

Interlaken Workshop Session

23.01.2026

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First case: M. C.

- The patient was admitted to the intensive care unit, intubated, in the setting of severe metabolic acidosis with hyperlactatemia
- Laboratory investigations revealed marked abnormalities in liver tests, with cholestasis and cytolysis, without evidence of hepatocellular failure.
- In view of suspected intestinal ischemia, an exploratory laparoscopy was performed. A liver biopsy was obtained during the procedure.
- Diagnosis: intravascular large B-cell lymphoma (IVLBCL)

Second case: Mme F.

- Rapid onset of cervical lymphadenopathy, B symptoms, dyspnea, purpura, and sensory-motor disturbances of the lower limbs
- Known for monoclonal gammopathy
- PET CT: hypermetabolic pulmonary infiltrates, hypermetabolic mediastinal, internal mammary, cervical, retroperitoneal and right cardio-phrenic lymphadenopathy. Hypermetabolic infiltration of the salivary glands. Hepatosplenomegaly
- Adenectomy and diagnosis: Extranodal marginal zone B-cell lymphoma of MALT type, stage IV (pulmonary, ENT, and nodal involvement)
 - Complication: vasculitic neuropathy with axonal sensory and motor polyneuropathy secondary to type II cryoglobulinemia

What do these patients have in common?

What do these patients have in common?



Coeliac disease

H.pylori infection

Sjogren disease

HIV

Multicentric Castelman disease

M. C

Intravascular
lymphoma IVLBCL



SJOGREN DISEASE



Mdm. F
MALT lymphoma

What do you tell to your patients?



30% of patients will develop lymphoma

Sero-negative (no anti SSA/B Ab) patients will not develop lymphoma

Most Sjogren's disease related lymphoma are indolent forms

There is no certain way to predict or prevent Sjogren's disease related lymphoma

Objectives:

- **Which patient will develop lymphoma?**
 - **Clinical and biological phenotypes**
 - **Follow up**
- **Which lymphoma most often complicate Sjögren's disease?**
 - **Treatment and prognosis of Sjogren's disease related lymphoma**
- **Is there a Sjogren's disease treatment that prevent progression to lymphoma?**
 - **Hydroxychloroquine**
 - **Anti B-cell therapies**

Which patient will develop lymphoma?

I look for lymphoma if : Yes or No?



- B symptoms
- Fatigue and brain fog
- Parotid swelling
- Purpura
- Neurologic complications
- Germinal center in MSGB
- High RF
- Cryoglobulinemia
- High IgG or MGUS
- Pulmonary involvement

Heterogeneity in Sjogren's disease

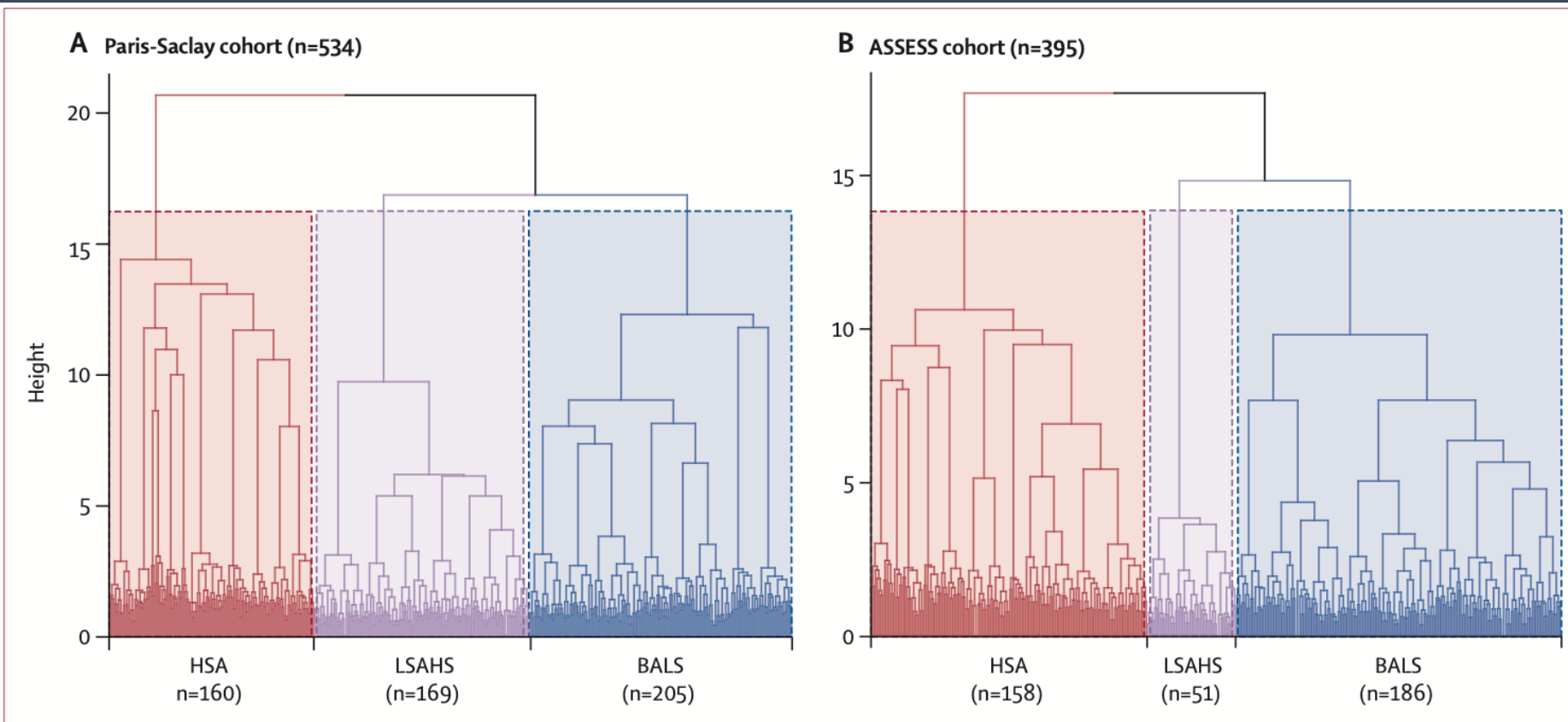


Figure 1: Dendrogram of identified clusters

Clusters identified in the Paris-Saclay cohort (A) and the ASSESS cohort (B). Horizontal branches represent the combination of two clusters, and vertical branches the degree of dissimilarity between combined clusters. The areas enclosed within the dotted lines represent the three groups after truncation. ASSESS=Assessment of Systemic Signs and Evolution of Sjögren's Syndrome. BALS=B-cell active disease and low symptom burden. HSA=high systemic disease activity. LSAHS=low systemic disease activity and high symptom burden.

-Disease activity:
ESSDAI (objective organ involvement, biology)

-Symptom burden:
ESSPRI (subjective dryness, fatigue, pain)

-24 (4%) of the 534 patients in the Paris-Saclay cohort had a history of lymphoma; of these, 19 (79%) were in the HSA cluster, three (13%) were in the BALS cluster, and two (8%) were in the LSAHS cluster.

-33 (100%) Black patients within the Paris-Saclay cohort were in the HSA cluster.

-30 (88%) of 34 Asian patients were in the BALS cluster and four (12%) were in the HSA cluster

Which patient will develop lymphoma?

- Incident lymphoma occurred mostly in the HSA > BALS clusters
- In the BALS cluster, lymphoma occurred later than in the HSA cluster
- After 5 years, systemic manifestations in BLAS cluster ended to be similar to those in the HSA cluster at inclusion
 - The BALS cluster could be an earlier stage of the disease and carry the risk of progressing towards a more systemic phenotype (HSA)

	Paris-Saclay cohort					ASSESS cohort				
	Total cohort (n=534)	BALS (n=205)	HSA (n=160)	LSAHS (n=169)	p value	Total cohort (n=395)	BALS (n=186)	HSA (n=158)	LSAHS (n=51)	p value
Age at diagnosis, years*	54 (43-64)	48 (35-61)	53 (43-63)	57 (50-65)	<0.0001†	53 (44-60)	51 (38-59)	54 (46-61)	53 (48-58)	0.035†
Sex*					<0.0001‡					0.033‡
Female	502 (94%)	205 (100%)	128 (80%)	169 (100%)		370 (94%)	169 (91%)	150 (95%)	51 (100%)	
Male	32 (6%)	0	32 (20%)	0		25 (6%)	17 (9%)	8 (5%)	0	
Race*					<0.0001‡					..
Black	33 (6%)	0	33 (21%)	0		
Asian	34 (6%)	30 (15%)	4 (3%)	0		
White	467 (87%)	175 (85%)	123 (77%)	169 (100%)		
Ever smoker	104 (19%)	36 (18%)	32 (20%)	36 (21%)	0.60‡	105 (27%)	52 (28%)	41 (26%)	12 (24%)	0.90‡
Patient-reported outcomes										
Pain (VAS or VNS)*§	51 (20-77)	37 (10-60)	52 (20-78)	67 (48-80)	<0.0001†	5 (2-7)	4 (2-6)	6 (3-8)	6 (4-7)	<0.0001†
Fatigue (VAS or VNS)*§	62 (40-80)	49 (20-70)	61 (38-81)	76 (60-87)	<0.0001†	6 (4-8)	5 (3-8)	7 (5-8)	7 (6-8)	<0.0001†
Overall dryness (VAS or VNS)*§	61 (40-77)	51 (31-72)	66 (46-80)	65 (47-80)	<0.0001†	6 (4-7)	5 (3-7)	6 (5-8)	6 (5-7)	<0.0001†
ESSPRI score§	6 (4-7)	5 (3-6)	6 (4-7)	7 (5-8)	<0.0001†	6 (4-7)	5 (3-6)	6 (5-7)	6 (5-7)	<0.0001†
Systemic manifestations according to ESSDAI domains										
Constitutional*	6 (1%)	0	6 (4%)	0	0.0007¶	16 (4%)	0	16 (10%)	0	<0.0001‡
Lymphadenopathy*	29 (5%)	2 (1%)	27 (17%)	0	<0.0001‡	12 (3%)	0	12 (8%)	0	<0.0001‡
History of lymphoma before inclusion	24 (4%)	3 (1%)	19 (12%)	2 (1%)	<0.0001‡	18 (5%)	2 (1%)	16 (10%)	0	<0.0001‡
Glandular*	152 (28%)	78 (38%)	47 (29%)	27 (16%)	<0.0001‡	47 (12%)	24 (13%)	18 (11%)	5 (10%)	0.80¶
Articular*	176 (33%)	58 (28%)	58 (36%)	60 (36%)	0.20‡	73 (18%)	33 (18%)	32 (20%)	8 (16%)	0.70¶
Cutaneous*	14 (3%)	0	14 (9%)	0	<0.0001¶	16 (4%)	1 (1%)	15 (9%)	0	<0.0001‡
Pulmonary*	21 (4%)	0	21 (13%)	0	<0.0001‡	57 (14%)	5 (3%)	52 (33%)	0	<0.0001¶
Renal*	3 (1%)	0	3 (2%)	0	0.027¶	11 (3%)	0	11 (7%)	0	0.0001‡
Muscular	2 (<1%)	0	1 (1%)	1 (1%)	0.52¶	13 (3%)	4 (2%)	6 (4%)	3 (6%)	0.30‡
Peripheral nervous system*	20 (4%)	0	20 (13%)	0	<0.0001‡	38 (10%)	4 (2%)	34 (22%)	0	<0.0001‡
Central nervous system	1 (<1%)	0	1 (1%)	0	0.30¶	8 (2%)	4 (2%)	4 (3%)	0	0.80‡
Haematological*	78 (15%)	29 (14%)	34 (21%)	15 (9%)	0.0063‡	62 (16%)	32 (17%)	29 (18%)	1 (2%)	0.02¶
Biological*	266 (50%)	124 (60%)	95 (59%)	47 (28%)	<0.0001‡	146 (37%)	71 (38%)	72 (46%)	3 (6%)	<0.0001¶
ESSDAI score	2 (1-5)	2 (1-4)	6 (3-10)	2 (0-3)	<0.0001†	3 (2-8)	2 (1-4)	8 (3-13)	0 (0-2)	<0.0001†
Paraclinical parameter										
Lymphocyte count (G/L)§	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-2)	0.023†	1 (1-2)	1 (1-2)	1 (1-2)	2 (1-2)	0.051†
IgG concentration >15 g/L*	203 (38%)	108 (53%)	64 (40%)	31 (18%)	<0.0001‡	147 (37%)	91 (49%)	55 (35%)	1 (2%)	<0.0001¶
Monoclonal gammopathy*	44 (8%)	20 (10%)	22 (14%)	2 (1%)	0.0001‡	44 (11%)	8 (4%)	35 (22%)	1 (2%)	<0.0001¶
Rheumatoid factor*	234 (44%)	113 (55%)	71 (44%)	50 (30%)	<0.0001‡	122 (31%)	60 (32%)	50 (32%)	12 (24%)	0.47¶
Anti-SSA antibody*	368 (69%)	171 (83%)	101 (63%)	96 (57%)	<0.0001‡	232 (59%)	126 (68%)	85 (54%)	21 (41%)	0.0008¶
Anti-SSB antibody*	182/530 (34%)	95/202 (47%)	42/160 (26%)	45/168 (27%)	<0.0001‡	132 (33%)	76 (41%)	48 (30%)	8 (16%)	0.0019¶
Anti-RNP antibody*	15 (3%)	0	15 (9%)	0	<0.0001¶	5 (1%)	0	5 (3%)	0	0.028‡
Anti-centromere antibody*	20 (4%)	0	20 (13%)	0	<0.0001‡	9 (2%)	0	9 (6%)	0	0.0007‡
Anti-DNA antibody*	29 (5%)	23 (11%)	5 (3%)	1 (1%)	<0.0001‡	38 (10%)	25 (13%)	13 (8%)	0	0.0020‡
Cryoglobulinaemia*	10 (2%)	0	10 (6%)	0	<0.0001¶	57 (14%)	24 (13%)	27 (17%)	6 (12%)	0.46¶
Low C4 concentration*	92 (17%)	53 (26%)	28 (18%)	11 (7%)	<0.0001‡	72 (18%)	38 (20%)	34 (22%)	0	0.0014¶

HSA and BALS patients

- B symptoms
- Lymphadenopathy
- Cutaneous
- Pulmonary/Renal
- PNS
- High IgG/ Monoclonal GM
- RNP and Centromere Ab
- Cryoglobulinemia
- Low C4

Sjogren's disease phenotype of our 2 patients :

- First case (IVLBCL):

- Recurrent nodular scleritis, auto-immune thyroiditis, interstitial nephritis, no sicca syndrome, lymphoma 8 years after SD
- Positive anti SSA 60-52kd, high RF 21 UI/ml and IgG 18g/l, normal C3-C4
 - -> BALS/HSA Cluster

- Second case (MALT):

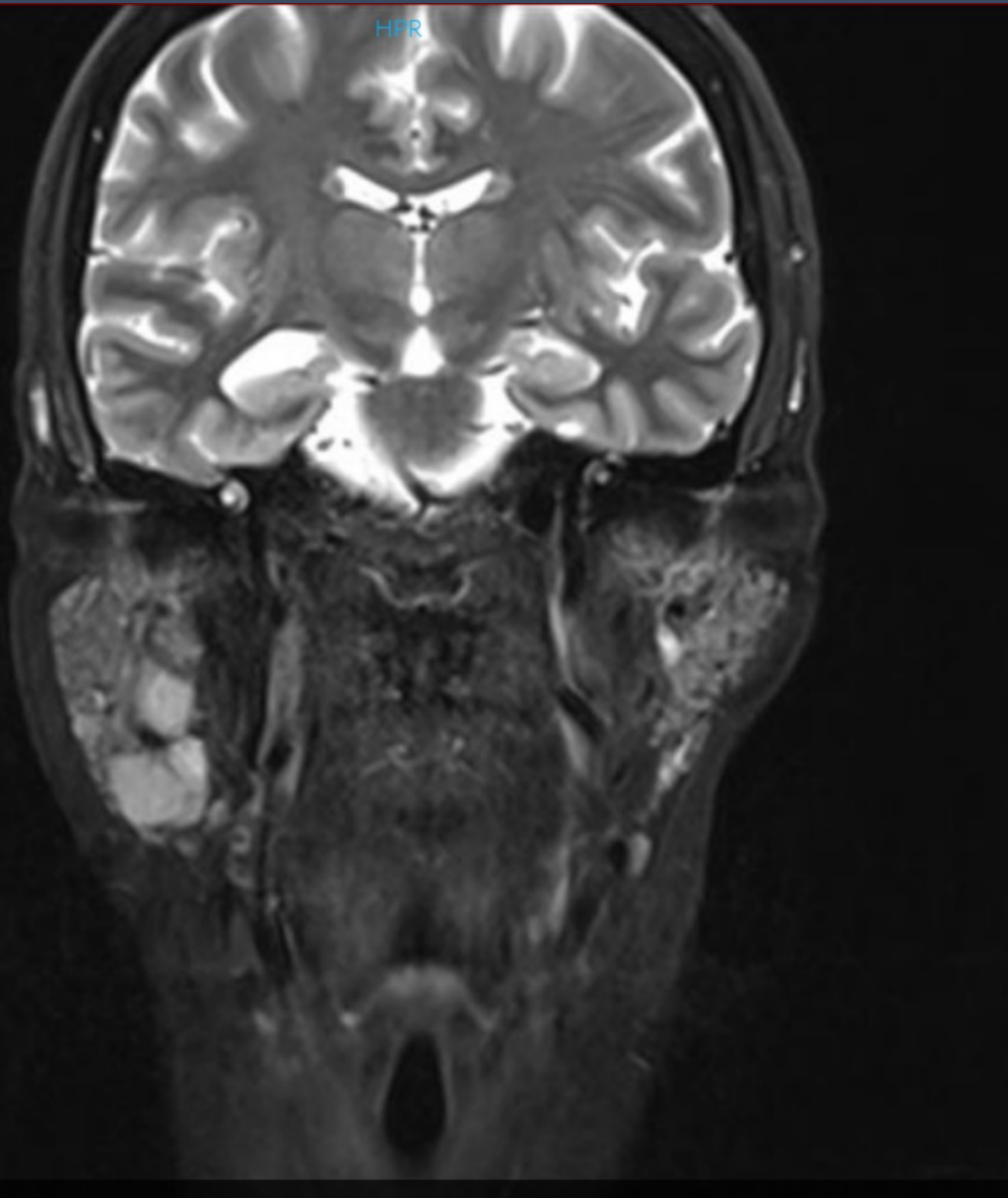
- Asthenia, sicca syndrome, parotitis, msk pain, Raynaud, PBC and auto-immune thyroiditis
- High RF 160 UI/ml (N <20), Monoclonal IgM kappa gammopathy (6 years prior to lymphoma), low C4 0.3 g/l(N 0.13-0.39), positive anti SSA 52 kd
 - -> HSA/BALS Cluster

Salivary glands swelling



Magnetic resonance imaging of a 40-year-old woman with Sjögren's disease and left parotid MALToma presenting with long-standing bilateral parotid swelling and 2 years increasing swelling on the left side

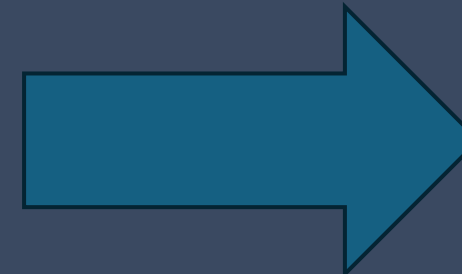
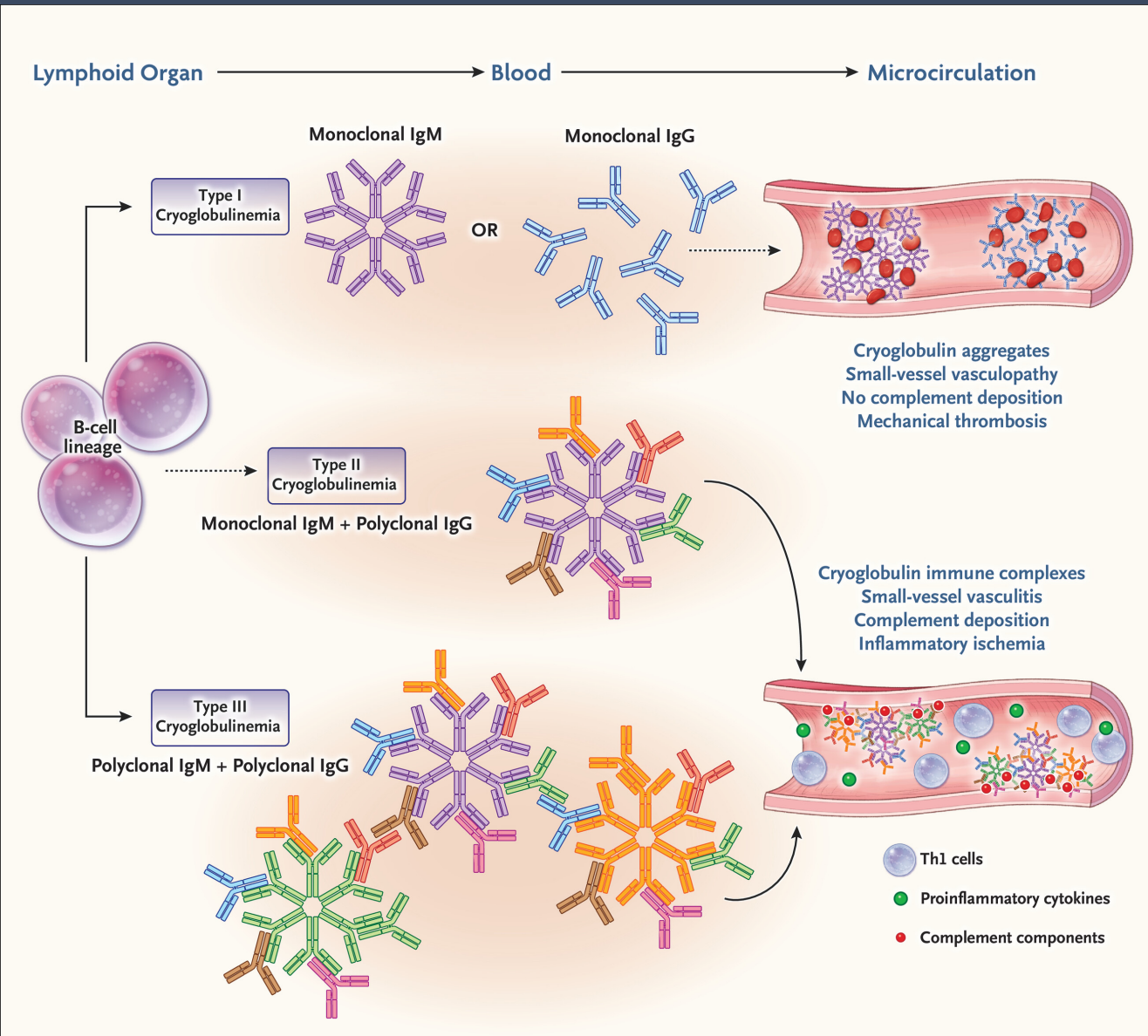
Ref : Imaging of head and neck mucosa-associated lymphoid tissue lymphoma (MALToma), Cancer Imaging Vol.21



60 years old female patient with Sjogren disease

- Dryness and arthralgia
- Lab test: anti SSA 60kDa 606 U, positive RF, IgG 16g/l
- Complication: Parotid MALT discovered after unilateral parotid swelling
- Trated with Rituximab with complete remission of the lymphoma

Cryoglobulinemia :

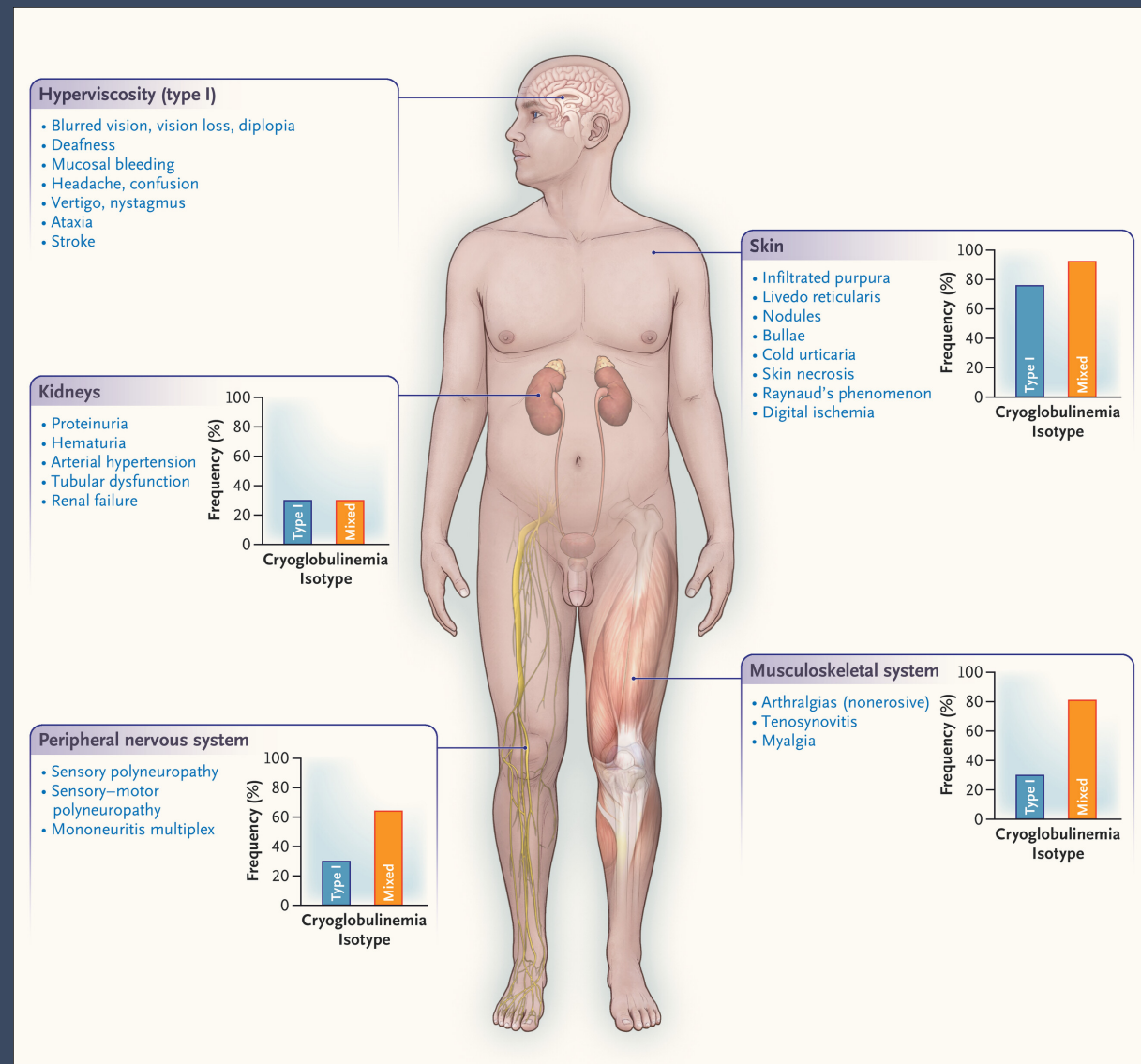


-Lymphoproliferative disease



-Lymphoproliferative disease
-Auto-immune disease
-Infections

Cryoglobulinemia manifestations:



Ref:
 Síndrome de Sjögren, P.-Y. Hatron
 Cryoglobulinemia — One Name for Two Diseases, P. Cacoub

Follow up :

- At each visit :
 - lung, cutaneous, neuro, lymphatic and ENT clinical examination
- At least once a year and before depending on the clinic:
 - CBC, renal fonction and urine, liver enzyme, C4, RF, immunofixation/electrophoresis.
- Imaging case by case:
 - US Salivary gland, abdomen
 - CT chest +/- abdomen
 - PET CT

Which lymphoma most often complicates Sjögren's disease?



Diffuse Large B Cell Lymphoma (DLBCL)

Mucosa-associated Lymphoid tissue Lymphoma
(MALT)

Hodgkin's Lymphoma (HL)

Intravascular B Cell Lymphoma (IVBCL)

Diffuse Large B Cell Lymphoma (DLBCL)

**Mucosa-associated Lymphoid tissue Lymphoma
(MALT)**



Hodgkin's Lymphoma (HL)

Intravascular B Cell Lymphoma (IVBCL)

- Prevalence of lymphoma in Sjogren's disease is +/- 5-10% (risk 4-16 fold higher than general population)
 - Proliferation and activation of auto-reactive B-cells
 - tissue infiltration, genetic abnormalities with clonal expansion
 - **50-80% are MALT (indolent lymphoma)**
 - **Salivary gland, orbits, ENT, lung, stomach etc**
 - Rarely (20-30%) DLBCL (aggressive lymphoma)-> transformation from an indolent form?
 - =< 10% HL, IVLBCL etc

Table 3. Classification of lymphoma, its treatment, and disease progression.

Case/Sex	Age at Lymphoma Diagnosis	Lymphoma Subtype	Initial Induction Therapy	Duration	Response to Therapy	Age at Relapse (Years)	Number of Relapses/ Location	Treatment at Relapse	Response to Therapy	Follow-Up Period (mo)	Disease Evolution
1/F	42	<u>MALT</u>	Rituximab	4 weeks	PR	43	1/parotid gland and lip nodule	Rituximab	CR	202	Free of disease
2/F	36	<u>MALT</u>	3000 cGY to right neck over 15 fractions	2 weeks	CR	41, 58	1/parotid gland and 2/parotid gland	1/radiation and 2/resection of gland and rituximab	CR	312	Death unrelated to disease progression
3/F	74	NSHL stage IVB	R-CHOP	6 months	CR	88	1/intrathoracic lymph nodes	Prednisone	PR	264	On maintenance treatment
4/F	72	MZL	Surveillance	-	-	-	-	-	-	12	Death unrelated to disease progression
5/M	55	DLBCL, stage III	CHOP	1 month	NR	-	-	-	-	2	Death by disease progression
6/F	59	<u>MALT</u>	Rituximab	weeks	CR	59	1/lacrimal	Rituximab	CR	24	Death unrelated to disease progression
7/F	54	<u>MALT</u>	Surveillance	-	-	-	-	-	-	165	Free of disease
8/F	67	DLBCL stage IV	RCHOP	4 months	CR	-	-	-	CR	30	Free of disease
9/F	71	DLBCL, stage 1AE	RCHOP	6 months	CR	-	-	-	-	21	Death unrelated to disease progression
10/F	65	Pulmonary <u>MALT</u> lymphoma	Surveillance	-	-	-	-	-	-	22	Under surveillance

MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; NSHL, nodular sclerosing Hodgkin's lymphoma; MZL, B cell marginal zone lymphoma; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone; CR, complete remission, NR, no response; and PR, partial remission. Follow-up period (mo) since lymphoma diagnosis.

Ref: Presentation, Characteristics and Features of Lymphoma in a Retrospective Case Series of Patients with Sjogren's Disease by Jennifer Behbodikhah Rheumato 2024

Treatment and prognosis of SD related lymphoma :

- Indolent lymphoma :
 - Watch and Wait approach
 - Anti CD-20 therapy (rituximab) +/- chemotherapy
 - -> depending on the burden of the disease
 - Sjogren and lymphoma complications, ex cryoglobulinemia
 - ->depending on bad pronostic factors
 - Older age
 - Extra-nodal involvement (lung>liver, spleen)
- Aggressive lymphoma :
 - Treatment is mandatory -> anti CD20 + chemio
- Prognosis comparable to non Sjogren's related lymphoma

Ref:

Characterization and risk estimate of cancer in SS, JHO

Treatment modalities of MALT and overall survival, haematologic response and SD activity: multicentre retrospective observational study, Lancet rheumatology

Is there a SD treatment that prevent progression to lymphoma?

How do you treat your Sjogren's patients?



I give hydroxychloroquine to every patient, to treat SD and prevent lymphoma

There is no effective treatment for SD or lymphoma progression, I'm not introducing anything except topical therapies for dryness

I'm trying to administer rituximab to every patient to prevent lymphoma

I'm considering belimumab, to treat SD and prevent lymphoma

I heard about a new treatment that will be coming to the market soon

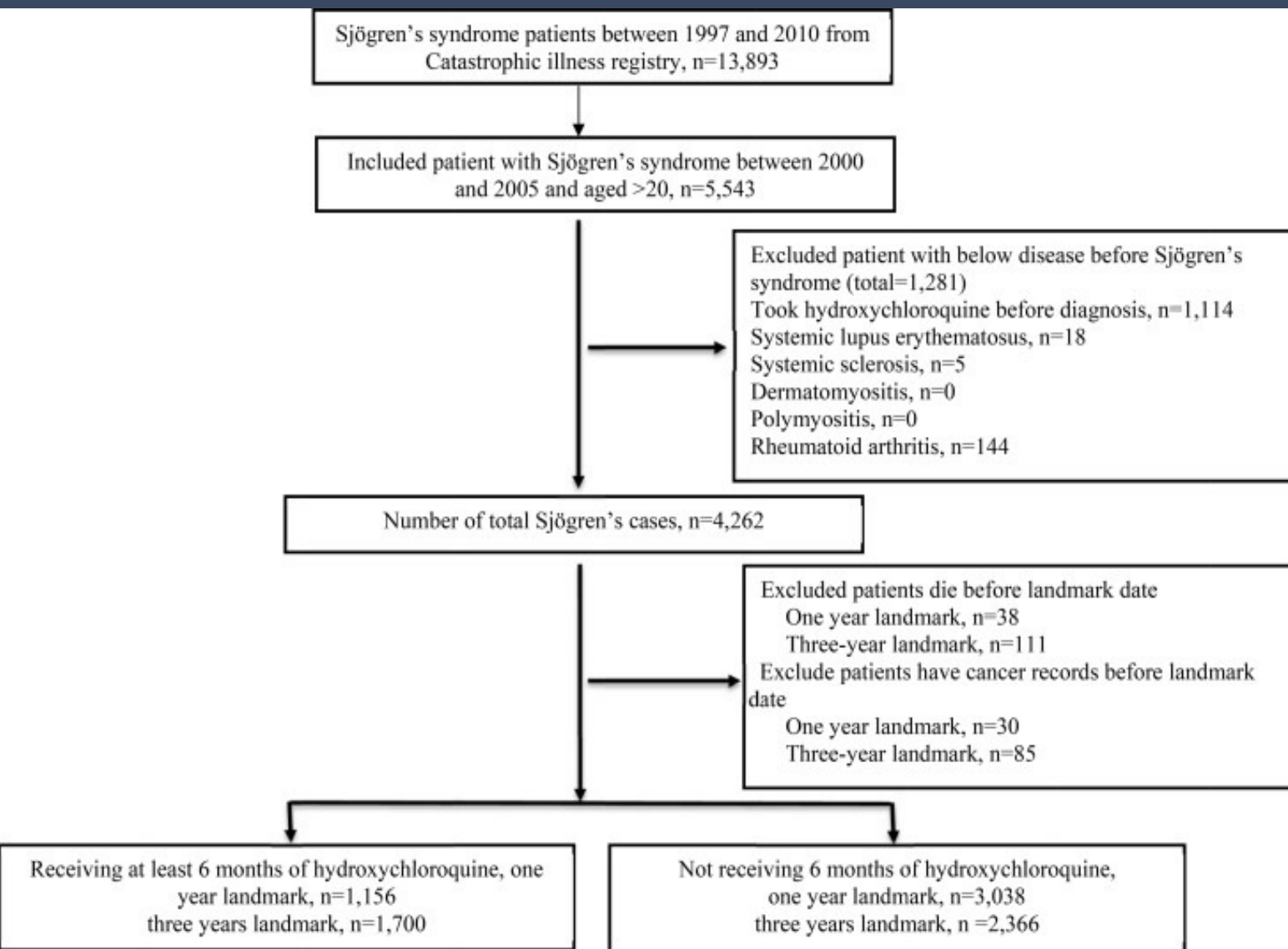
Hydroxychloroquine

Parameter, by Week	Placebo		Hydroxychloroquine		Differences in Changes From Baseline (Week 0) Score Adjusted on Baseline Score, Mean (95% CI)	P Value
	No.	Value, Mean (SD)	No.	Value, Mean (SD)		
ESSPRI^a						
0	62	5.85 (2.00)	55	5.87 (1.96)		
12	58	6.15 (1.72)	50	5.62 (2.14)	-0.57 (-1.10 to -0.05)	.03
24	52	5.58 (1.99)	51	5.81 (1.94)	-0.05 (-0.68 to 0.57)	.87
ESSDAI, median (25th-75th percentile)^b						
0	64	2.5 (2.0 to 6.0)	55	2.0 (0 to 5.5)		
12	43	2.0 (0 to 4.0)	39	2.0 (0 to 5.5)		
24	52	2.0 (0 to 5.3)	50	2.0 (0 to 3.0)		
12-0	43	0 (-2.0 to 0)	38	0 (-2.0 to 0)		.68
24-0	52	0 (-2.0 to 0)	49	0 (-2.0 to 0)		.63
ESR, mm						
0	58	21.0 (14.1)	56	21.5 (23.4)		
24	48	24.7 (16.6)	44	17.5 (21.0)	-7.8 (-12.0 to -3.7)	<.001
0, median (25th-75th percentile) ^c	58	20 (10 to 30)	56	13 (6 to 29)		
24, median (25th-75th percentile) ^c	48	22 (12 to 32)	44	11 (6 to 20)		
C-reactive protein, mg/L						
0	61	4.42 (3.38)	52	4.35 (4.31)		
24	45	6.91 (7.03)	46	4.42 (3.99)	-2.40 (-4.53 to -0.27)	.03
0, median (25th-75th percentile) ^c	61	4 (1 to 6)	52	4 (2 to 6)		
24, median (25th-75th percentile) ^c	45	5 (3 to 6)	46	4 (2 to 6)		
Serum IgG, g/L						
0	60	14.18 (5.74)	52	14.46 (6.11)		
24	46	14.01 (5.90)	48	13.37 (5.53)	-0.75 (-1.74 to 0.23)	.13
Serum IgA, g/L						
0	60	3.26 (1.74)	51	2.64 (1.16)		
24	45	3.08 (1.38)	48	2.86 (1.89)	0.03 (-0.27 to 0.32)	.85
Serum IgM, g/L						
0	60	1.40 (0.74)	52	1.29 (0.77)		
24	46	1.44 (0.68)	48	1.14 (0.75)	-0.19 (-0.31 to -0.06)	.004

No significant difference in reducing activity disease in the HCQ group comparing to Placebo at week 24

Ref: Effects of Hydroxychloroquine on Symptomatic Improvement in Primary Sjögren Syndrome, Randomized clinical trial, 2014, JAMA

Hydroxychloroquine



Follow up ~ 6 years with no significant difference in the HCQ users comparing to the non users in the incidence of lymphoma

Anti B-Cell therapies

- Rituximab :
 - Meta-analysis of the efficacy and safety of rituximab in the treatment of primary Sjogren's syndrome, Frontiers
 - 5 RCT with 340 patients
 - No significant improvement in ESSDAI , salivary and lacrimal tests
 - Reduction in IgG and B cell count
 - BUT 1st mAb approved for lymphoma treatment
- Belimumab :
 - BELISS open-label phase II study, 30 patients, 28 weeks evaluation after 24 weeks of IV treatment
 - safety profile
 - reduction of 30% in at list 2 VAS (fatigue , pain and dryness) in 60% of patients, ESSDAI significantly reduction
 - extension study at 52 weeks for responders at 28 weeks
 - no long-term evaluation for lymphoma but some reduction on B cell activation biomarker (ex IgG and RF)
 - modest reduction of ESSDAI > ESSPRI was maintained
- Ianalumab :
 - Safety and Efficacy of Ianalumab in patients with SD: 52 weeks results from a randomized, placebo-controlled , PII study
 - safety profile
 - ~40 patients, 300mg/4 weeks for 24weeks than switch to placebo or continuation for 52 weeks
 - significant reduction in ESSDAI, ESSPRI, patient and physician global assessments
 - some reduction in anti SSA/B Ab, RF, IgG

Conclusions:

- Aggressive SD are more prone to develop lymphoma
 - High ESSDAI, organ involvement, high biological activity
 - Development of follow up and treatment guidelines depending on cluster?
- 5-10% of SD patients develop lymphoma, mostly indolent form (MALT type)
- Treatment and prognosis are ~ comparable to lymphoma not related to SD
- Hydroxychloriquine : no evidence of efficacy in SD and probably no efficacy in reducing lymphoma risk BUT no good studies available
- Anti B cell therapy probably more helpful in reducing the clinical activity of the disease-> we can suppose that a reduction in SD activity can correlate with lymphoma risk reduction
 - some hope for the future with ianalumab