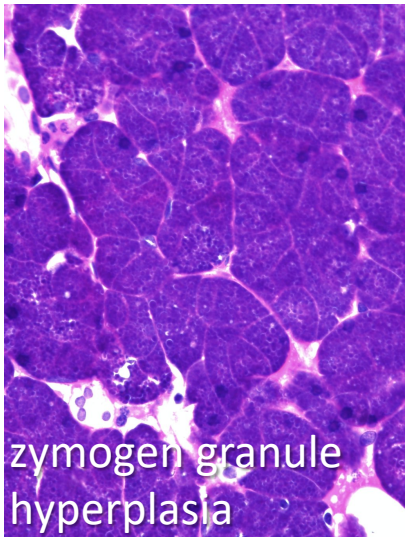




Fatty infiltration



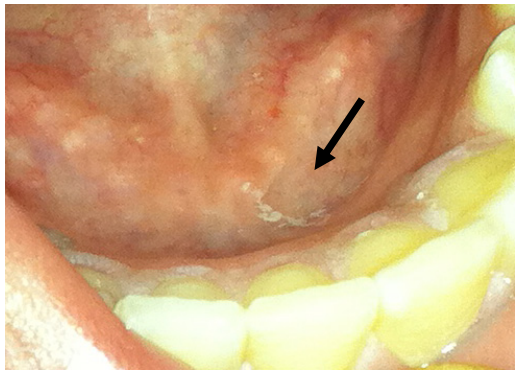
IgG4-related disease

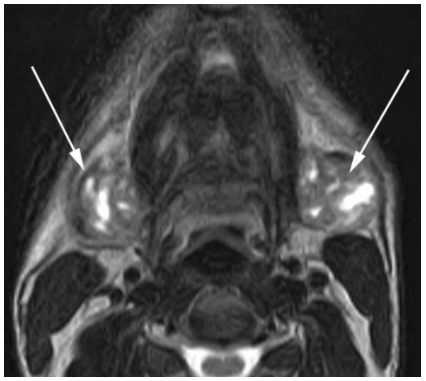


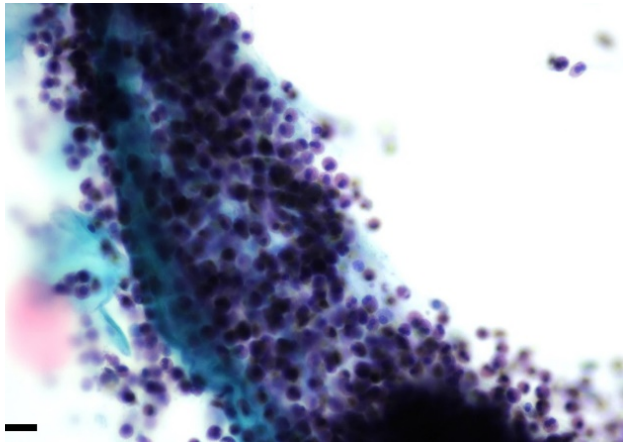
Sialadenosis (anorexia)

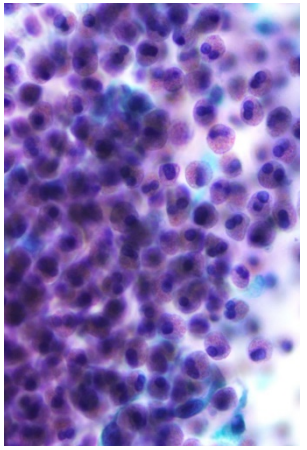
Eosinophilic sialodochitis (allergic parotitis)

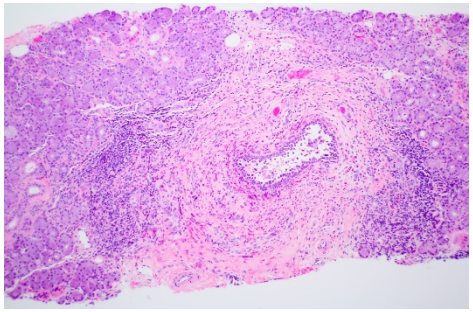
- Recurrent paroxysmal swelling of the salivary glands
- Salivary duct mucus plugs containing eosinophils
- Peripheral blood eosinophilia and elevated IgE level
- Associated atopic disease
- Ductal dilatation and occasional focal narrowing of the major salivary gland ducts
- Periductal eosinophil- and lymphocyte-rich inflammation and fibrosis with associated reactive ductal epithelial cells

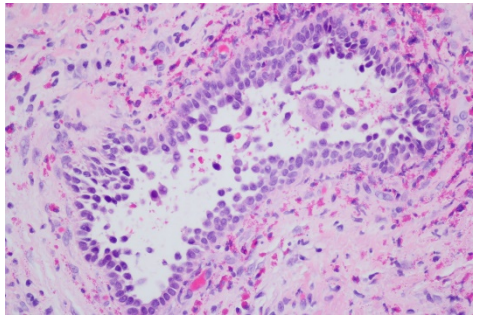






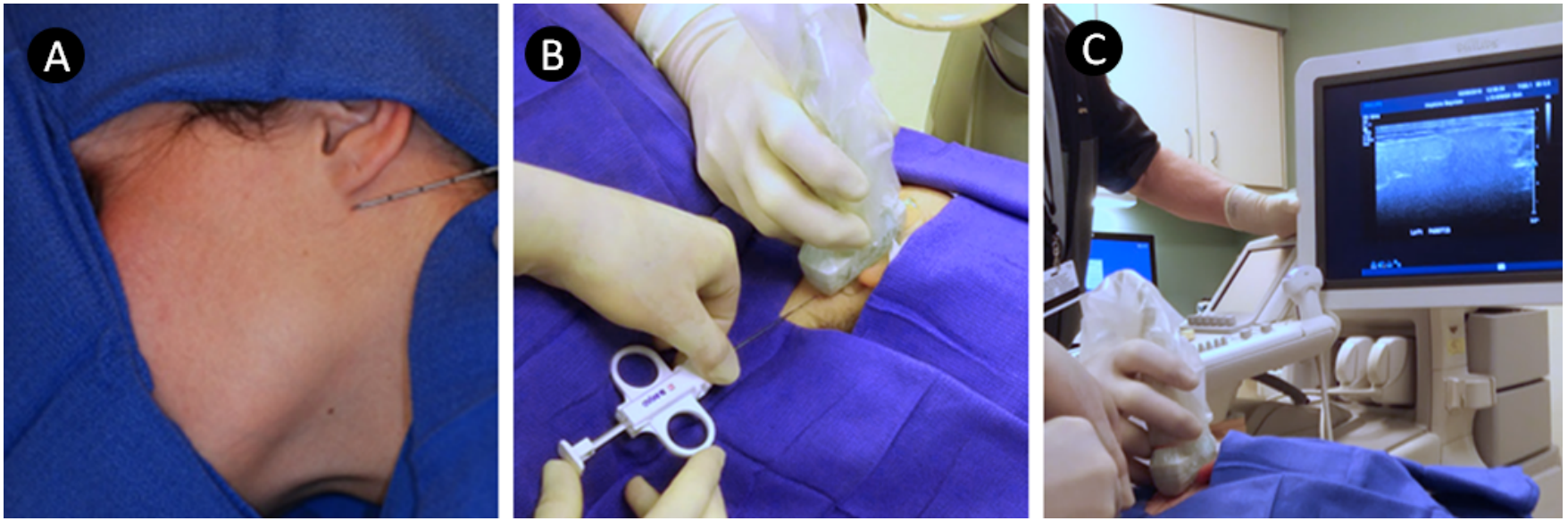




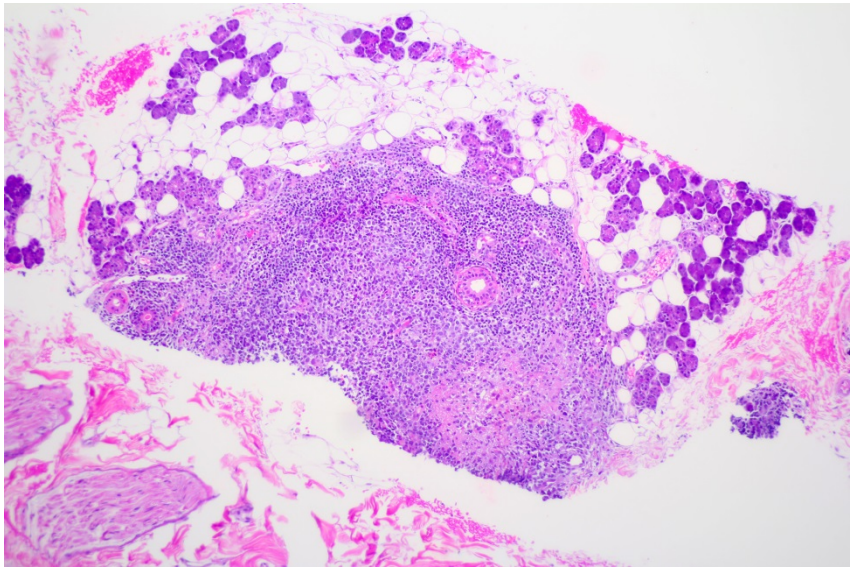


Baer et al, Oral Dis 2016

Ultrasound-guided core needle biopsy/FNA



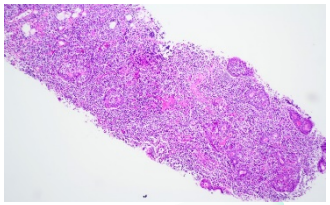
- In suspected lymphoma, use ≥1 core/FNA for histology/cytology and ≥1 core/FNA for flow cytometry

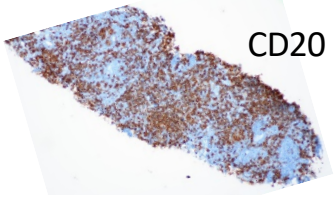


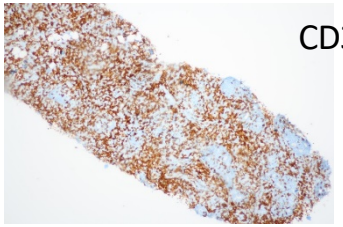
Benign lymphoepithelial sialadenitis is a precursor of MAL T lymphoma

2011

- Admixture of T and B cells, with T-cells predominating
- CD43-negative B cells
- Most lymphocytes in LELs are CD3+ T cells
- Low Ki-67 proliferation index
- 10% monoclonal B cell population, kappa-restricted







2015

2020

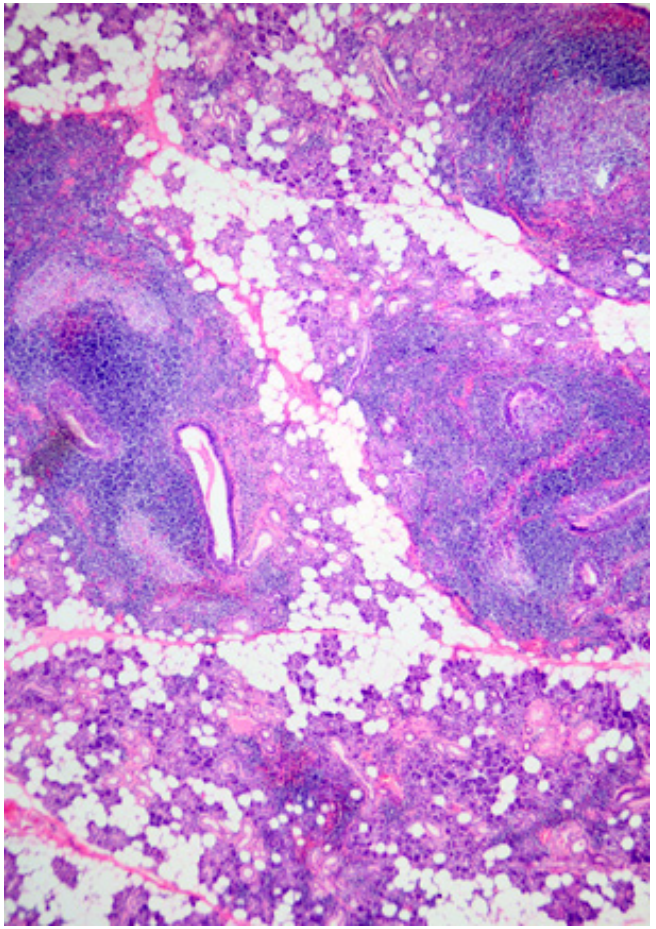
Enlarged tonsil

Enlarged cervical node

FNA of node: monoclonal B cell population (7%); kappa+
Core: atypical lymphoid infiltrate

Management of benign lymphoepithelial sialadenitis

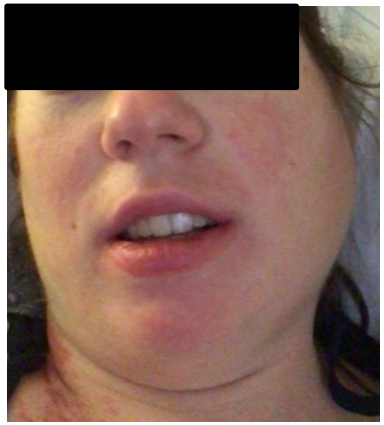
- Corticosteroids
- Rituximab[1]
- Belimumab[2]
- Low dose radiotherapy[3]
- Surgical excision if unilateral, nodular
- Monitor closely for lymphoma
  - New lymphadenopathy
  - New salivary/lacrimal gland masses

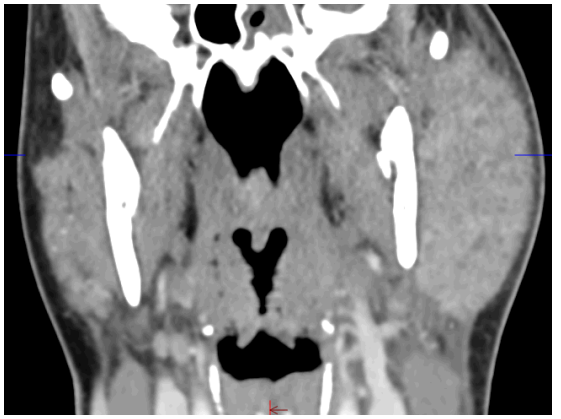


[1]Ann Rheum Dis 2013;72:1026
[2]Ann Rheum Dis 2013 Dec 17
[3]Oral Surg 1974; 38:735

Acute salivary gland enlargement in Sjögren's

- Usually intermittent, often from mucus plug but may be infectious
- Acute episodes of parotitis
  - Antibiotics
  - Corticosteroids
  - Sialogogues
  - Local heat, glandular massage
- Prevention of recurrent sialadenitis
  - Sialogogues
  - Daily self massage
  - Prophylactic antibiotics
  - Sialoendoscopy with rinsing, dilation, steroid instillation
  - Superficial or total parotidectomy
- Persistent enlargement should be evaluated for lymphoma



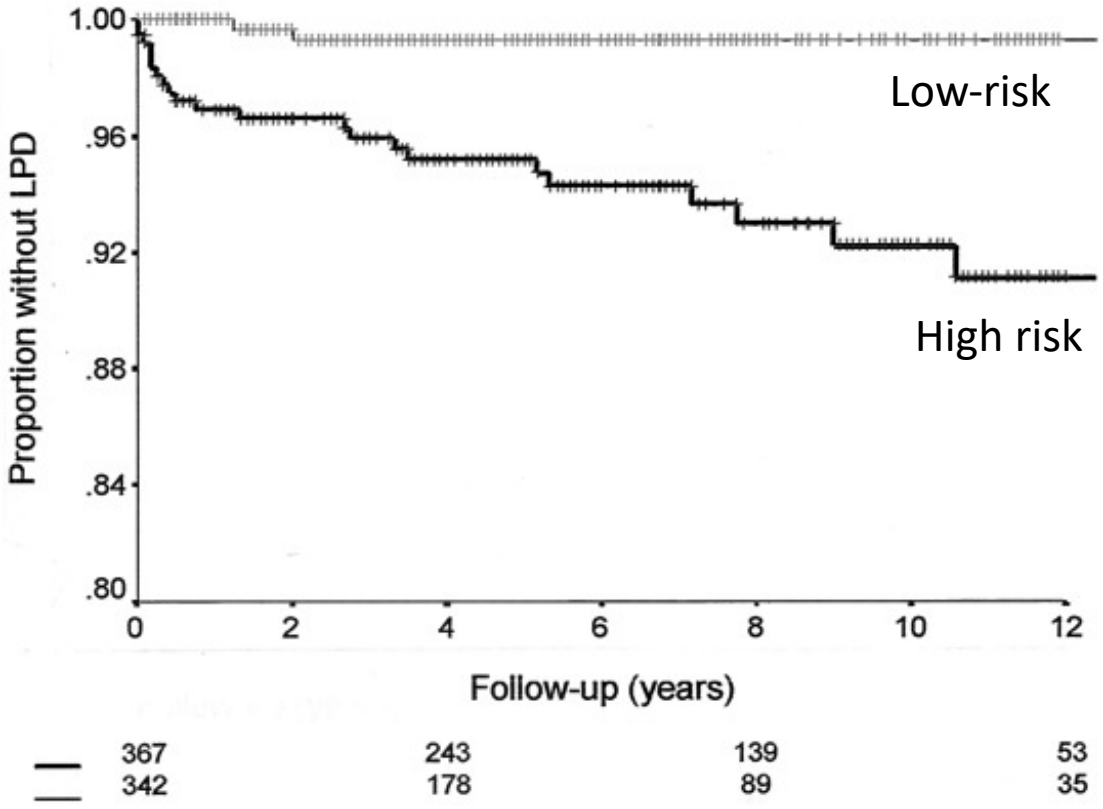


Suspicion of lymphoma

New systemic manifestations of Sjögren's, such as cryoglobulinemic vasculitis, pulmonary nodules

Salivary gland lymphoma	Other types of lymphoma
• Intraglandular mass/nodule • Persistent glandular swelling, including bilateral • Cervical lymphadenopathy	• Lymphadenopathy • Rapidly growing mass • B symptoms (night sweats, fever, weight loss) • Hepatomegaly • Splenomegaly • Cytopenia

Predictors of lymphoma



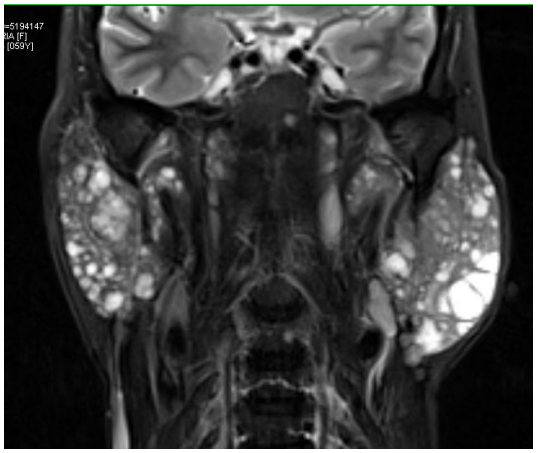
High risk: those with at least one of the following:

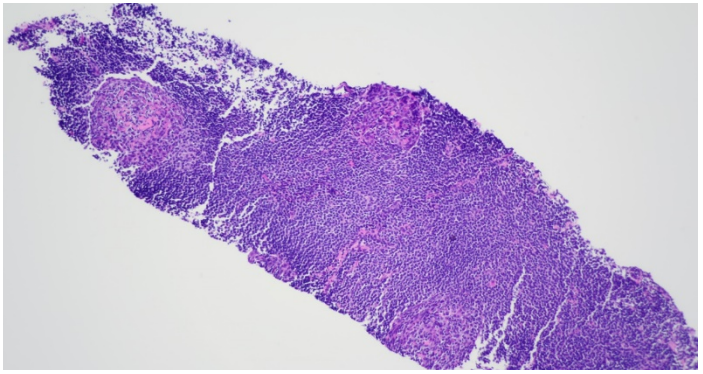
- low C4
- palpable purpura
- parotid enlargement

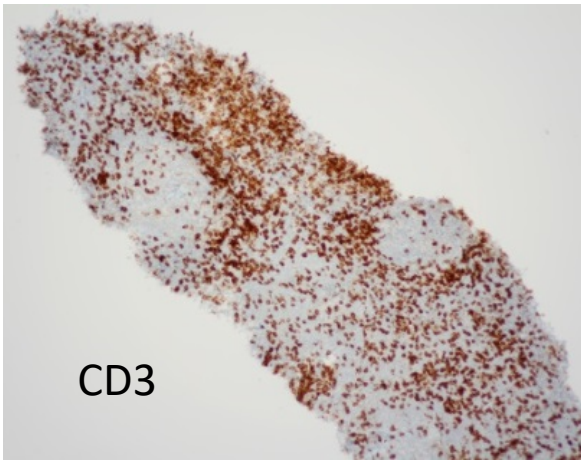
Arthritis Rheum 2002; 46:741

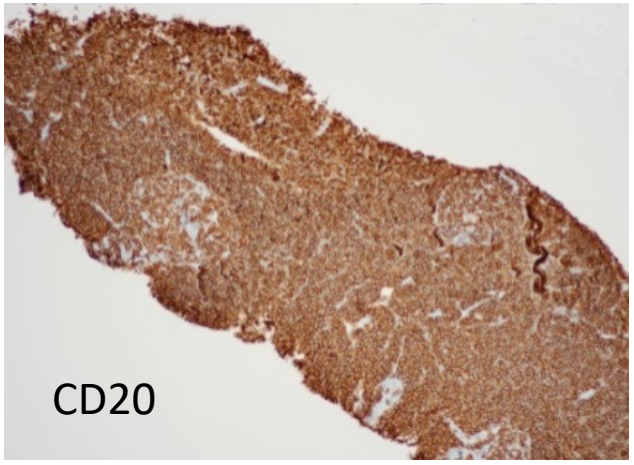
- Other risk factors for lymphoma
  - Germinal center-like structures in labial salivary gland biopsy
  - IgM kappa monoclonal protein
  - Mixed monoclonal cryoglobulinemia

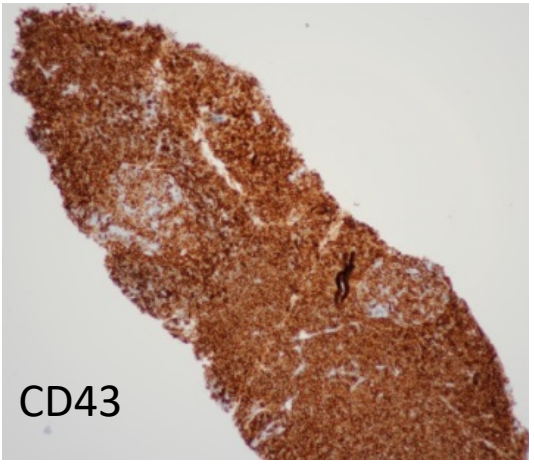
MALT lymphoma: representative sampling





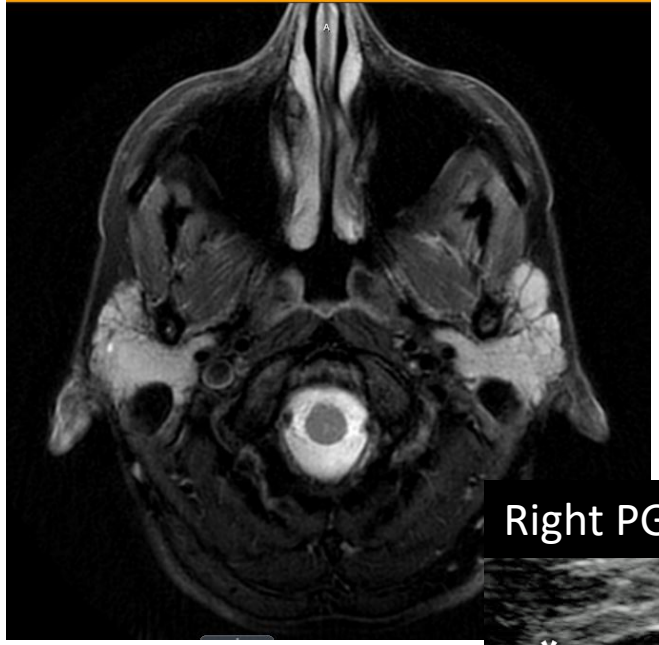


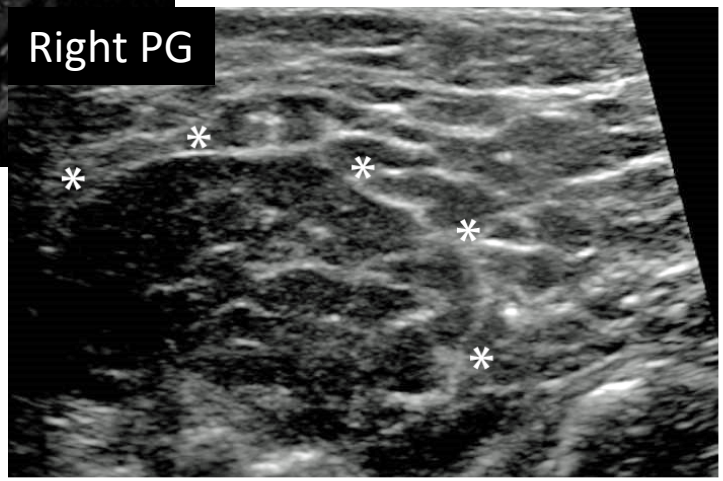


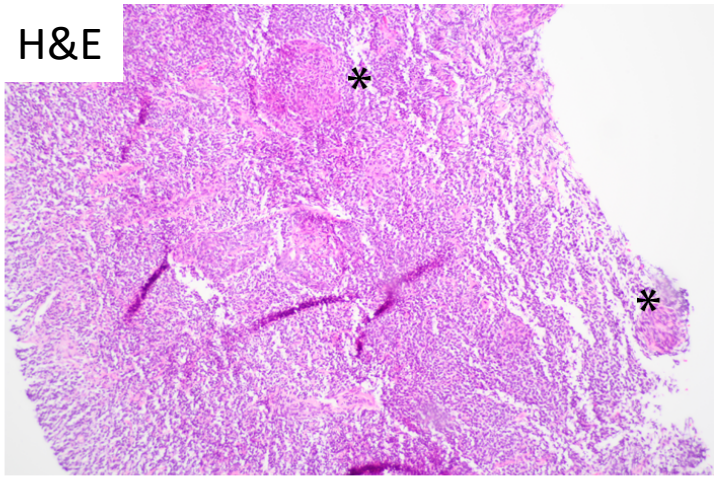


Flow cytometry: suspicious small population of kappa-restricted B cells

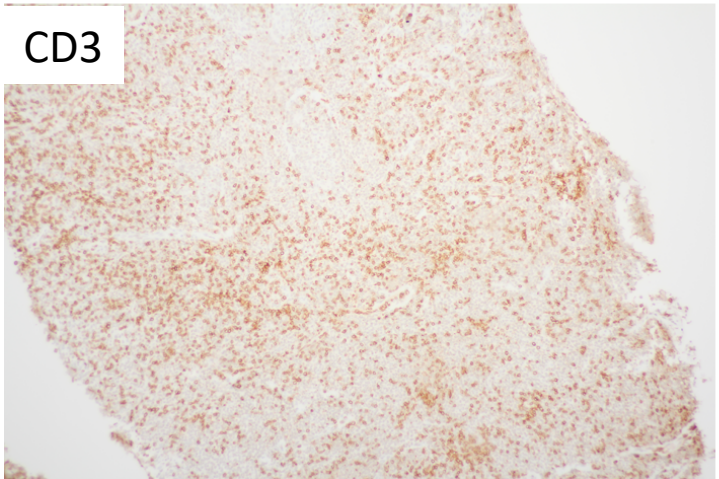
MALT lymphoma: targeted sampling

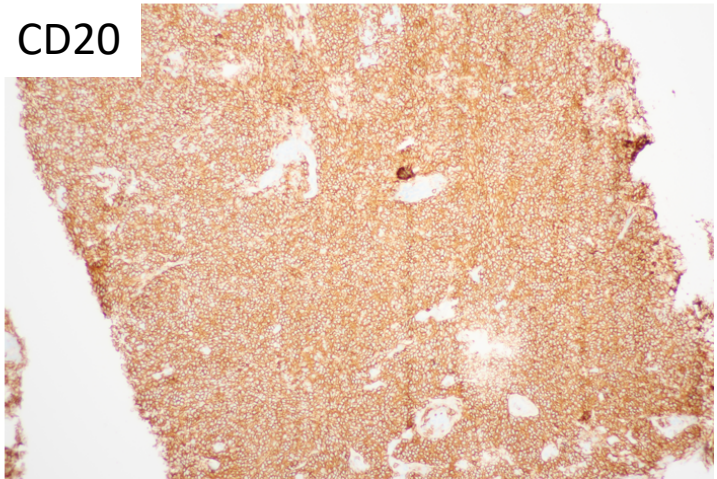




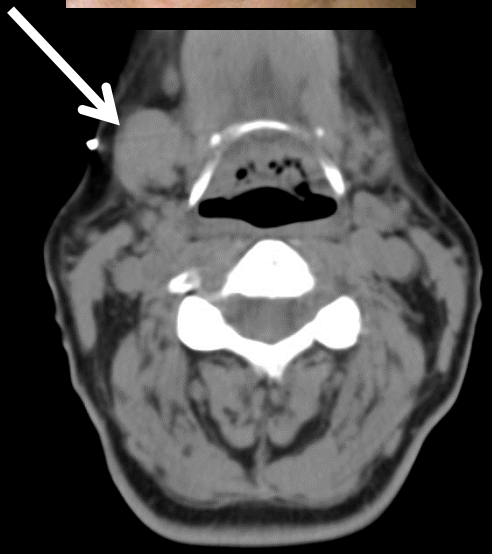


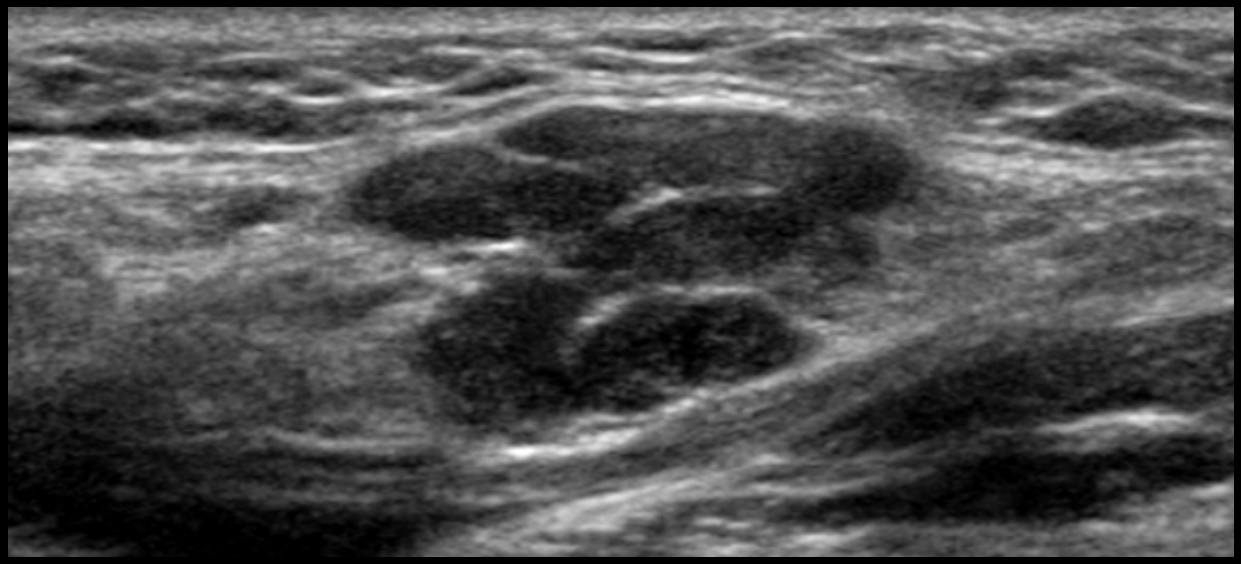
Flow cytometry: 41% clonal population of B-cells that expressed CD19, CD20, and kappa light chain

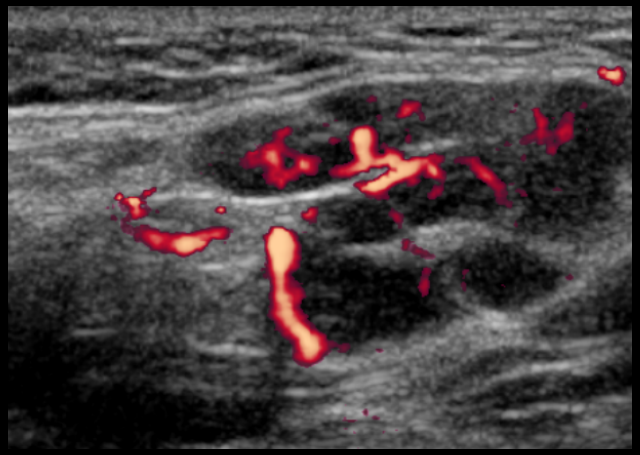


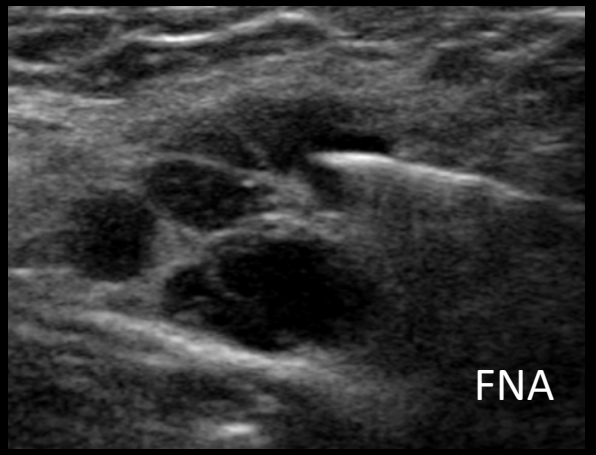


Solitary right submandibular gland mass

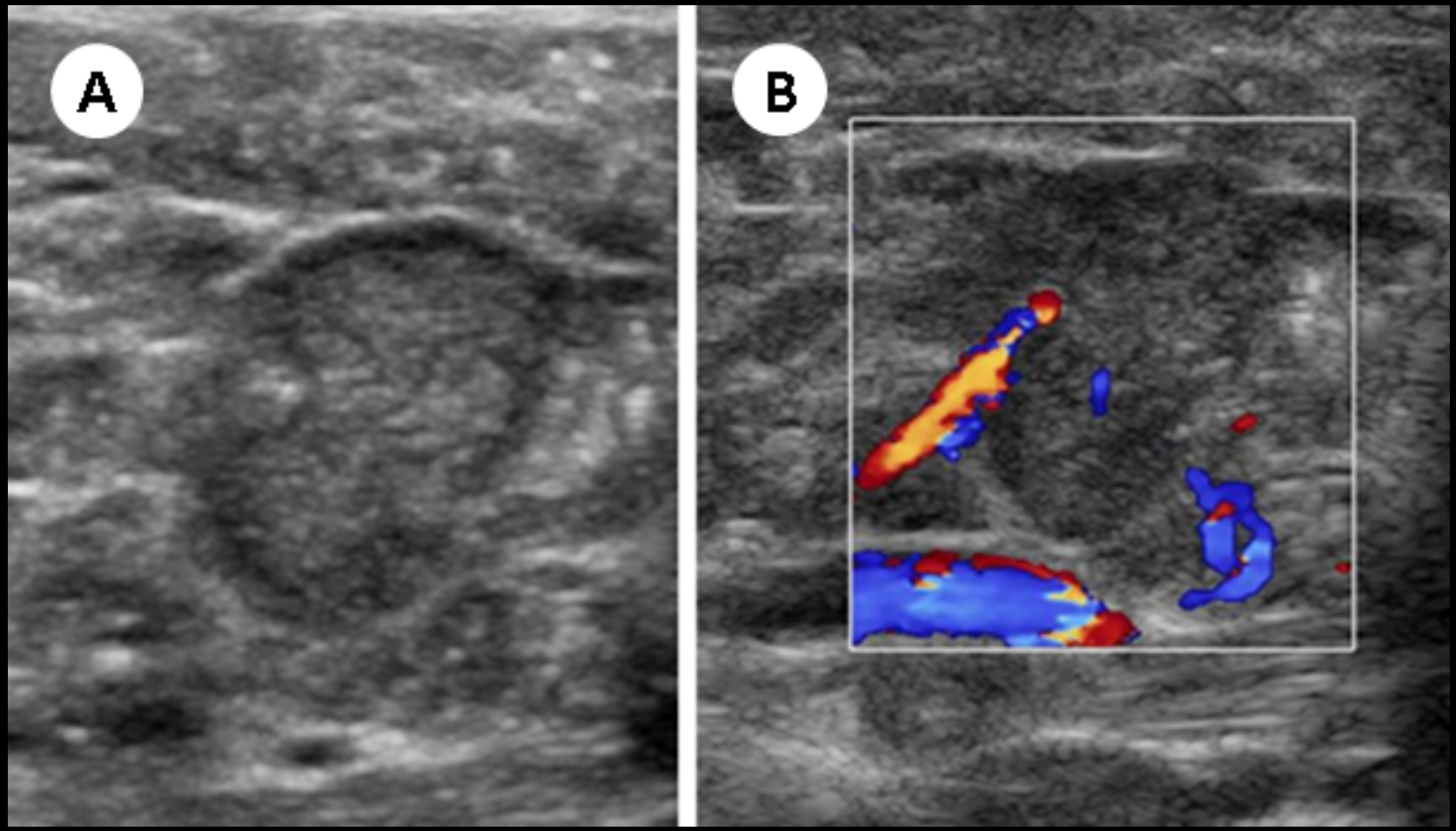








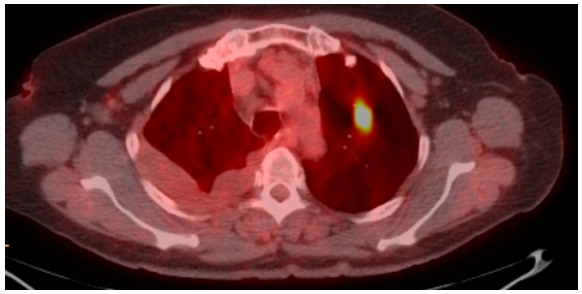
Bilateral parotid gland enlargement with abnormal intraparotid lymph node

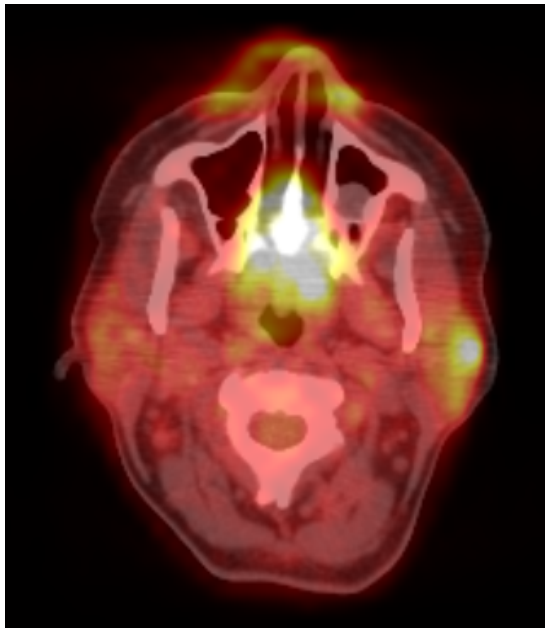


Left parotid longitudinal

PET/CT imaging in suspected lymphoma in Sjögren's

- Less sensitive for detection of indolent as compared to high-grade NHL
- MALT lymphoma of the head and neck region and lungs is more FDG-avid than it is at other sites, such as the stomach or ocular adnexa
- In SS patients with high systemic disease activity, PET/CT may show pathologic uptake in multiple sites, including salivary glands, lymph nodes, lungs and thyroid
- PET/CT has particular sensitivity for detecting MALT lymphoma of the lung





MALT lymphoma of salivary gland

Asymptomatic Low systemic disease activity	Symptomatic Low systemic disease activity	High systemic disease activity Advanced stage Rapid response needed Relapsed disease
• **Watchful waiting (all stages)**	• **Low-dose involved field RT (localized disease)** • **RTX with/without chemotherapy or targeted therapy (locally disseminated or disseminated)**	• **RTX with/without chemotherapy or targeted therapy (all stages)**

Options for chemotherapy or targeted therapies, in combination with rituximab

- cyclophosphamide and prednisone
- cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)
- fludarabine alone or with cyclophosphamide
- chlorambucil
- ibrutinib

Acknowledgements

Hopkins Jerome Greene Sjogren's Syndrome Center

- Thomas Grader-Beck, MD
- Jean Kim, MD, PhD
- Esen Akpek, MD
- Lee Guo, OD
- Anne Burke, MD
- Susan Robinson, MS

NIDCR Sjogren's Syndrome Clinic

- Blake Warner, DMD, PhD
- Zohreh Khavandgar, DDS, PhD
- Margaret Grisius, DDS
- Margaret Beach, PA
- Eileen Pelayo, RN
- Donna Kelly
- Brian Walitt, MD, MPH
- Jill Jacobs, RDH
- NEI Eye Clinic

Funding

NIH National Institute of Dental and Craniofacial Research

JLGreene