



Παθολογική
Φυσιολογία

Sjogren Syndrome

Epidemiology - Diagnosis - Clinical Phenotype

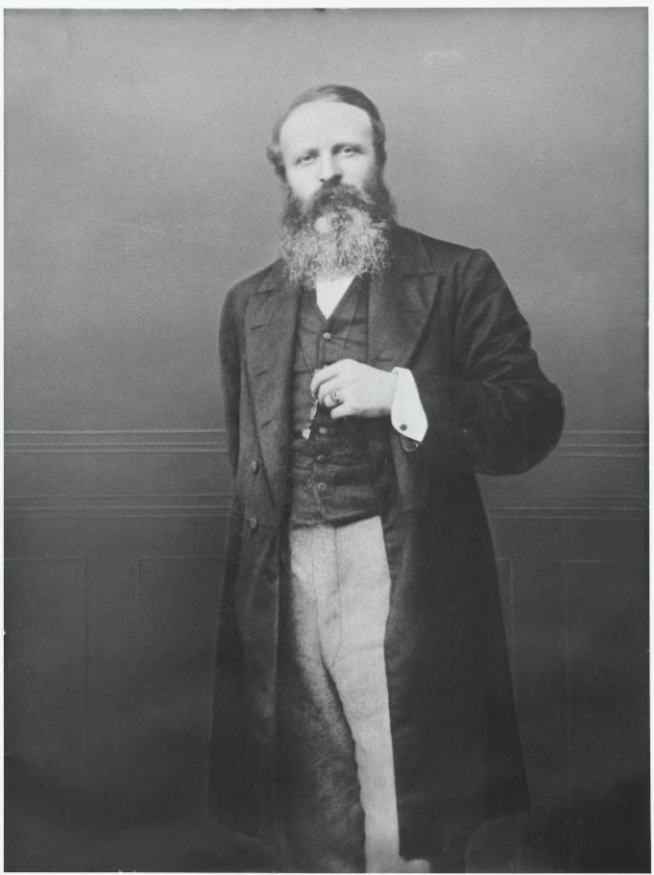


Εθνικό &
Καποδιστριακό
Πανεπιστήμιο
Αθηνών

Loukas Chatzis

Academic fellow, Department of Pathophysiology, Laiko general hospital

ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ



Dr Bartley

Letter to the Editor

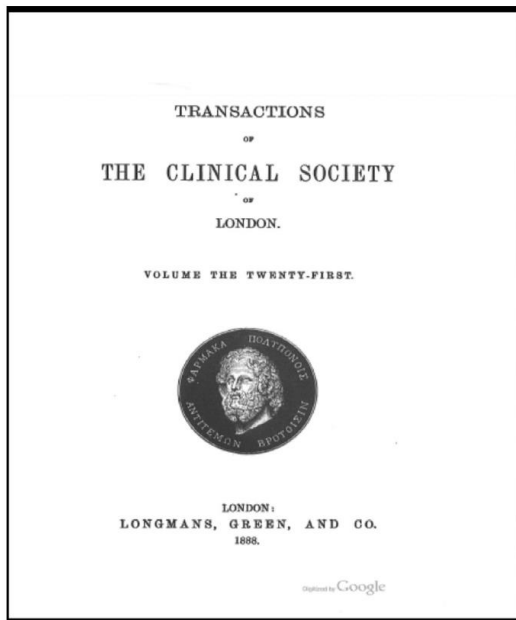
I should feel obliged if you would give or procure me some advice in a case of *suppressed salivary secretion*. The patient, a quaint old French lady of 77, states that eight months ago she suffered about three weeks from *dryness and soreness of the tongue*. On examination of the mouth, uvula, tonsils and pharynx appear quite healthy, but the mucous membrane is *perfectly dry like pink satin, that on the tongue with longitudinal rugae*. Salt and sugar remain undissolved and quite *tasteless* on the tongue, the former causing slight uneasiness. The patient sips cold tea to relieve the feeling of dryness and the clinging together of gums, cheeks and tongue. *The teeth are all gone*. There is no discoverable opening in the parotid ducts. Under the tongue are two papillae where the sublingual ducts might be looked for, but they appear impervious. There does not seem to be any marked ill effect on health. *The old lady is wonderfully well and cheery*. Is there anything to be done?





Dr Hadden

Her symptoms included difficulty in swallowing, frequent fluid intake, and being unable to cry, though her overall health status was fine. Dr. Haddon described her tongue as “red, devoid of epithelium and cracked in all directions like a crocodile’s skin”. He continued, “No tears appeared when she tried to cry.”



The patient spent 2 weeks in the hospital for observation and other diagnostic measures of the day. Finally, at the conclusion of the observation period, the decision was made to treat her with a medicinal remedy (tincture of jaborandi) administered both orally and subcutaneously three times a day. The patient responded and continued this therapy as an outpatient.

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-237/S-007

Trade Name: SALAGEN TABLETS

Generic Name:(pilocarpine HCL)

Sponsor: MGI Pharma, Inc.

Approval Date: February 11, 1998

Indication: Provides for the treatment of symptoms of dry mouth in patients with Sjogren's syndrome.

Pilocarpus pennatifolus (Jaborandi) derived from the Greek Pilo (hat) + carpus (fruit). About 0.5-0.8% of the total weight of the leaves is pilocarpine.

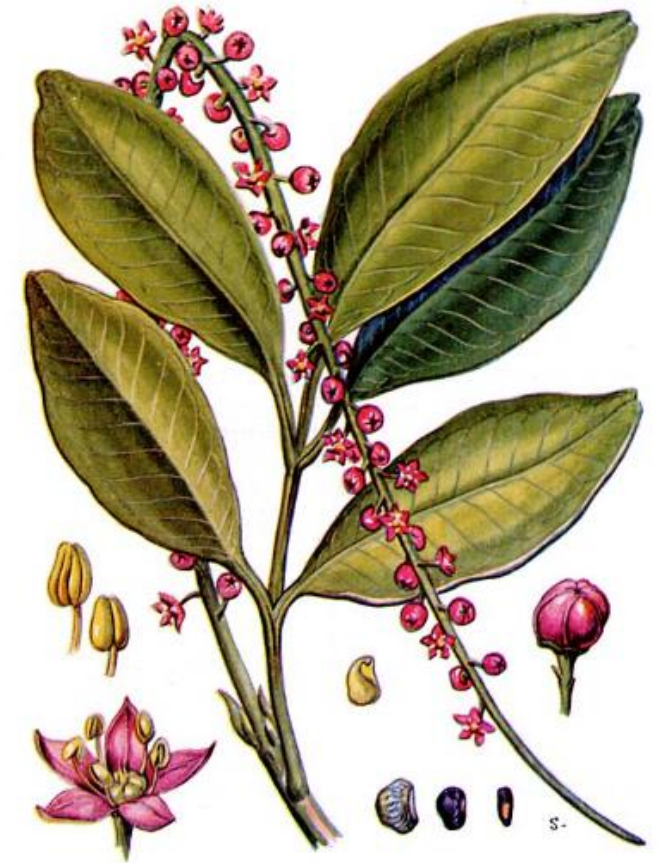
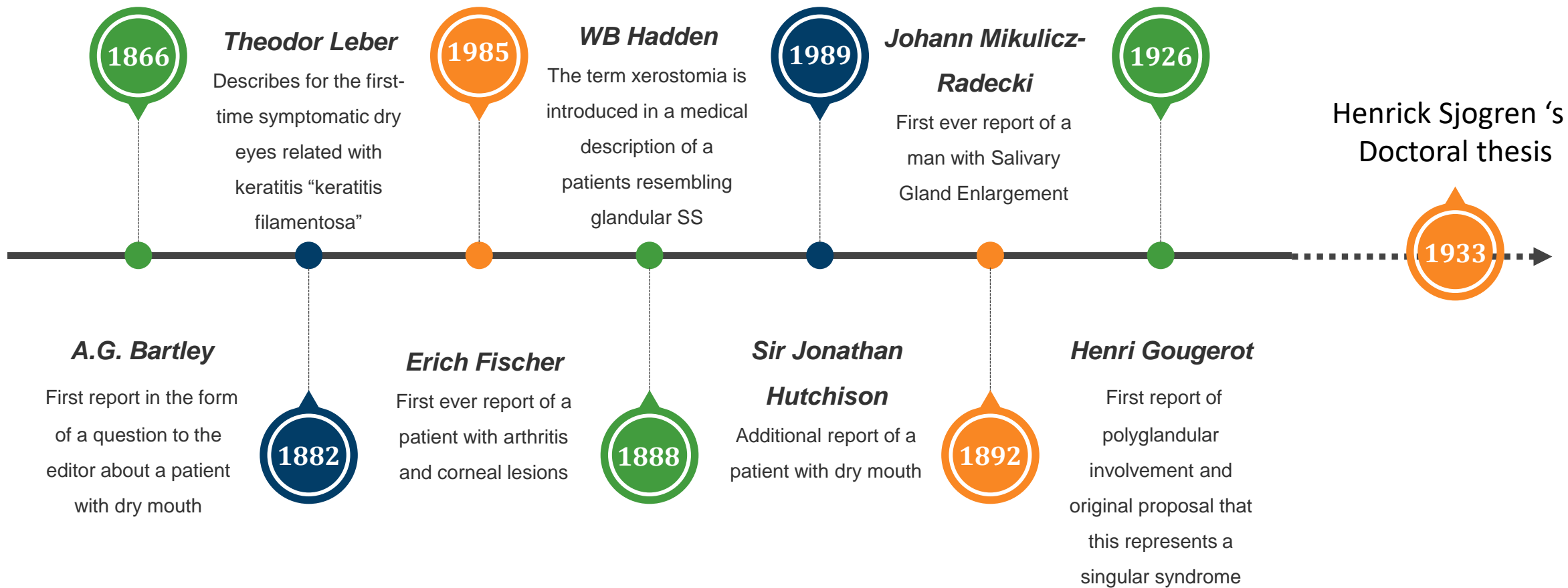
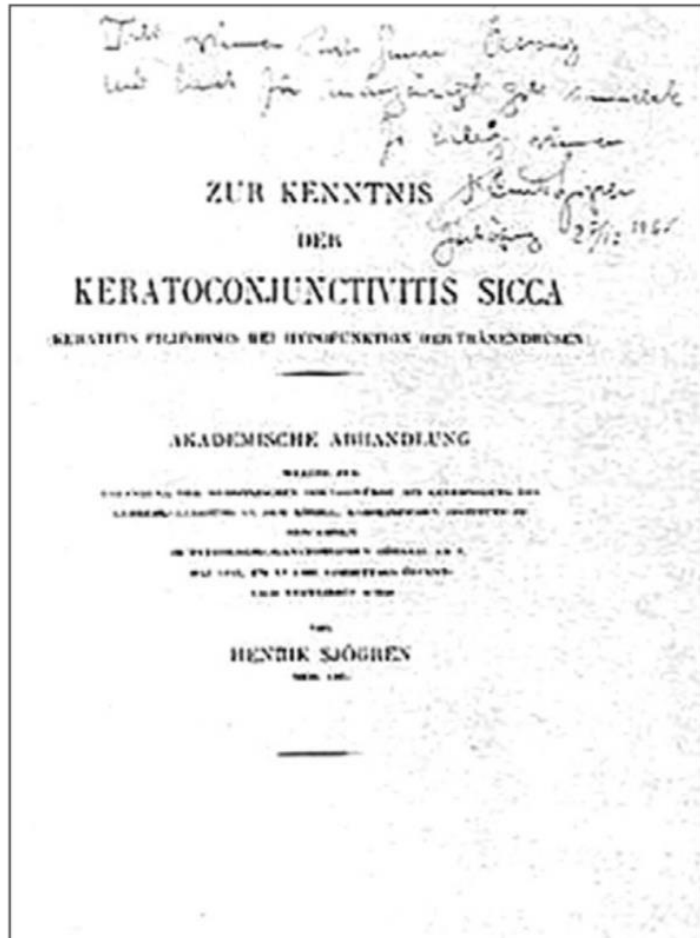


PLATE XVIII.—*Pilocarpus pennatifolus* (Jaborandi). The alkaloid, pilocarpine, is obtained from the leaflets. (From Jackson: *Experimental Pharmacology and Materia Medica*.)

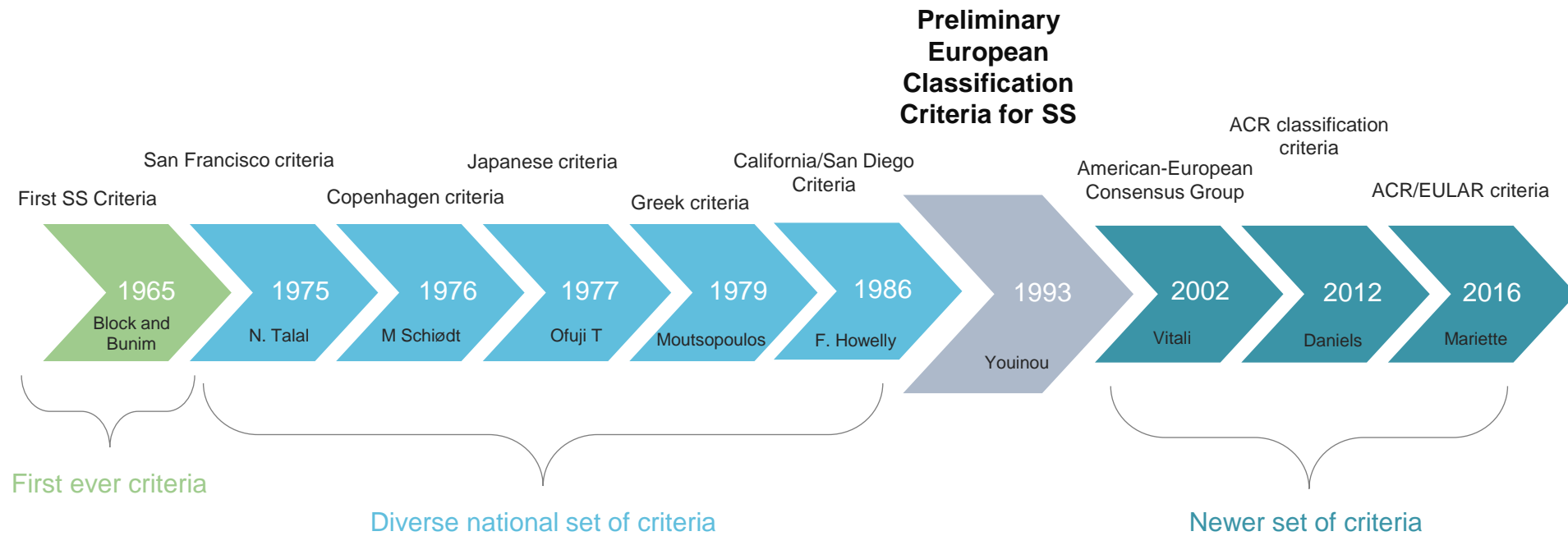


Timeline of milestones that led to Henrick Sjogren seminal doctoral thesis



- 19 patients with dry mouth and dry eyes
- All women
- 11 had arthritis
- 2 had parotid gland enlargement
- Almost all were perimenopausal
- The manuscript included a pathological part, with microscopic analysis of lacrimal glands and conjunctiva





✓ Sjögren's Syndrome: *Classification Criteria*

For the first time there is an entry criterion: at least one symptom of ocular or oral dryness or ESSDAI ≥ 1

	Item	Weight / Score
01	Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1	3
02	Anti-SSA (Ro) +	3
03	Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) on at least one eye	1
04	Schirmer ≤ 5 mm/5min on at least one eye	1
05	Unstimulated whole saliva flow rate ≤ 0.1 ml/min	1

A patient is classified as having SS when he has a score ≥ 4

Dryness criteria

I. Ocular symptoms: 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 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?



Clinical and laboratory findings of primary Sjögren's syndrome patients without sicca symptoms



- ❖ 2% of patients lack the sensation of dry mouth and dry eyes
- ❖ 50% of non-dryness patients have positive ocular tests
- ❖ No differences were found between non-dryness pSS patients and controls regarding focus score or any other extraglandular manifestation.



The disease cannot be ruled out in the absence of sicca symptoms

pSS patients without sicca complaints are younger, sharing common immunopathologic mechanisms with typical sicca patients.

✓ Sjögren's Syndrome: *Classification Criteria*

For the first time there is an entry criterion: at least one symptom of ocular or oral dryness or ESSDAI ≥ 1

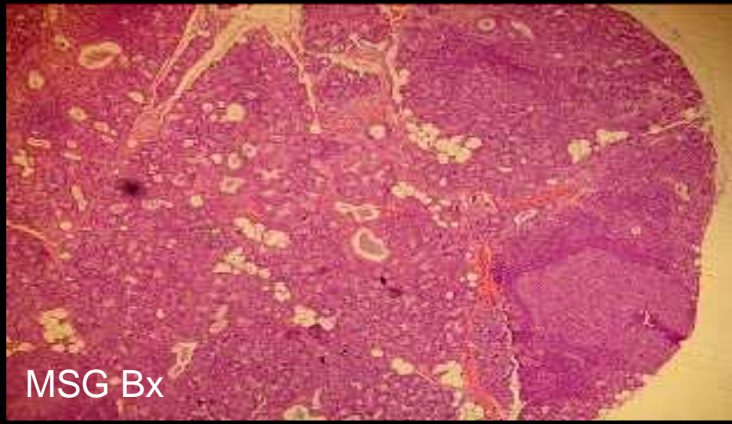
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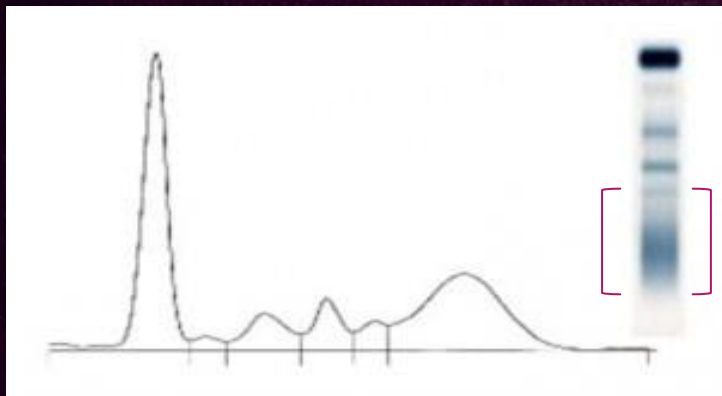


SS is the best diagnostic option for patients with sicca syndrome and isolated La autoantibodies

✓ Sjögren's Syndrome: Immunopathology

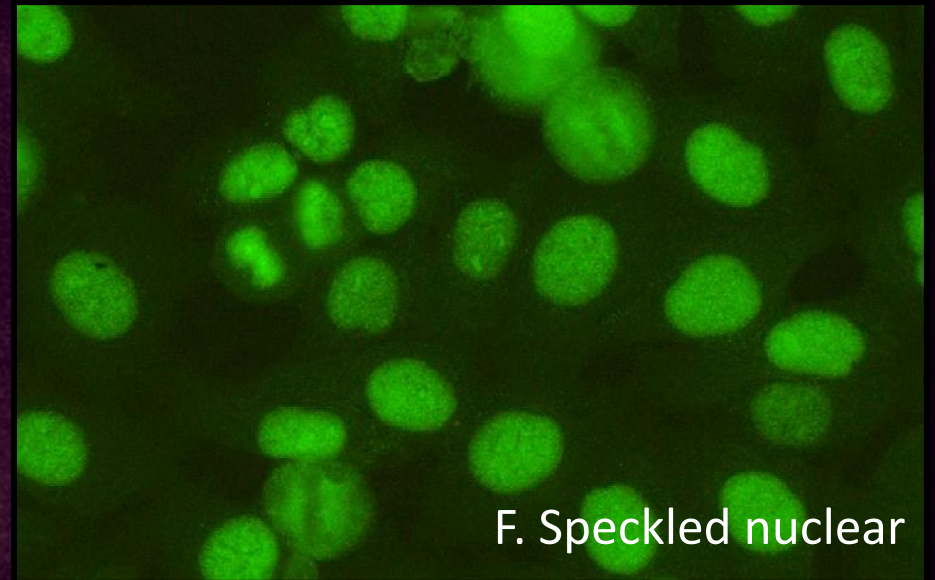


Infiltration by activated T- & B- cells



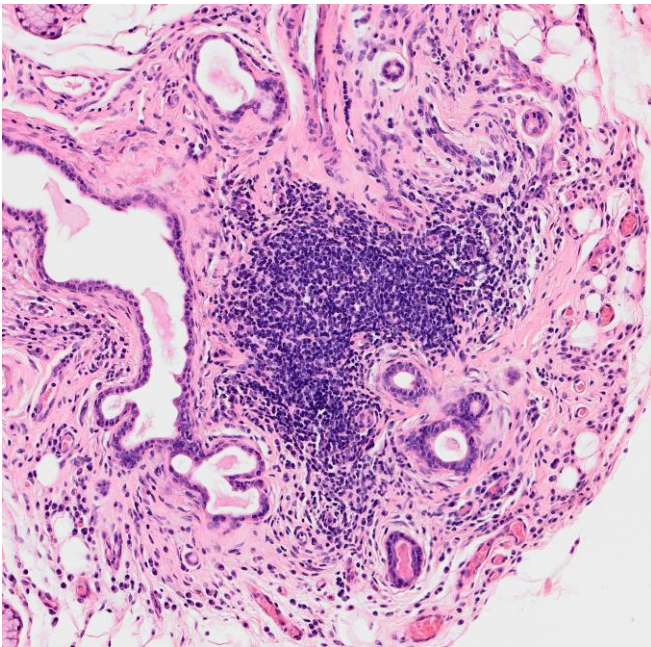
Alb

γ-glob



Histology

Focus score



Perivascular infiltrates in SS associated with other autoimmune diseases

The histopathologic signature of primary Sjögren's syndrome

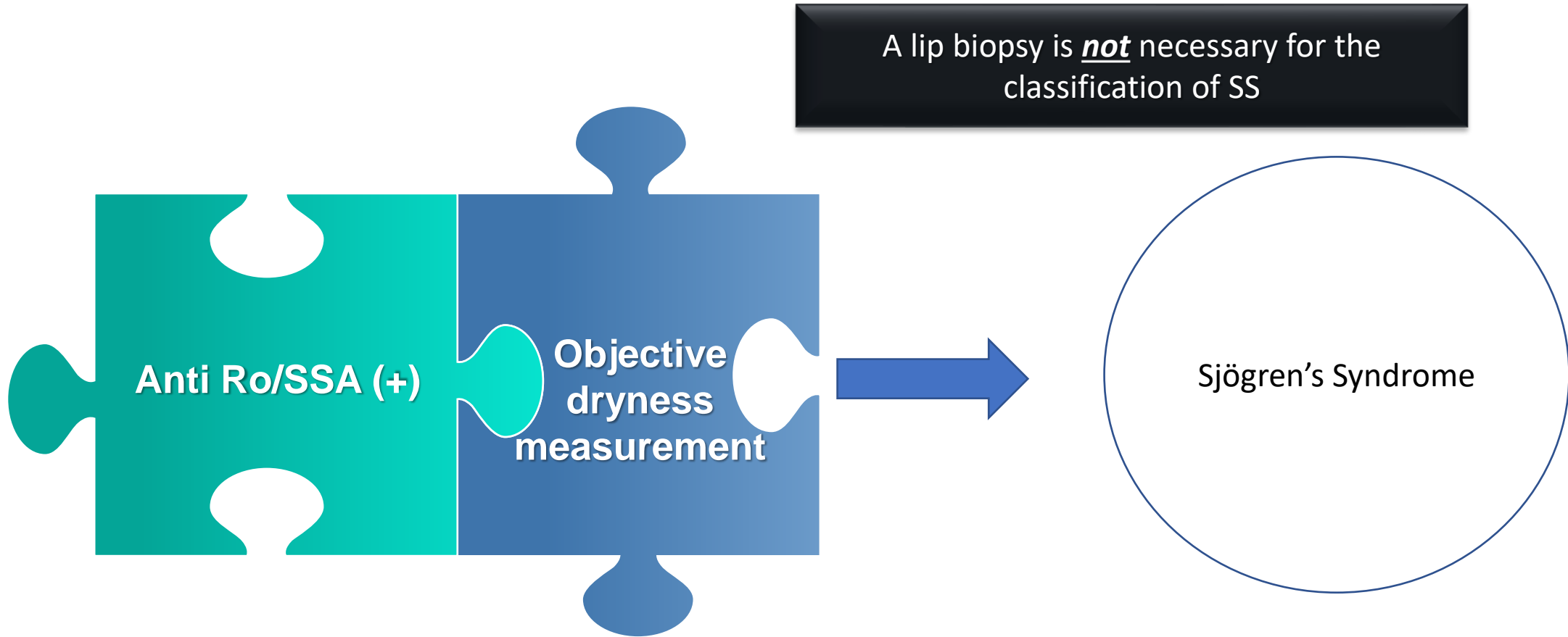
Lymphocytic infiltrate that is localized around the ductal epithelium of the salivary and lacrimal glands

A score determined by the number of mononuclear-cell infiltrates containing ≥ 50 inflammatory cells per 4 mm^2

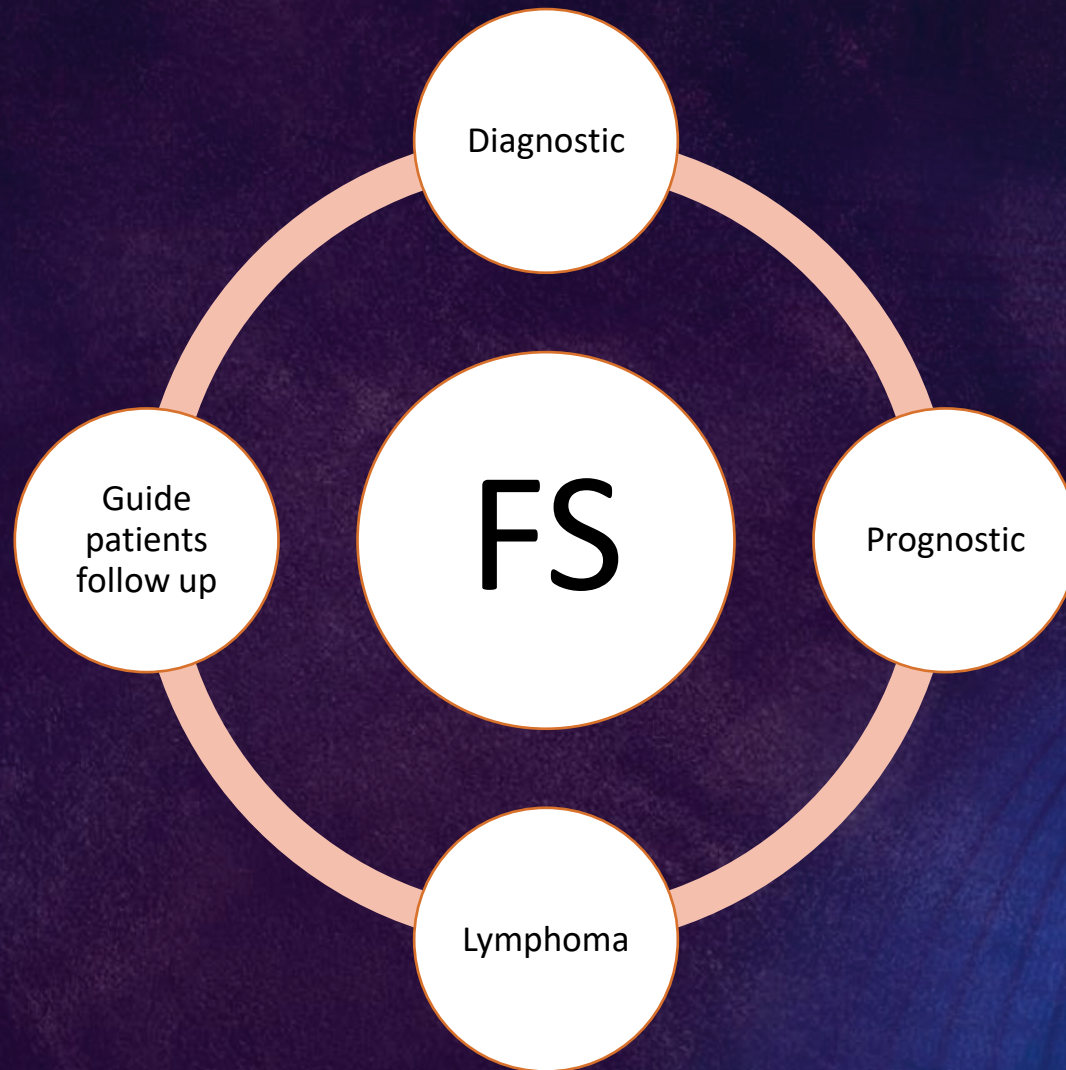
Focus score ranges from 0 to 12

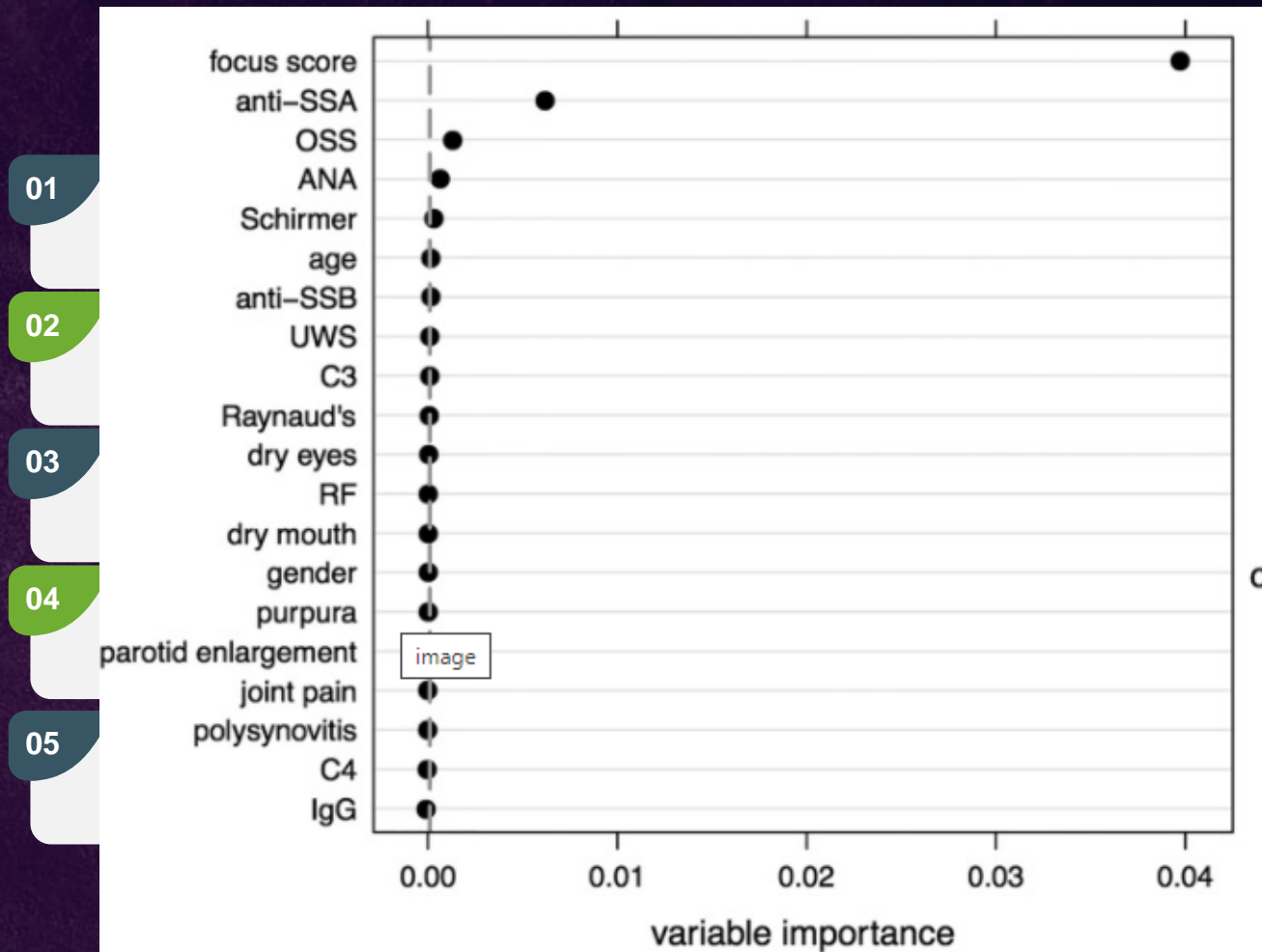
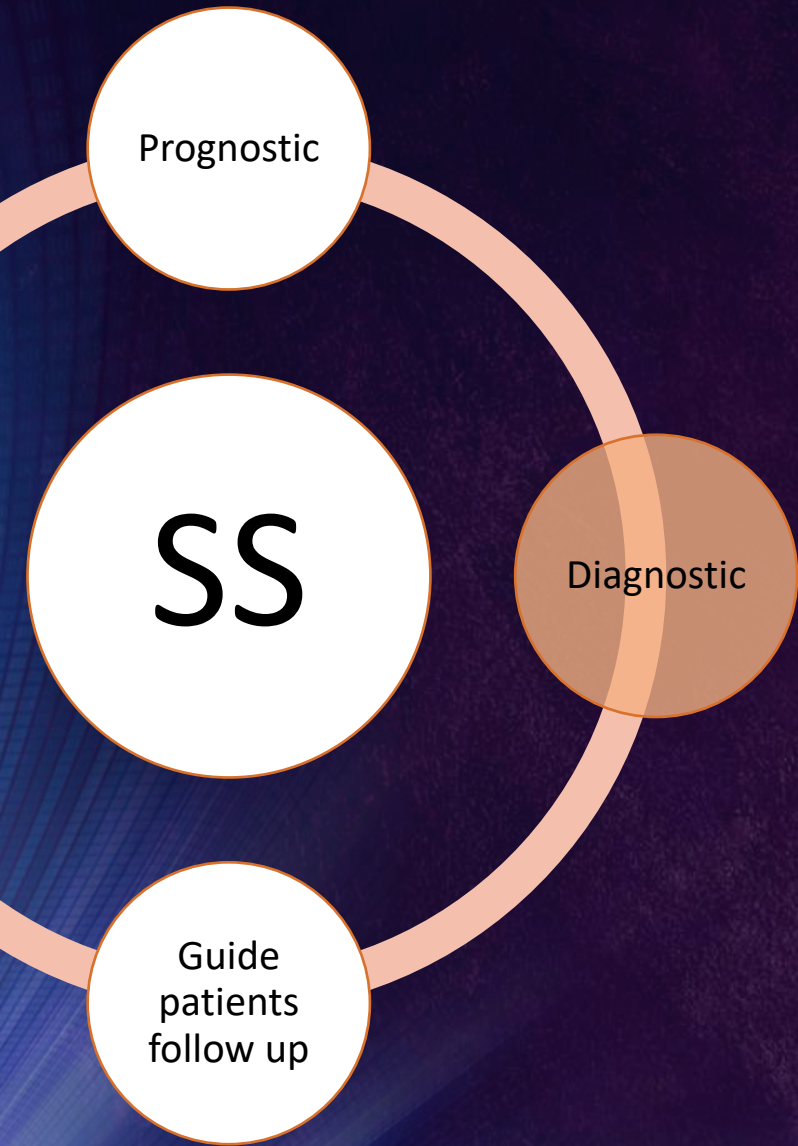
A Focus score ≥ 1 is considered a positive biopsy

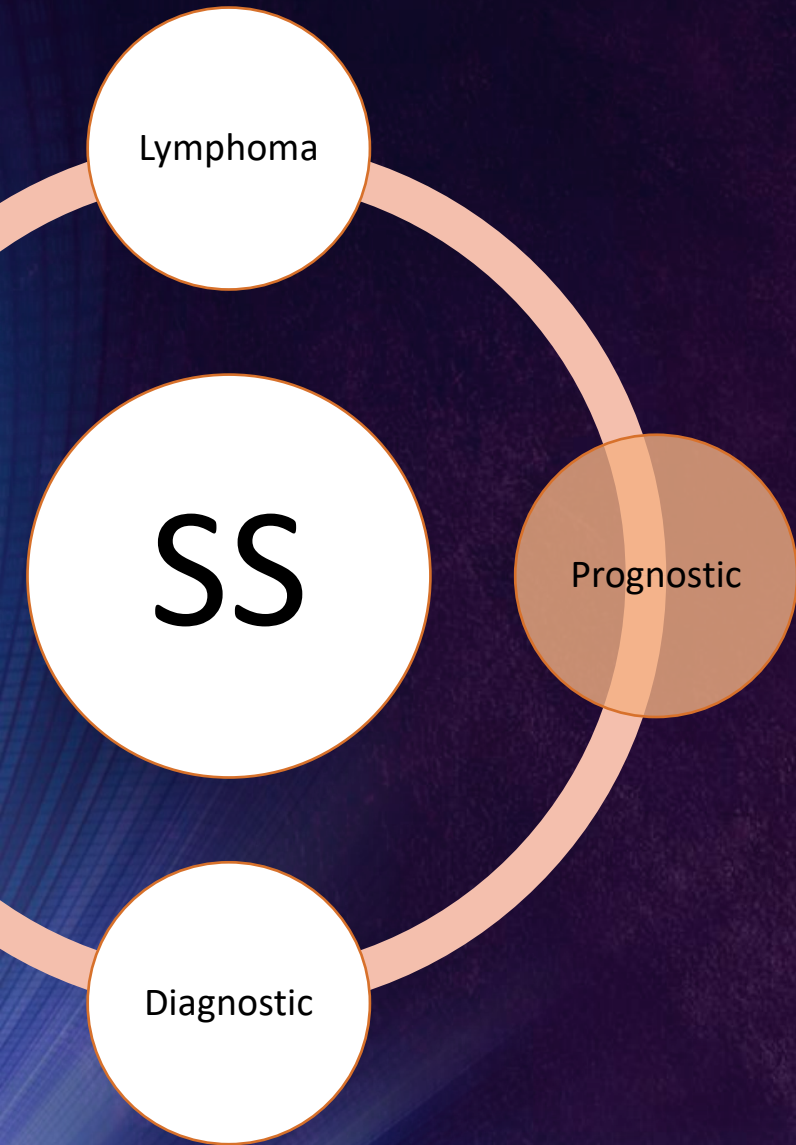
✓ Sjögren's Syndrome: *Classification Criteria*



Always perform a lip biopsy even if a classification of SS has been already reached







- Inflammation severity of the minor salivary gland biopsy is correlated with more autoantibodies

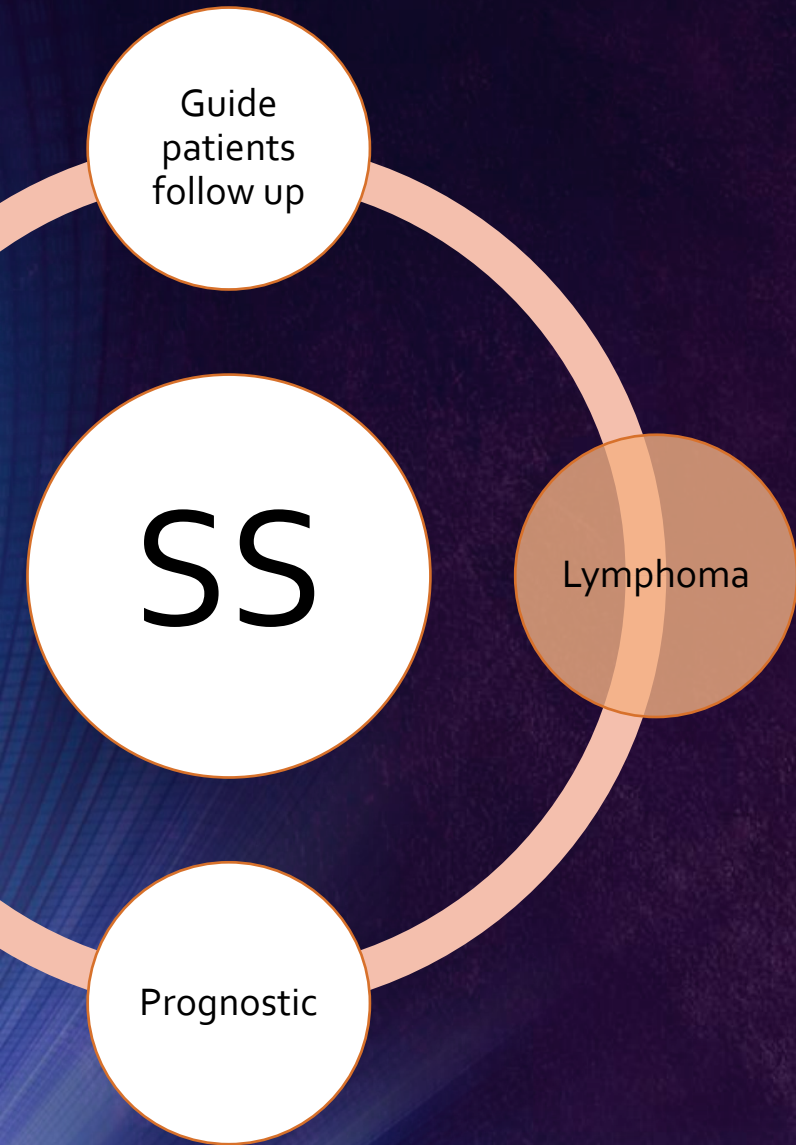
M. N. Manoussakis, A. G. Tzioufas, P. J. Pange, H. M. Moutsopoulos.
Serological profiles in subgroups of patients with Sjögren's syndrome.
Scandinavian journal of rheumatology Supplement, 1986;61:89-92.

- Gerli et al. after studying 82 patients, supported that FS was related to extra-glandular manifestations

R. Gerli *et al.* Quantitative assessment of salivary gland inflammatory infiltration in primary Sjogren's syndrome: its relationship to different demographic, clinical and serological features of the disorder. Br J Rheumatol, 1997

- Carubbi et al. after evaluating 383 biopsies confirmed the prognostic value of FS regarding the extra glandular Sjogren's related manifestations and also proposed an association with future lymphoma development

F. Carubbi, et al. A retrospective, multicenter study evaluating the prognostic value of minor salivary gland histology in a large cohort of patients with primary Sjogren's syndrome. Lupus, 2015

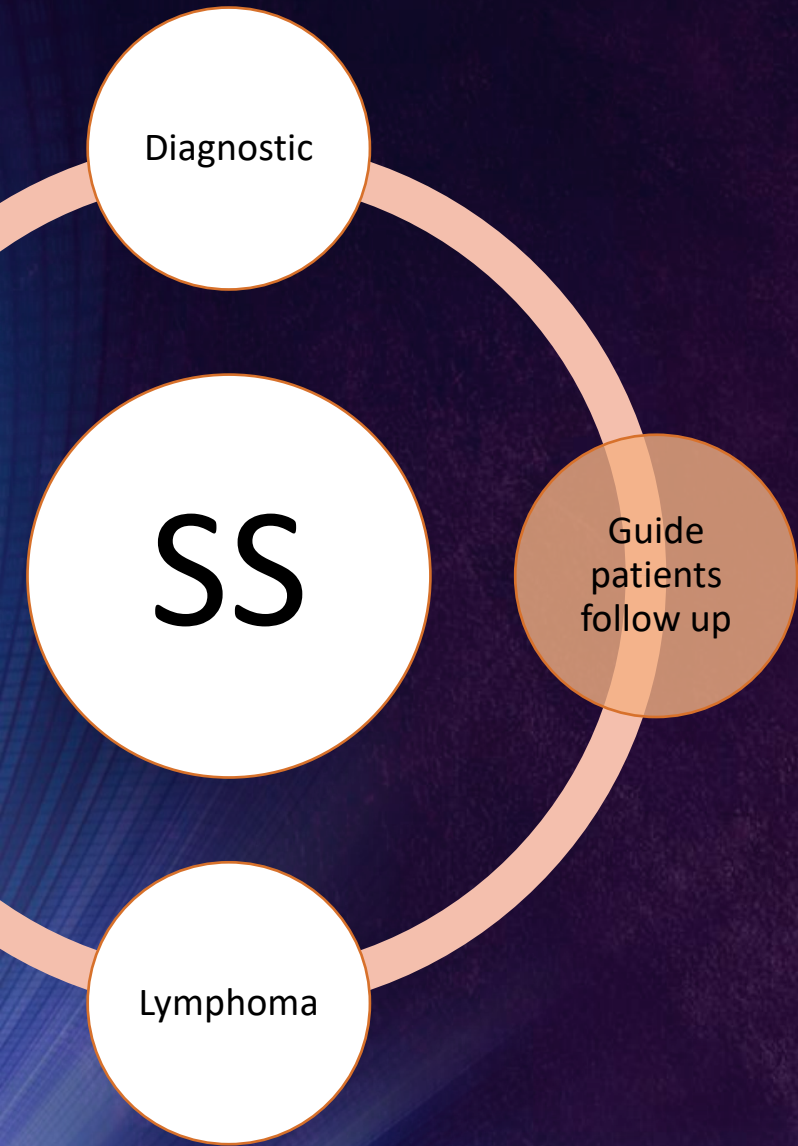


CONCISE REPORT

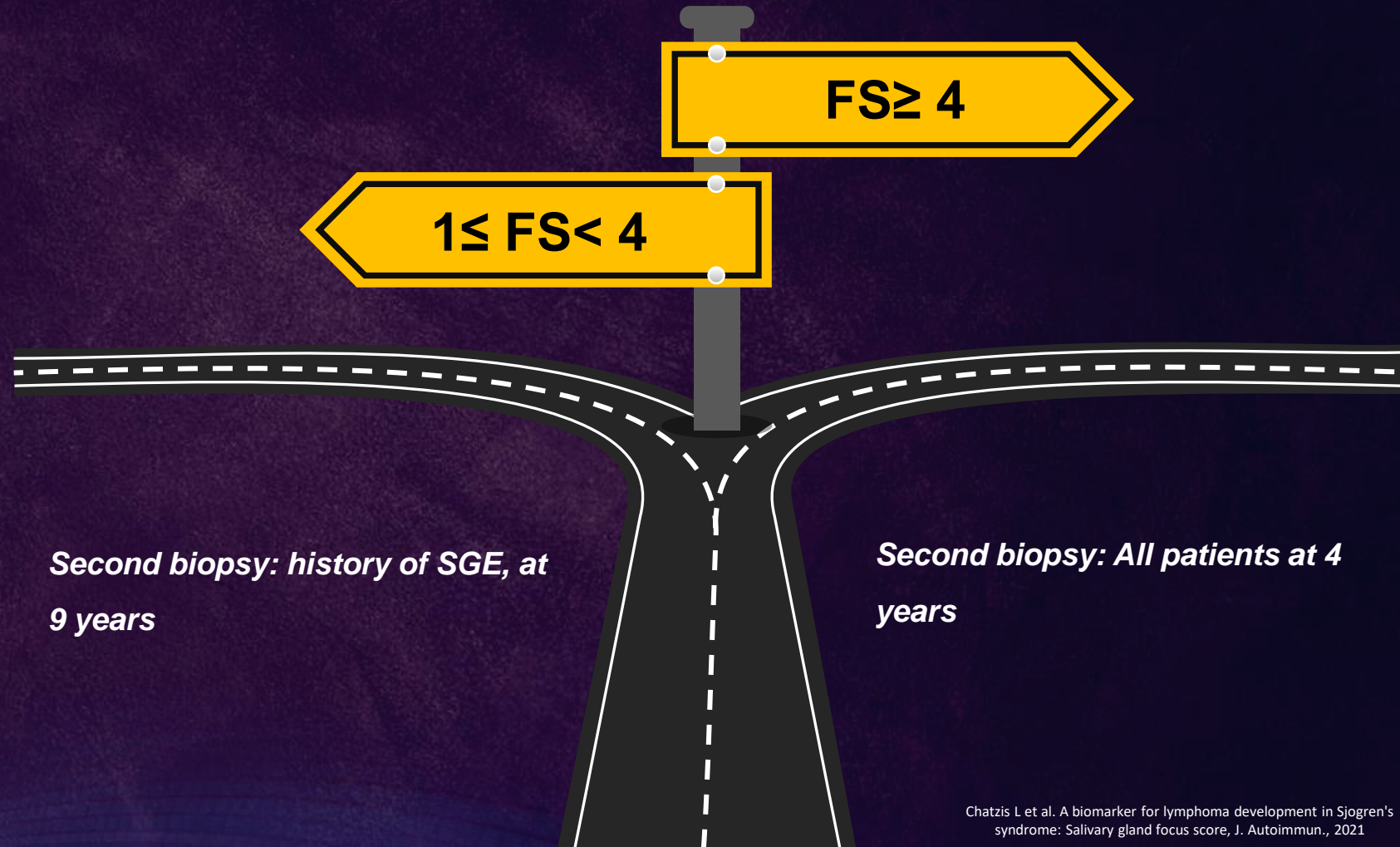
The prognostic value of routinely performed minor salivary gland assessments in primary Sjögren's syndrome

Anna P Risselada,¹ Aike A Kruize,¹ Roel Goldschmeding,² Floris P J G Lafeber,¹ Johannes W J Bijlsma,¹ Joel A G van Roon¹

- Risselada et al. were the first to show that a positive biopsy associates with lymphoma development, although the number of SS NHL patients was rather low (16 patients)
- She was the first to propose a FS threshold (FS=3) based on the mean value of the lymphoma patient's focus score
- Focus score as a continuous variable is related to future lymphoma development



- Offers guidance for the performance of a second biopsy



✓ Sjögren's Syndrome: *Global prevalence*

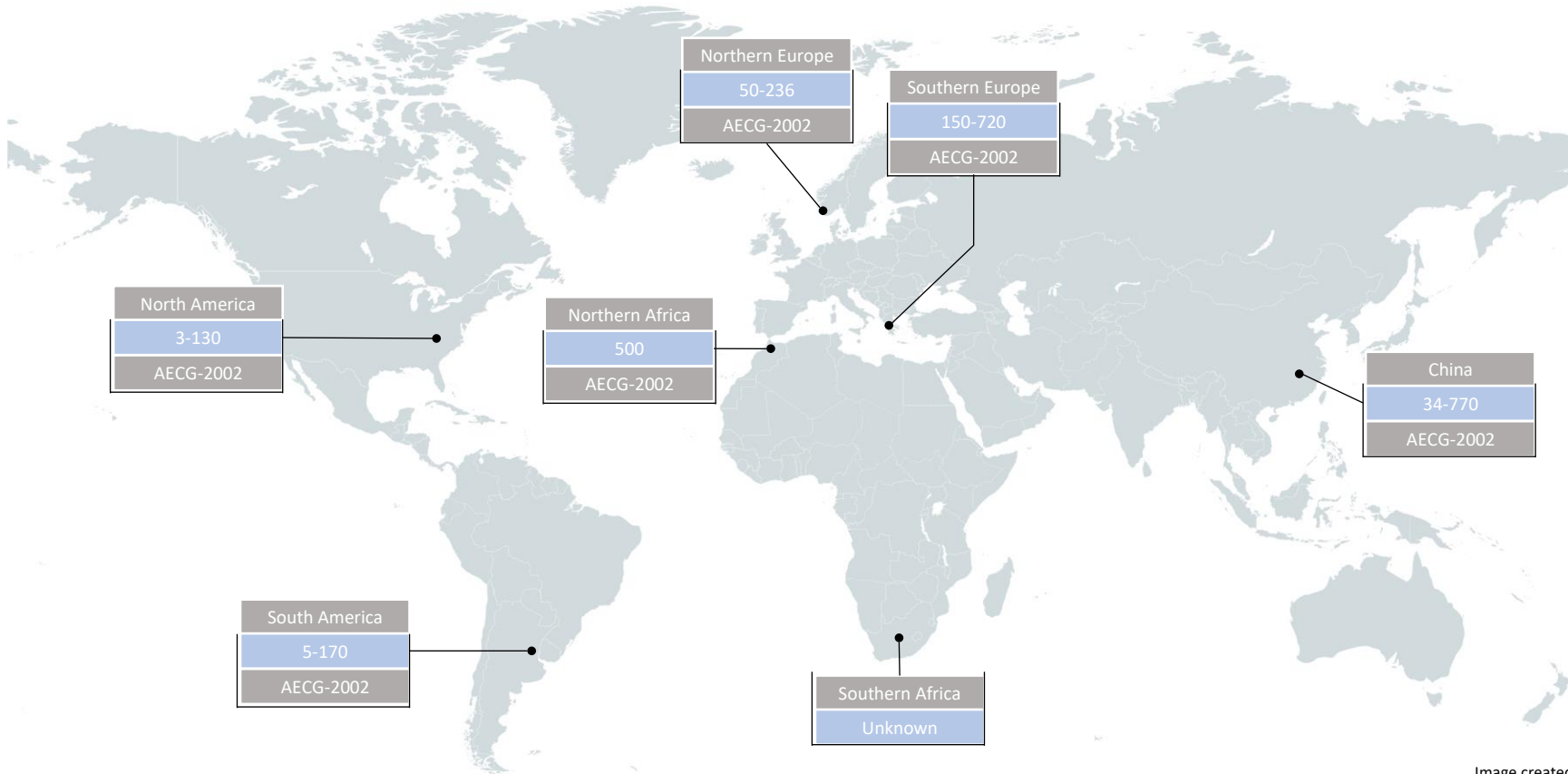


Image created by Chatzis L

Global prevalence of Sjogren Syndrome per 100.000 people

OPEN Prevalence of Sjögren's syndrome in the general adult population in Spain: estimating the proportion of undiagnosed cases

**SCIENTIFIC
REPORTS**
nature research



50 / 100



For every patient diagnosed with Sjogren Syndrome there is another one with dryness symptoms and no diagnosis

✓ Sjögren's Syndrome: *Gender differences*

Country	Year	Classification criteria	Female/male Ratio
Japan	1999	Modified Japanese criteria	9.7:1
Spain	2000	Preliminary European Classification Criteria for SS	10:1
Spain	2004	Preliminary European Classification Criteria for SS	18:1
Greece	2006	AECG	20:1
Spain	2007	AECG	12:1
Turkey	2009	AECG and European classification	10:1
Norway	2011	AECG	6:1
China	2015	AECG	27:1
USA	2017	AECG	6:1
Worldwide	2019	AECG	14:1
Australia	2020	AECG	9:1
Greece and Italy	2020	ACR/EULAR	20:1


Table created by Chatzis L

For Sjogren Syndrome, even though the unbalanced gender ratio is common between all epidemiological studies, its exact quantification is problematic given the vast geographic disparity. For years, it was traditionally reported as 9 women to 1 male, but a number of newer highly populated studies set the bar even higher.



Sjögren Syndrome
does not respect
gender equality





Sjögren Syndrome
does not respect
gender equality

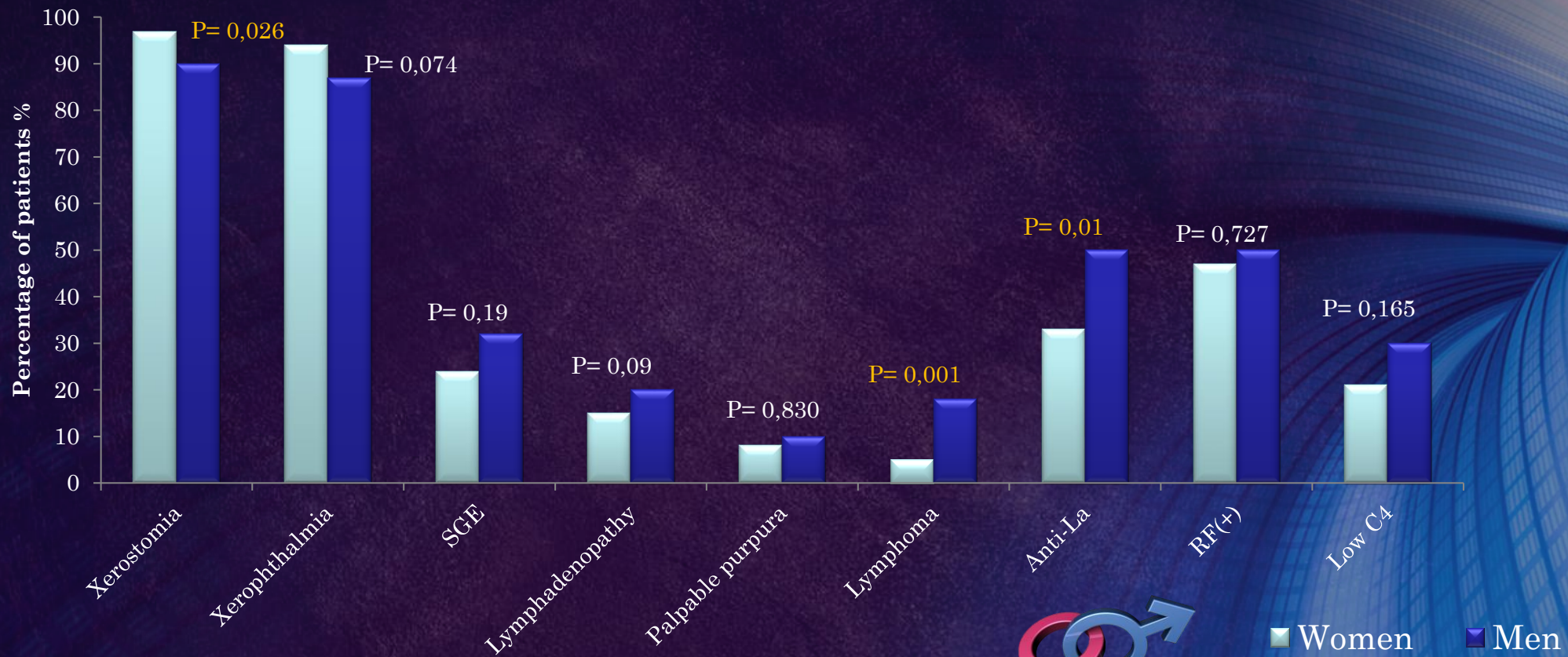
THE



SAME

✓ Sjögren's Syndrome: Clinical and serological associations according to gender (UPAHI)

1987 PATIENTS / 96 MALES
 Female : Male ratio = 20:1

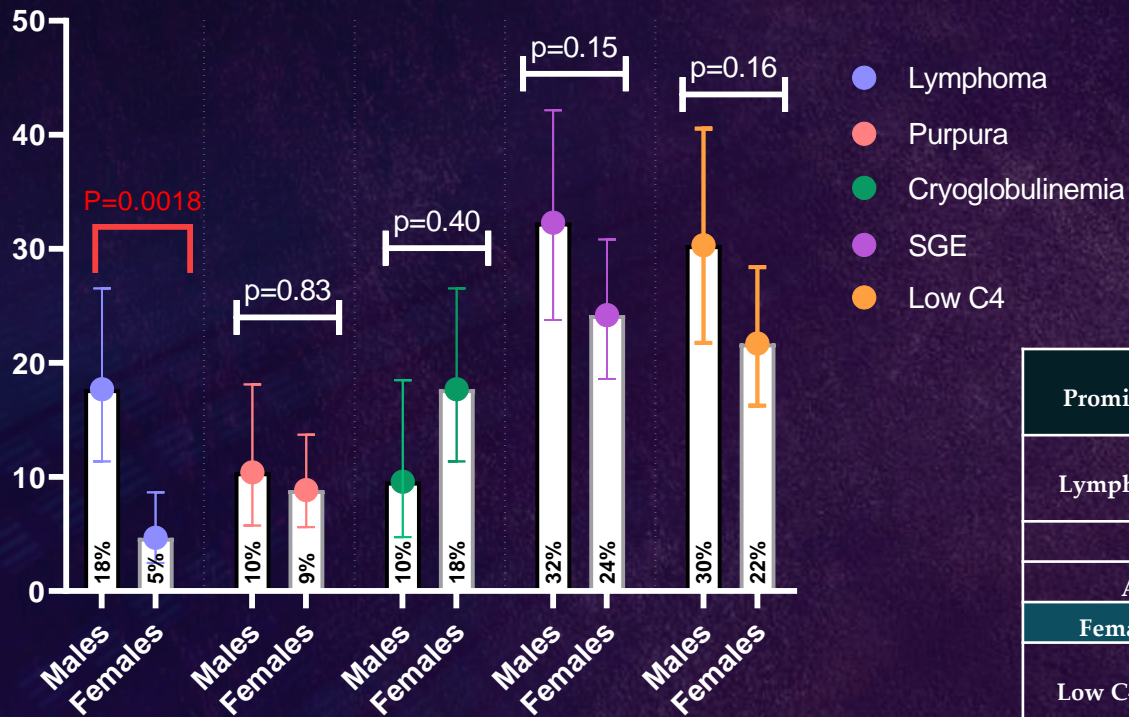


Male patients with SS have a higher frequency of developing lymphoma



■ Women ■ Men

➤ *Sjögren's Syndrome: Clinical and serological associations according to gender (UPAHI)*

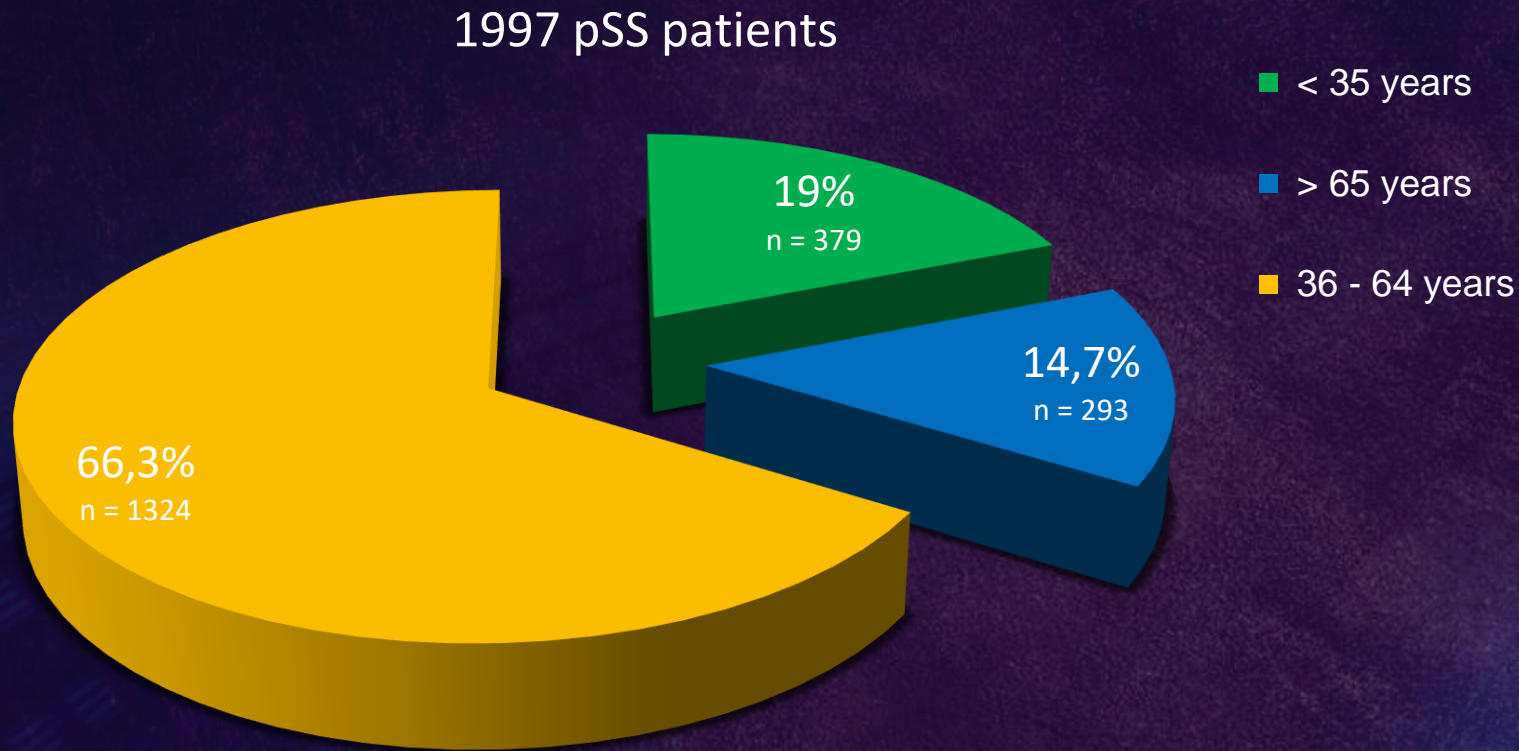


Prominent feature	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Lymphadenopathy	1.869	6.549	0.0003*	2.456	17.482
SGE	0.689	2.006	0.129	0.853	4.724
Anti-La	0.682	1.989	0.11	0.884	4.477
Female Gender	-1.119	0.332	0.011*	0.148	0.742
Low C4 (< 20mg/dl)	0.465	1.599	0.337	0.629	4.069
Monoclonal gammopathy	0.537	1.728	0.512	0.353	8.592



Male patients with SS have a higher frequency of developing lymphoma

✓ *Sjögren's Syndrome: patients with early or late disease onset (UPAHI)*



➤ Young SS patients have a more lupoid phenotype with an increased lymphoma risk

➤ Old SS patients have a milder phenotype, but they also have an increased lymphoma risk

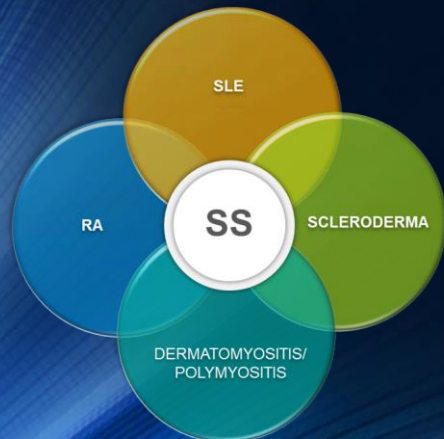


Consider age at diagnosis a key driver of how the disease is clinically expressed.

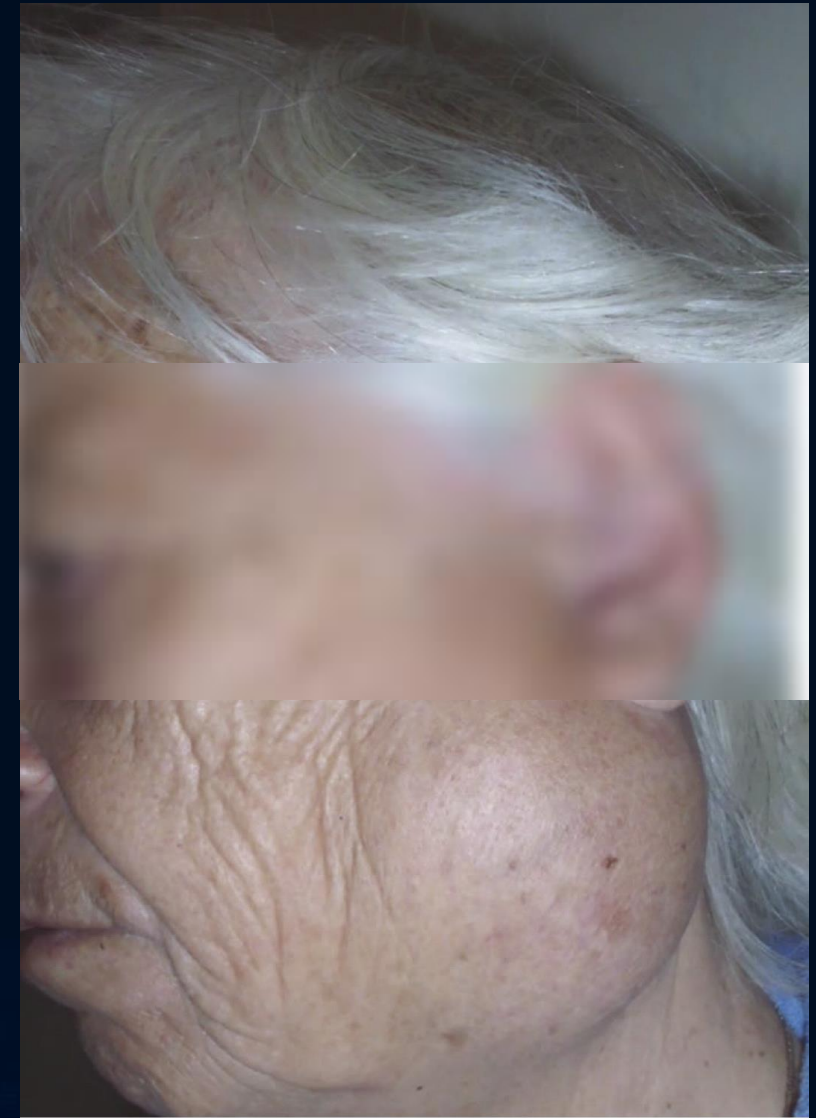
✓ Sjögren's Syndrome: Overview

- Female disease
♀/♂ : 9/1 → 19:1
- Common disease
0,1% prevalence
- 4th -5th decade of life
- Slowly progressive and difficult to treat
- Primary or secondary to:

2nd most common
rheumatic disease
2nd most common autoimmune disease
affecting women



For the practical management of patients, it makes no sense to separate between "primary" and "secondary" (associated) patients since the key target should be the same, the management of SS in both groups



A variety of Systemic Clinical Manifestations



Non-specific (e.g Raynaud, fatigue, arthralgias)



Peri-epithelial (sialadenitis, interstitial renal disease, PBC, small airways disease, myositis)



Extra-epithelial (Immune-complex mediated)



B-cell lymphomas

A 50-year-old lady complains of dryness in the mouth and eyes and pain in the joints

Case 1

Case presentation

- Symptoms are slowly progressive
- She had the first recollection of dryness in the mouth about 6-8 years ago
- She has noticed increased tooth decay
- She was referred by an ophthalmologist who noticed increased objective dryness in the eyes
- During the last year generalized pain throughout the body but especially in the joints had emerged
- She had no further medical history, she received no treatments, and she did not smoke or drink alcohol

Clinical examination

- Clinical examination has no major findings



Dental implants perform well in people with SS

Laboratory findings



01 **CBC**
Normal

02 **Blood Chemistry**
• Within Normal Limits

03 **Immunologic profile**
• **Hypergammaglobulinemia (IgG 19.7)**
• ANA positivity (1/320)
• Anti-Ro/SSA positivity

***Differential
diagnosis***



Next steps



Treatment

Prognosis



Causes of oral and ocular dryness

Oral dryness

Medications
Anti-hypertensives (e.g. ACEi, nifedipine, diuretics)
Anti-histamines (first generation)
Anti-depressants (tricyclic, MAOIs, SSRI's)
Alpha and beta blockers
Anti-anxiety (benzodiazepines)
Anti-psycotics (first and second generation)
Anti-parkinson
Anti-cholinergic drugs (antimuscarinic for overactive bladder, spasmolytics, inhaled bronchodilators)
Dehydration
Diabetes mellitus
Anxiety or stress
Head and neck radiotherapy
Chemotherapy
Infections
Hepatitis C virus
Epstein-Barr virus
Human immunodeficiency virus
HTLV-1
Salivary gland disease
Age related sicca syndrome
Sjögren's syndrome
IgG4 related disease
Lymphoma
Sarcoidosis

Ocular dryness

Primary causes
Aging
Dysautonomia
Secondary causes
Inflammatory and infiltrative causes
Medications
Sjögren's syndrome
IgG4 related disease
Lymphoma
HIV infection
Sarcoidosis
Obstruction of lacrimal gland ducts
Chemical and thermal burns
Trachoma
Erythema multiforme
Hyposecretion
Contact lens
Diabetes mellitus
Facial nerve block
Reflex sensory or motor block

✓ Sjögren's Syndrome: *Classification Criteria*

	Item	Weight / Score
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02	Anti-SSA (Ro) +	3
03	Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) on at least one eye	1
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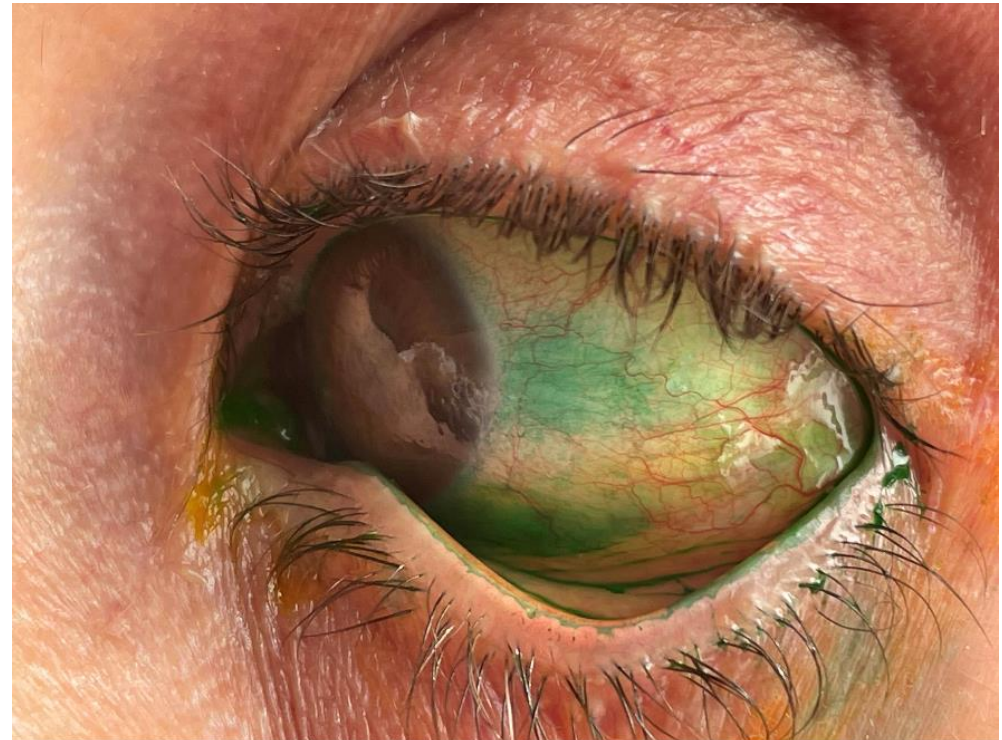
A patient is classified as having SS when he has a score ≥ 4

Eye examination

▶ Schirmer



▶ Lissamine green



The use of contact lens should not be contraindicated.

Unstimulated saliva flow rate



Outcome

- ▶ Focus score 1.2
 - ▶ Schirmer test 4mm bilateral
 - ▶ Lissamine green 5/9
 - ▶ USFR: 2.3cc in 15 minutes
-
- ▶ **DIAGNOSIS: SJOGREN'S SYNDROME WITHOUT EXTRAGLANDULAR MANIFESTATIONS**

A 45-year-old lady complains of dryness of the eyes, polyuria, slightly elevated creatinine and liver enzymes, arthralgias and Raynaud phenomenon

Case 2

Case presentation

- Raynaud 10 years ago
- Dryness in the mouth about 2 years ago. Creatinine 1.6mg/dl
- Past medical history: Hashimoto thyroiditis and celiac disease
- Her medication include levothyroxine and a strict gluten-free diet
- She was referred by her endocrinologist

Clinical examination

- Clinical examination



Laboratory findings



01 **CBC**
Normal

02 **Blood Chemistry**

- Elevated γ -GT, alp, AST and ALT, elevated creatinine
- Urine SG 1005, Ph 7.00, negative for RBCs WBCs

03 **Immunologic profile**

- ANA positivity (1/640)
- Anti-Ro/SSA positivity, Anti-LA/SSB positivity
- AMA positivity (1/640)
- Anti-Tg positivity
- Hypergammaglobulinemia (28.7%) (IgG=2303)

What would you do?

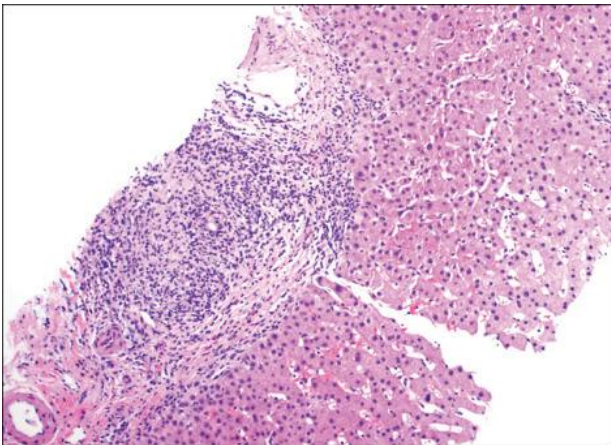
- Ask for a fibroscan of the liver?
- Ask for Renal US?
- Perform a minor salivary gland biopsy?
- Start Tx with steroids?

Biopsy findings

Liver

Liver biopsy

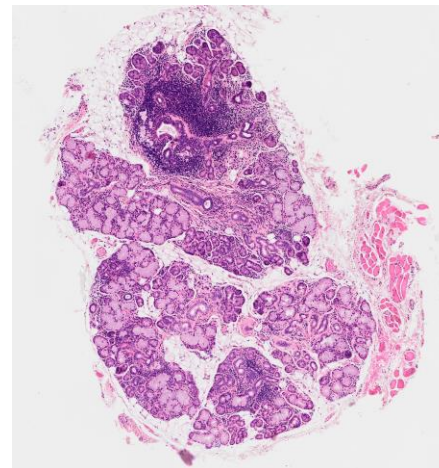
- Biopsy findings reveal a pericholangial lymphocytic infiltration injury a pattern compatible with mild Primary Biliary Cholangitis



MSG

Minor salivary gland biopsy

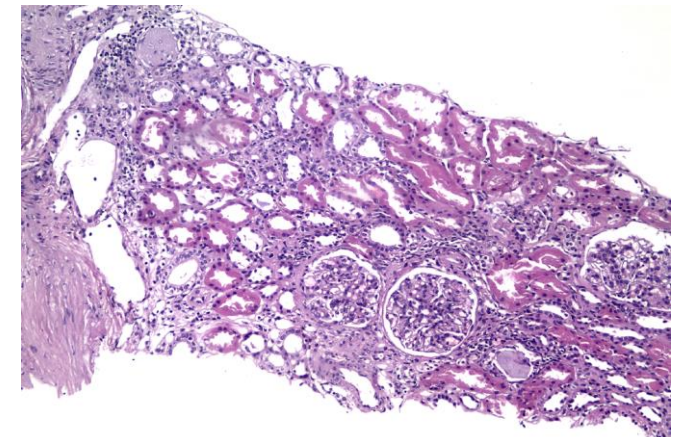
- Periductal infiltrates of the minor salivary glands, Sjogren Syndrome's pathologic signature
- Focus score=1.8



Kidney

Kidney biopsy

- Interstitial nephritis with diffuse interstitial mononuclear cells infiltrate with interstitial fibrosis, tubular atrophy, and occasional tubulitis.
- Glomeruli have a normal structure



Occam's Razor

“Diagnostician should assume a single cause for multiple symptoms”



Hickam's Dictum

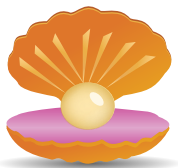
“Patients can have as many diseases as they damn well please”

Outcome

- ▶ Kidney biopsy: peritubular lymphocytic infiltration
- ▶ Liver biopsy: pericholangial lymphocytic infiltration
- ▶ Minor salivary gland biopsy: periductal lymphocytic infiltration



- ▶ Hashimoto thyroiditis and celiac disease
- ▶ **DIAGNOSIS: SJOGREN'S SYNDROME WITH MANY EXTRAGLANDULAR PERIEPITHELIAL MANIFESTATIONS**



Gastrointestinal involvement (including pancreatitis) is not a systemic manifestation of the disease. With symptoms think of IBD

A 39-year-old man is admitted
for peripheral edema and
parotid gland enlargement

Case 3

Case presentation

- Diagnosed with Sjogren's syndrome 8 years ago. Recurrent parotid gland enlargement from the disease onset. Raynaud's phenomenon 10 years ago
- Permanent bilateral salivary gland enlargement present for 6 months
- He has received many antimicrobial regimens with minimal effect
- For the last 3 weeks gradually deteriorating pitting edema and palpable purpura appeared in the lower extremities

Clinical examination

- Increased blood pressure in both arms (BP: 150/95)
- Pitting edema
- Purpura
- Firm, painless bilateral parotid gland enlargement



Laboratory findings



01 **CBC**
Normal

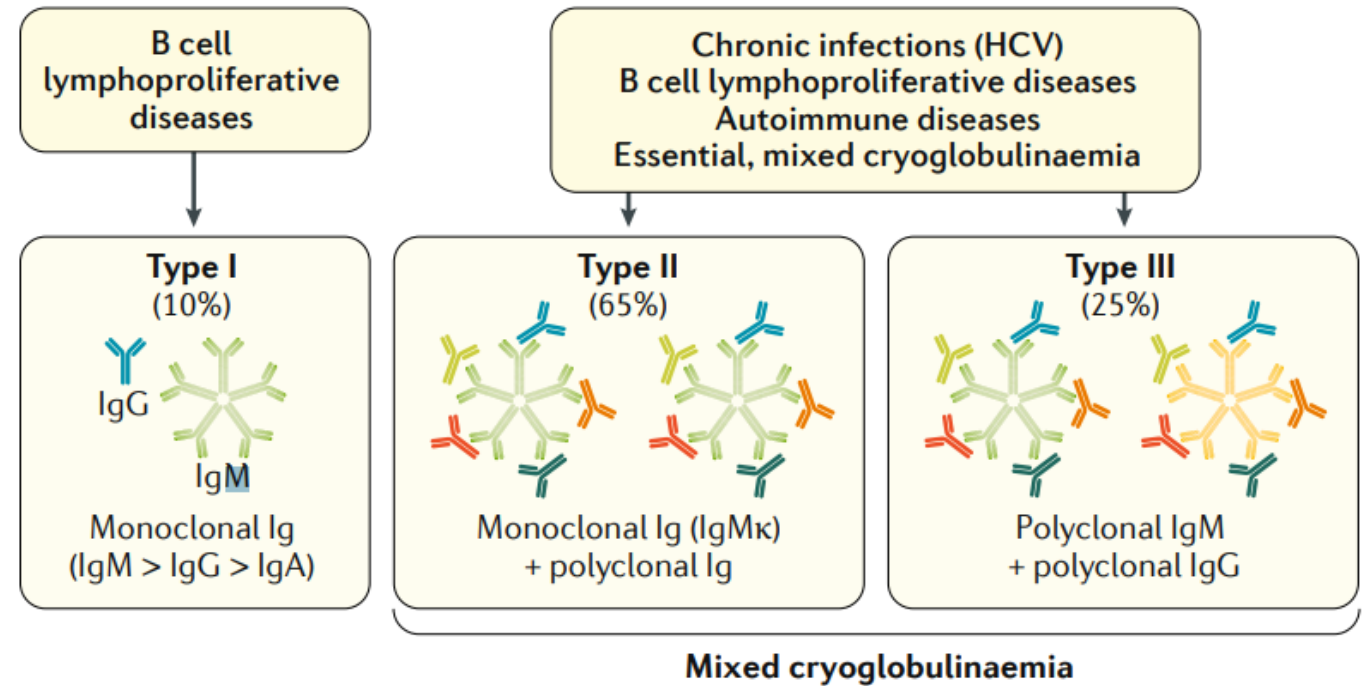
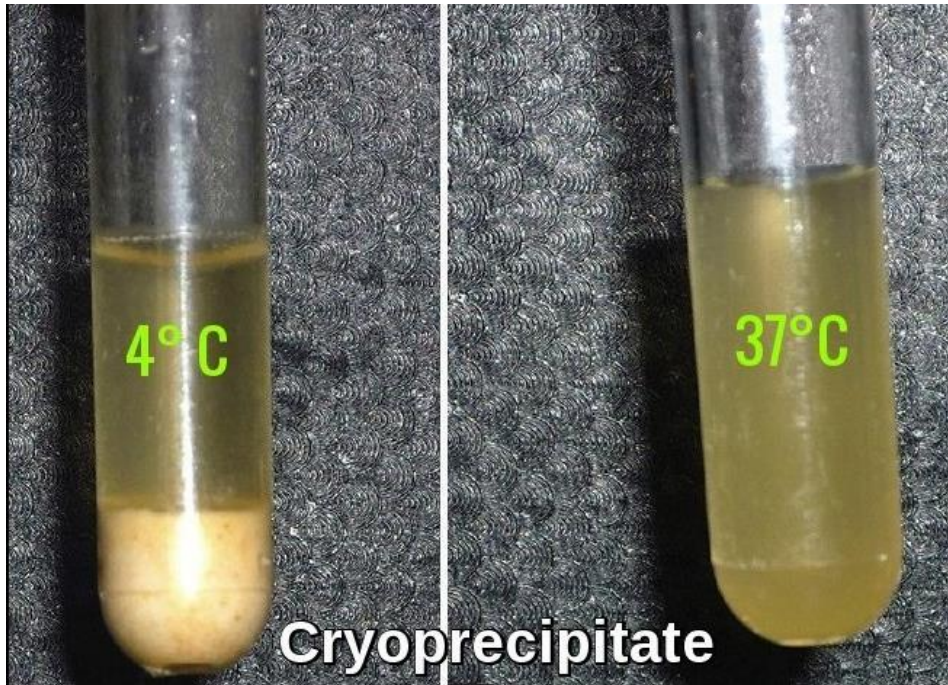
02 **Blood Chemistry**

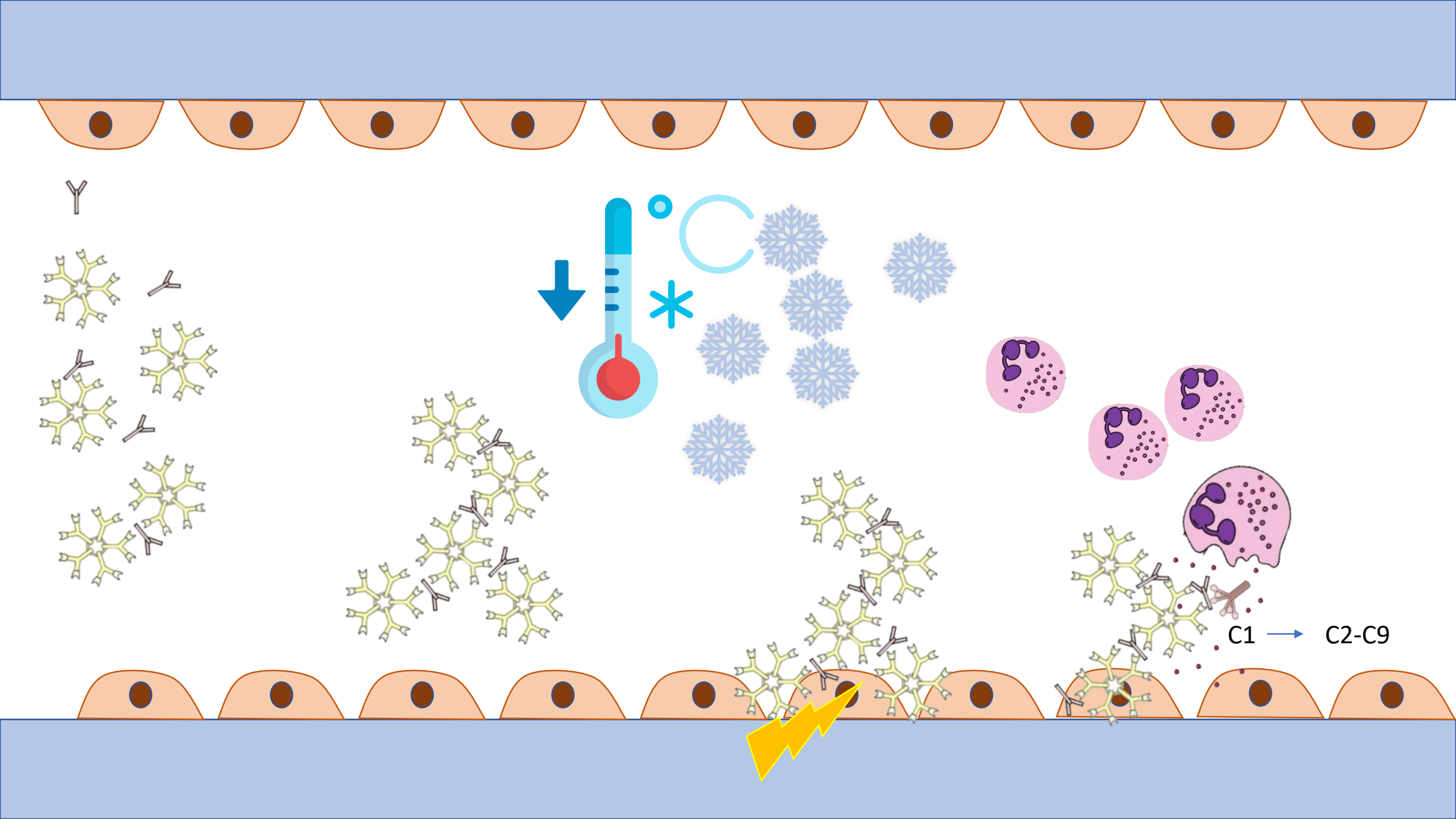
- Ur:60, Cr: 2.4
- Low albumin
- CRP:35, ESR:64
- Active urine sediment: 25 RBC with RBC casts
- 24 hour proteinuria:2.5 gr

03 **Immunologic profile**

- ANA positivity (1/640)
- Anti-Ro/SSA positivity, Anti-LA/SSB positivity
- RF: 640
- C4: 2

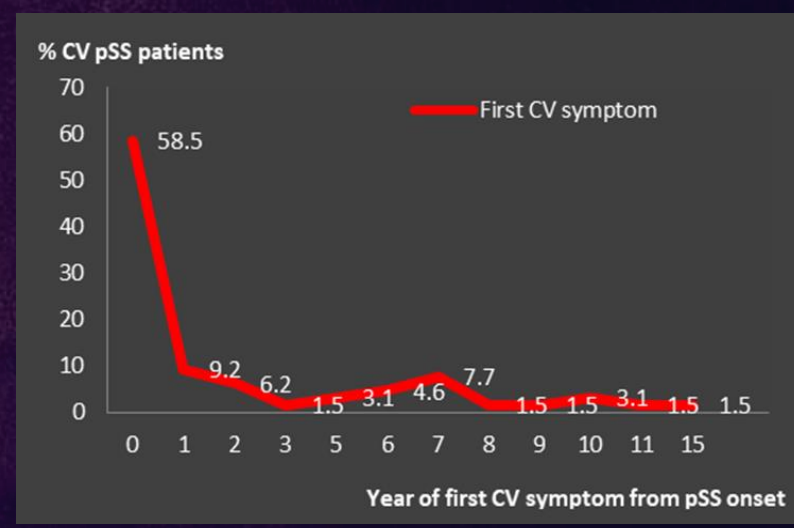
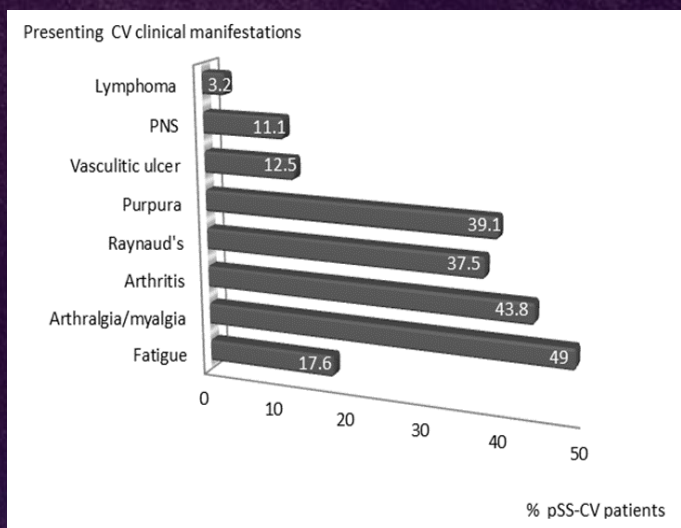
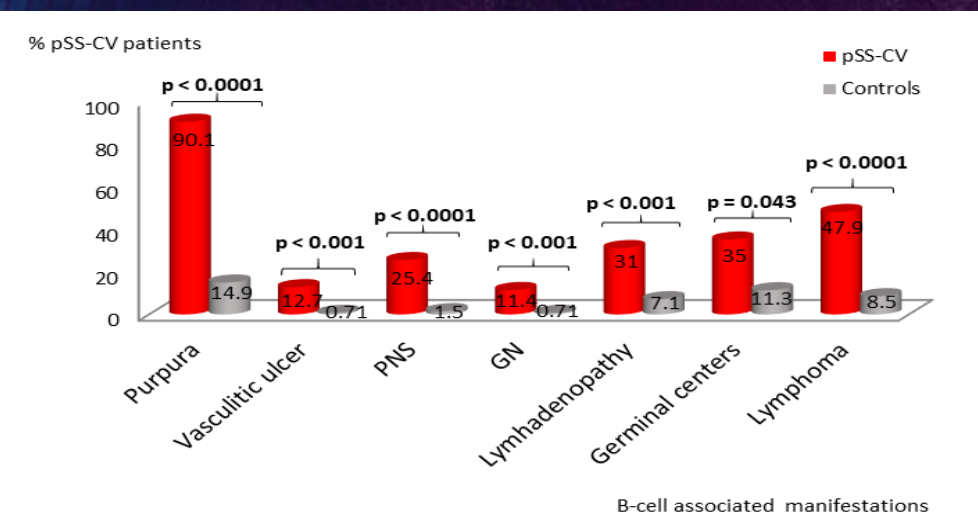
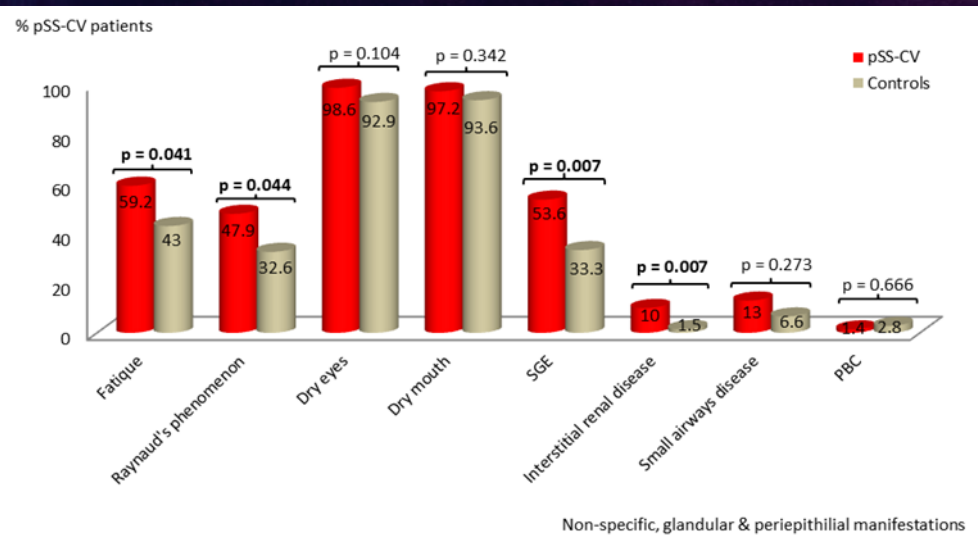
Cryoglobulinemia



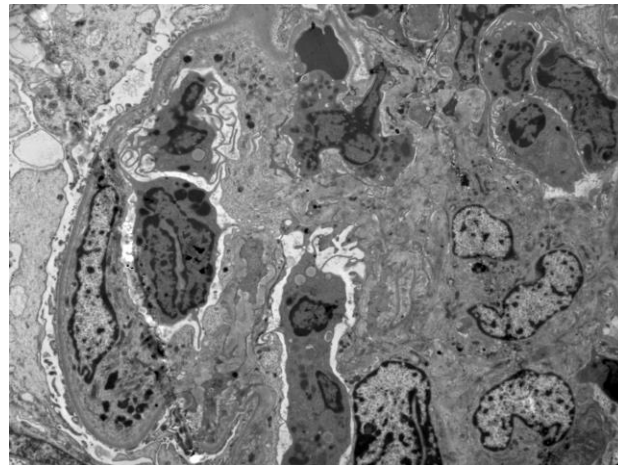
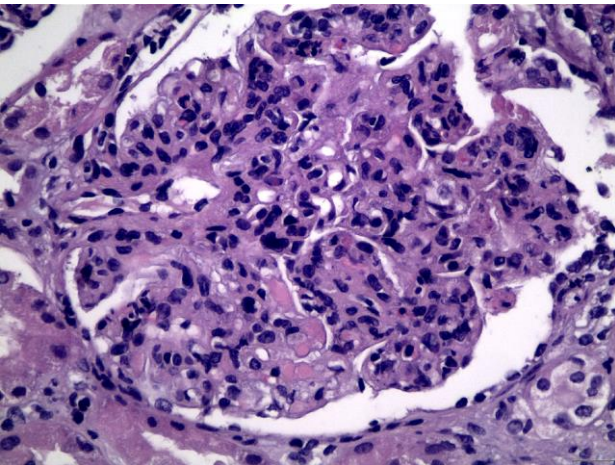
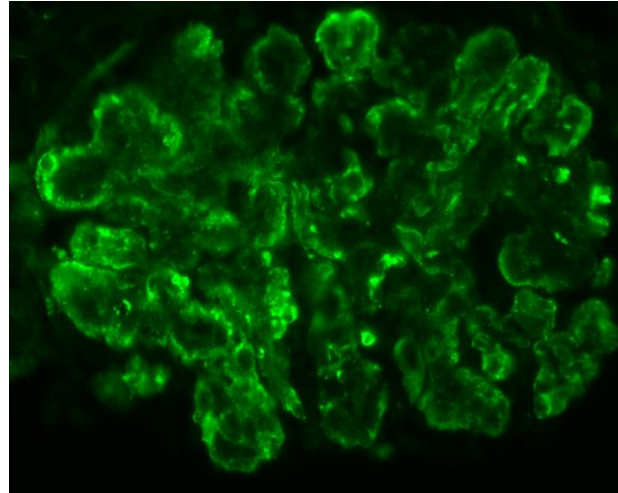
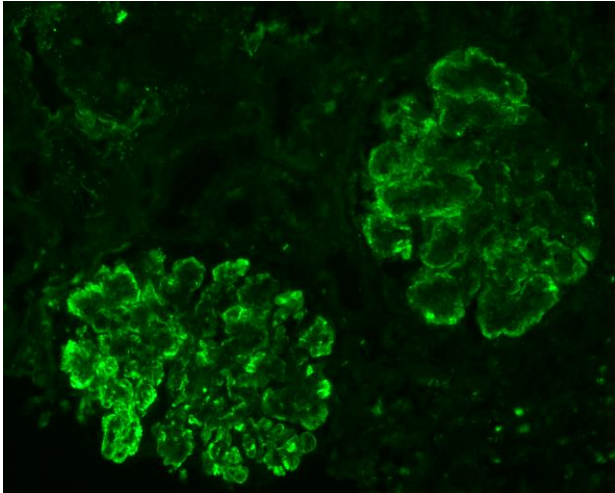


✓ Sjögren's Syndrome: clinical and serological features of CV

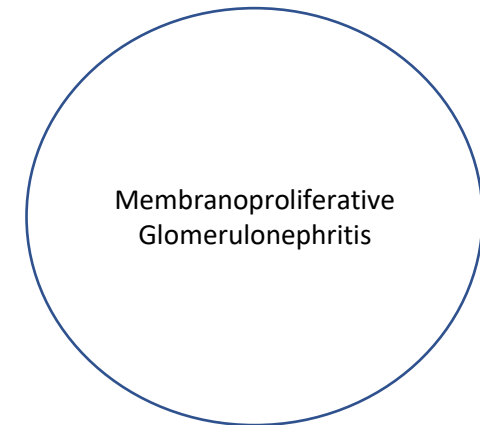
- pSS-CV patients had higher frequency of extraglandular manifestations and lymphoma (OR=9.87) compared to pSS patients without cryoglobulins
- Compared to HCV-CV patients, pSS-CV individuals displayed more frequently lymphadenopathy, type II IgMk cryoglobulins and lymphoma and less frequently C4 hypocomplementemia and peripheral neuropathy.



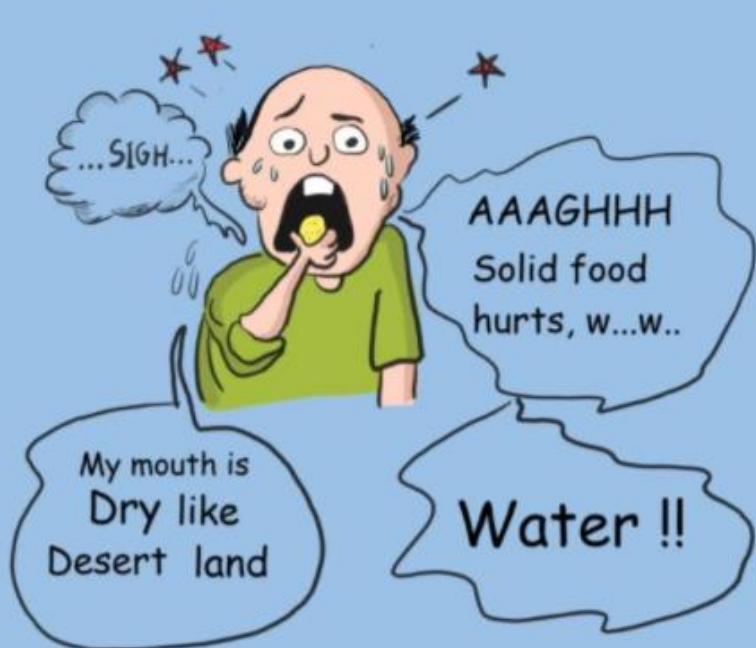
Kidney Biopsy findings



Panel 1. Intense IgM granular expression of the subendothelial deposits along glomerular capillary walls (Immunofluorescence, IgM X200), Panel 2. Intense k light chain granular expression along glomerular capillary loops (Immunofluorescence, k light chain X200), Panel 3. Membranoproliferative pattern with accentuation of lobular glomerular architecture and “hyaline thrombi” into glomerular lumens (H&E X400), Panel 4. Mesangial cell expansion and cellularity, inflammatory cells into glomerular capillary lumens, endothelial cell activation along with segmental thickening of GBM and glomerular lumen obstruction



Watch out for IgM and k light chain in immunofluorescence



ΕΡΩΤΗΣΕΙΣ

