National University
of Athens
Greece

Sjögren's Syndrome

Clinical-Prognostic and therapeutic aspects

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November 2004

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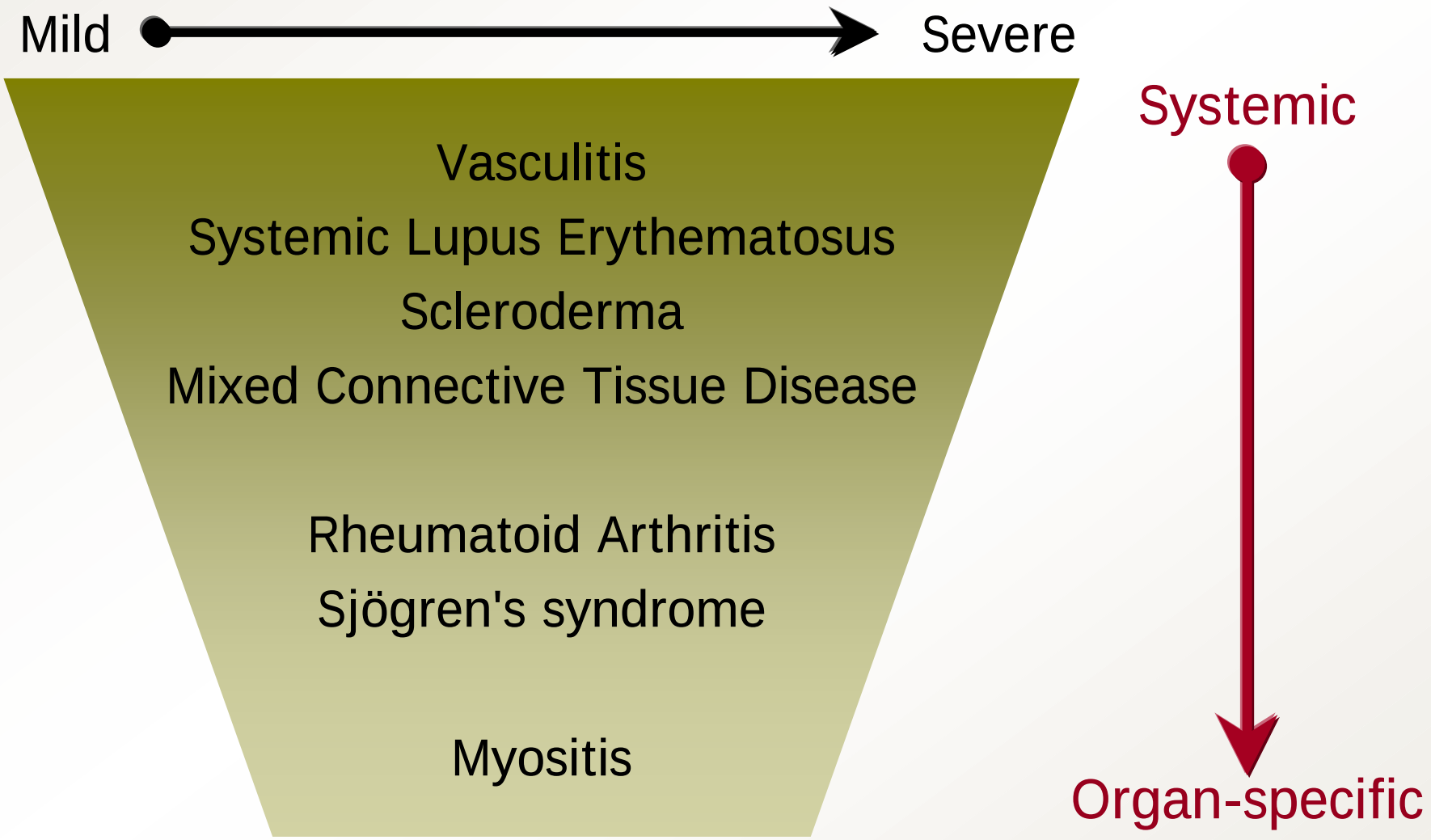
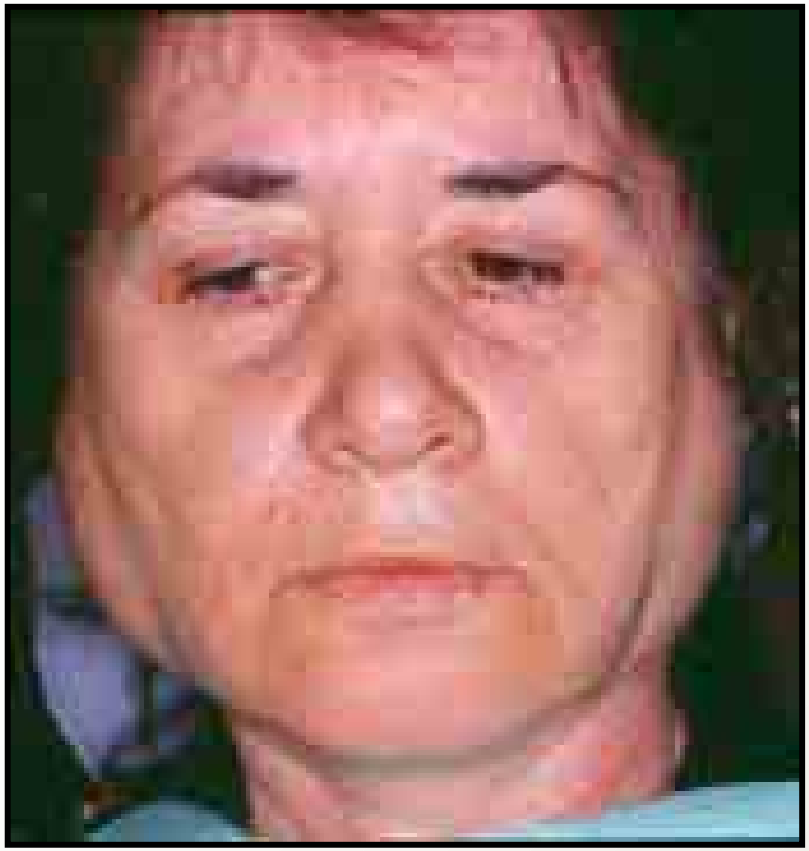
Pathophysiology
Medical School

Autoimmune Rheumatic Diseases



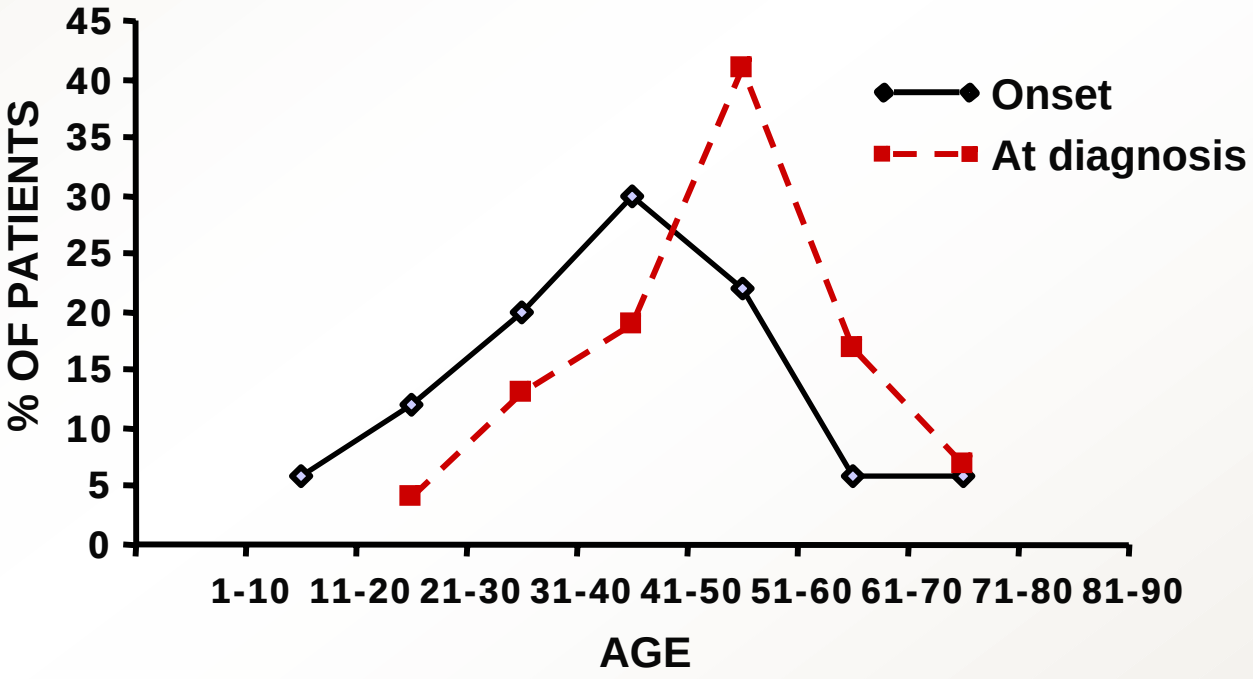
Sjögren's Syndrome – Autoimmune Epithelitis

- Female disease
  - ♀/♂ : 9/1
- Common
  - 0.5-1% of adult females
- 4^{th} -5^{th} decade of life
- Slowly progressive



Sjögren's Syndrome – Autoimmune Epithelitis

The frequency distributions of ages at onset of symptoms & at diagnosis of primary Sjögren's syndrome



Pavlidis et al, J Rheumatol 19982, 9:5

Sjögren's Syndrome – Autoimmune Epithelitis

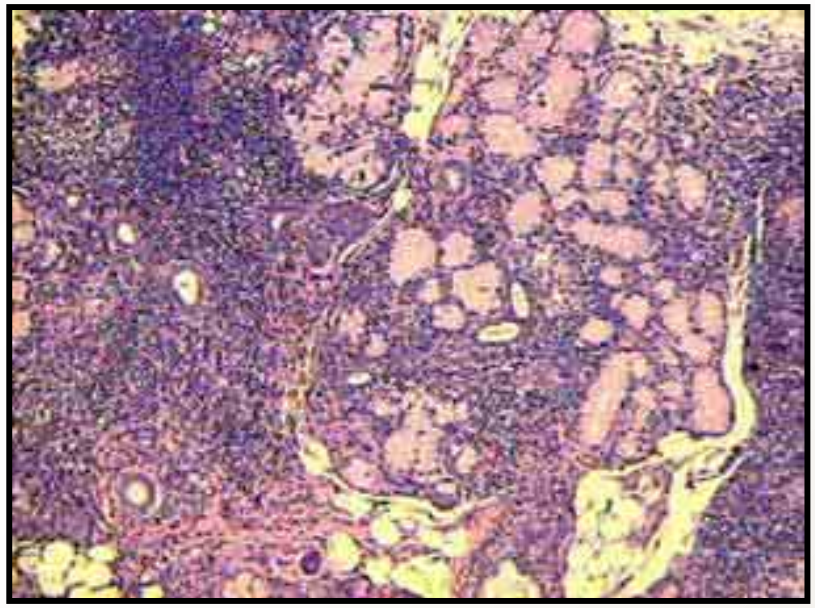
- Center of autoimmune disorders
  - alone (primary)
  - with other (secondary)
- Wide clinical spectrum
  - organ-specific
  - systemic
  - neoplasia
- Prototype autoimmune disease
  - humoral
  - cellular

Sjögren's Syndrome – Autoimmune Epithelitis

Autoantibodies	% positive
Rheumatoid factors (Igs)	80
Cryoglobulins (type II)	*30*
Ro/SSA	60
La/SSB	30
a-fodrin	95

Sjögren's Syndrome – Autoimmune Epithelitis

- Lymphocytic infiltrates with destruction of epithelial tissues
- B-lymphocytic hyperactivity



Labial Minor Salivary Gland

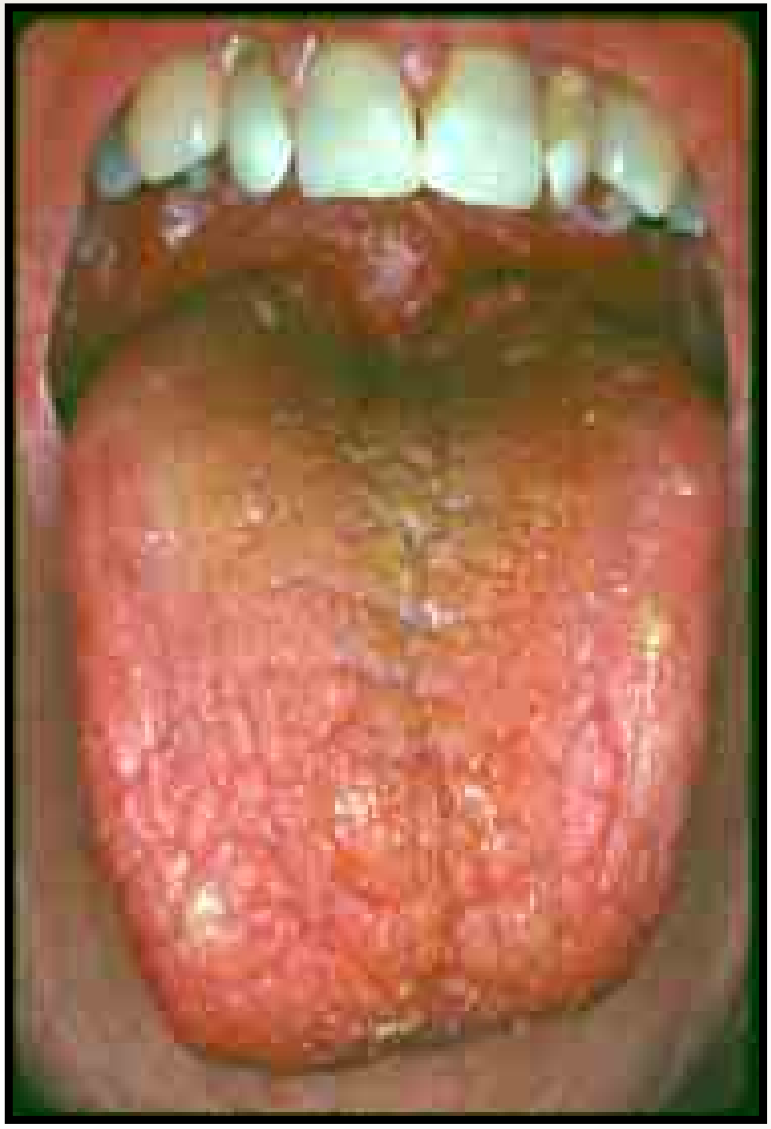
Sjögren's Syndrome – Autoimmune Epithelitis

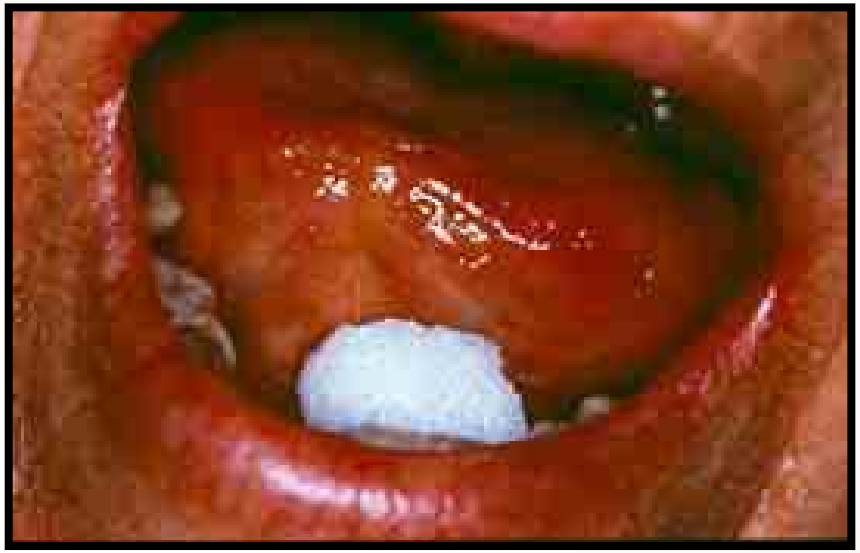
Glandular manifestations

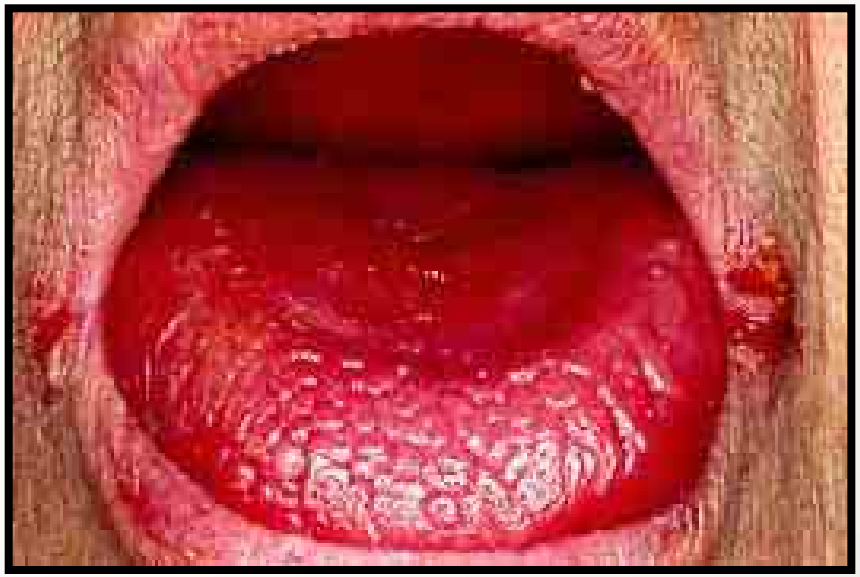
Salivary Gland Involvement

- Subjective:
  - Dry mouth
    - difficulty with chewing, swallowing
    - excessive fluid use
  - Intermittent parotid gland enlargement
- Objective:
  - Dry oral mucosa – mouth ulcers
  - Tongue
    - red
    - devoid of epithelium
    - cracked “crocodile skin”
  - Teeth
    - multiple caries
    - early loss
  - Parotid gland enlargement
  - Tests

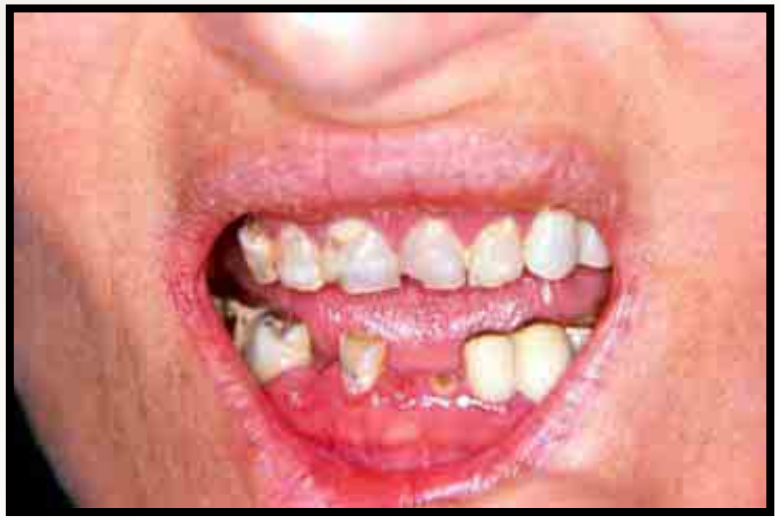
Sjögren's syndrome – autoimmune epithelitis

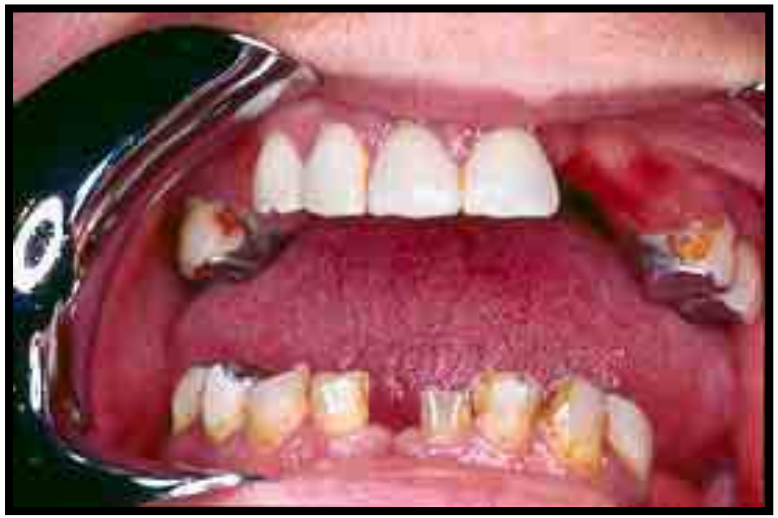


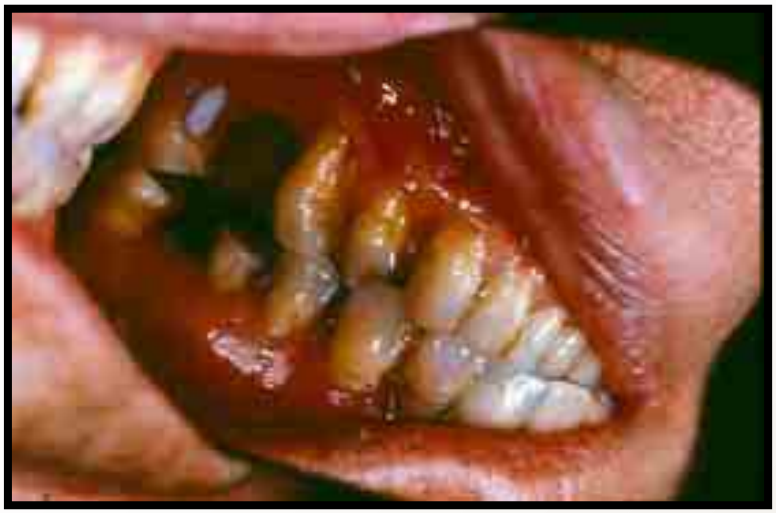




Sjögren's syndrome – autoimmune epithelitis

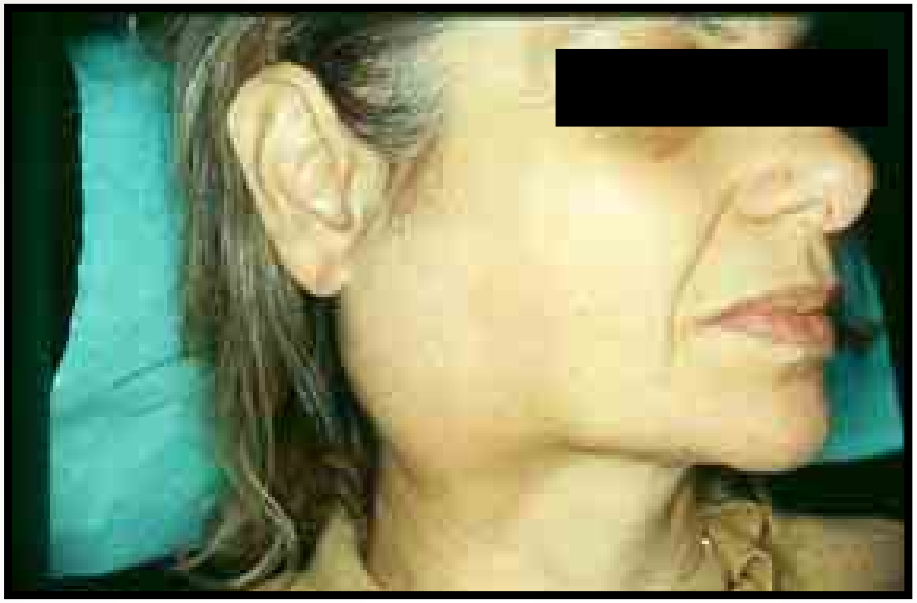


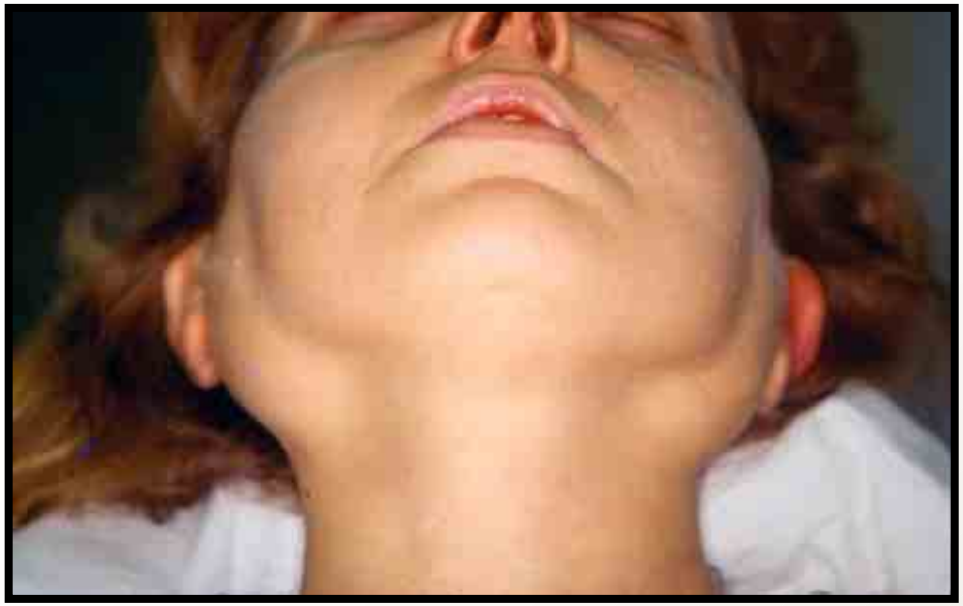




Sjögren's syndrome – autoimmune epithelitis

Parotid gland enlargement





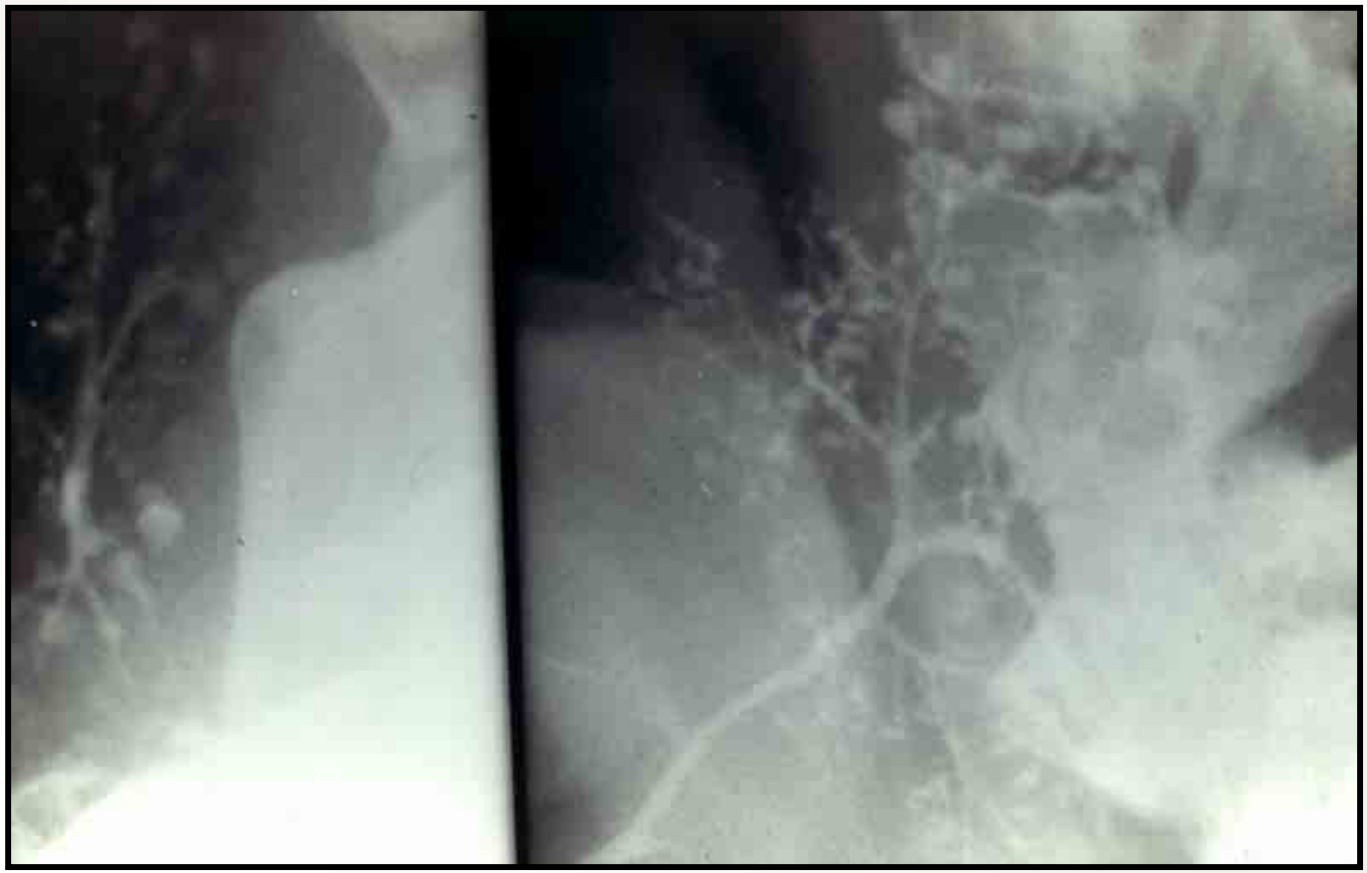
Sjögren's syndrome – autoimmune epithelitis

Salivary flow:

- Stimulated
- Unstimulated

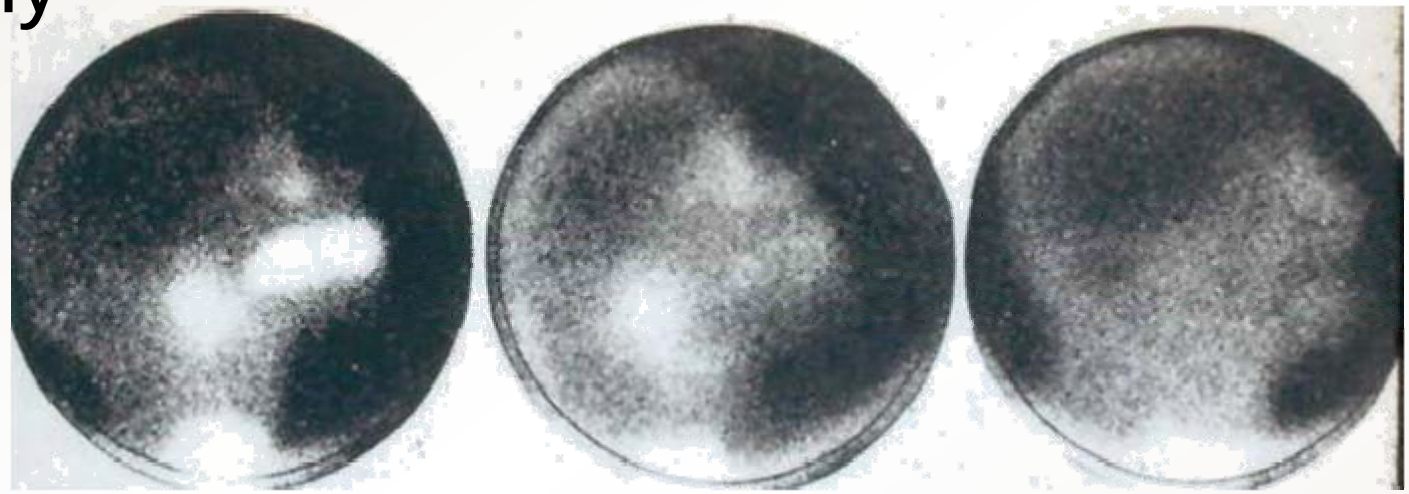
Sjögren's syndrome – autoimmune epithelitis

Sielography



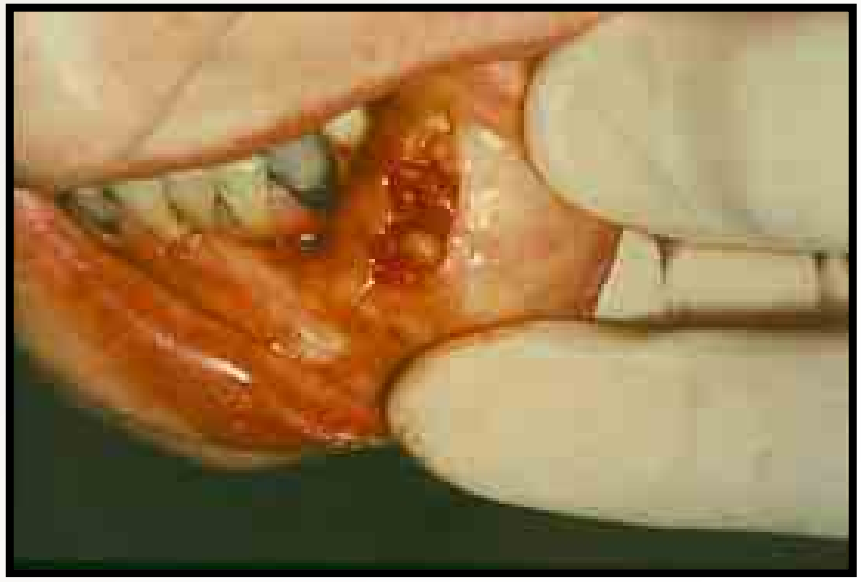
Sjögren's syndrome – autoimmune epithelitis

Scintigraphy

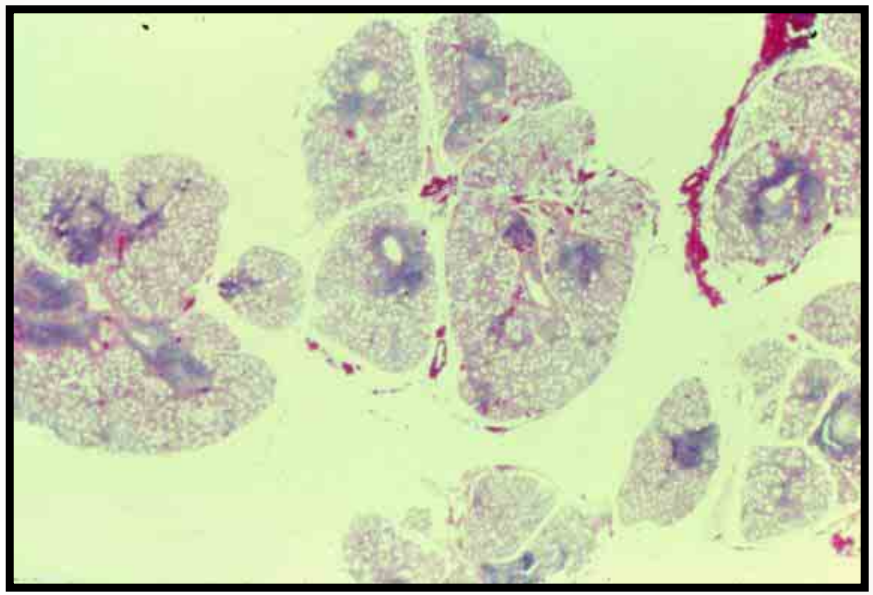


Scintigraphy diagnosis	Normal	Moderate involvement	Marked involvement
Degree of xerostomia	None	Mild	Severe
Salivary flow rate *(ml/5-min/gland)*	1.60	0.42	0.00

Sjögren's Syndrome – Autoimmune Epithelitis



Salivary gland biopsy



Chilsom focus score ≥ 1

foci/4mm^2

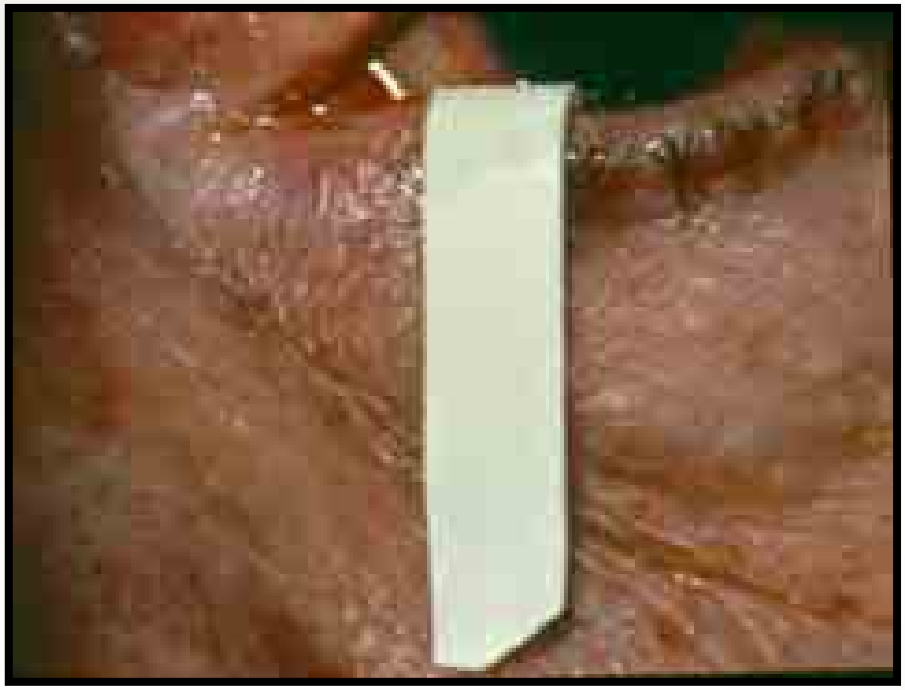
Sjögren's Syndrome – Autoimmune Epithelitis

Glandular manifestations

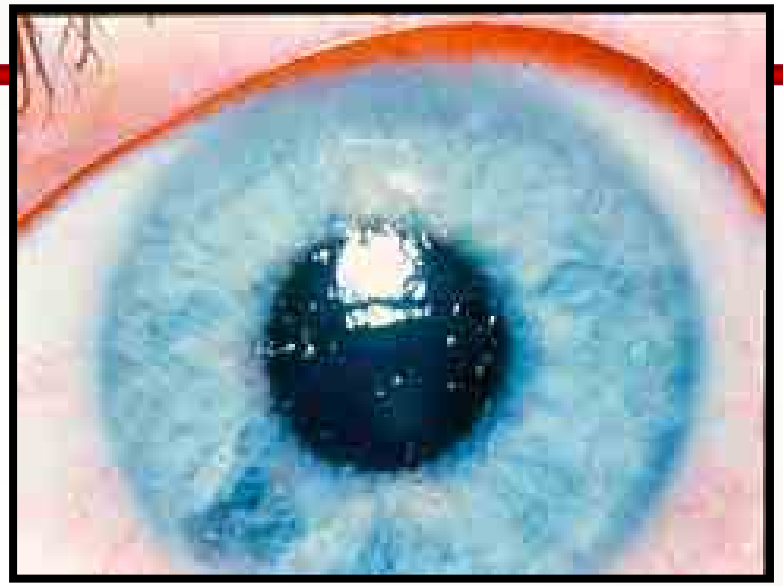
Lacrimal Gland Involvement

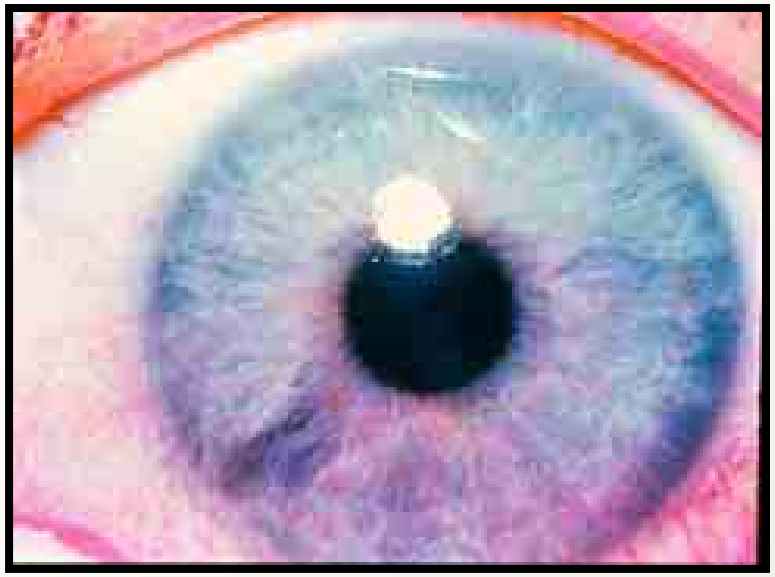
- Subjective:
  - Foreign body sensation { "gitty" / "sandy" }
  - Lack of tearing → "sticky" eyelids
- Objective:
  - Conjunctival injection
  - Lacrimal gland enlargement (rare)
  - <u>Keratoconjuctivitis sicca</u>

Sjögren's syndrome – autoimmune epithelitis



Schirmer's test





Rose-Bengal staining

Sjögren's Syndrome – Autoimmune Epithelitis

The American-European Consensus Group classification criteria

I. Ocular symptoms: a positive response to at least one of the three following questions:

- Have you had daily, persistent, troublesome dry eyes for more than 3 months?
- Do you have a recurrent sensation of sand or gravel in the eyes?
- Do you use tear substitutes more than three times a day?

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

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

III. Ocular signs: objective evidence of ocular involvement defined as a positive result in at least one of the following two tests:

- Schirmer's I test, performed without anesthesia (≤ 5 mm in 5 minutes) ¶
- Rose-Bengal score or another ocular dye score (≥4 according to van Bijsterveld's scoring system)

IV. Histopathology: presence of focal lymphocytic sialadenitis in minor salivary glands (obtained through normal-appearing mucosa), evaluated by an expert histopathologist with a focus score ≥1, defined as a number of lymphocytic foci which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes per 4 mm2 of glandular tissue.

V. Salivary gland involvement: objective evidence of salivary gland involvement defined as a positive result in at least one of the following three diagnostic tests:

- Unstimulated salivary flow (≤ 1,5 ml in 15 minutes)
- Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts.
- Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer.

VI. Autoantibodies: presence in the serum of the following autoantibodies:

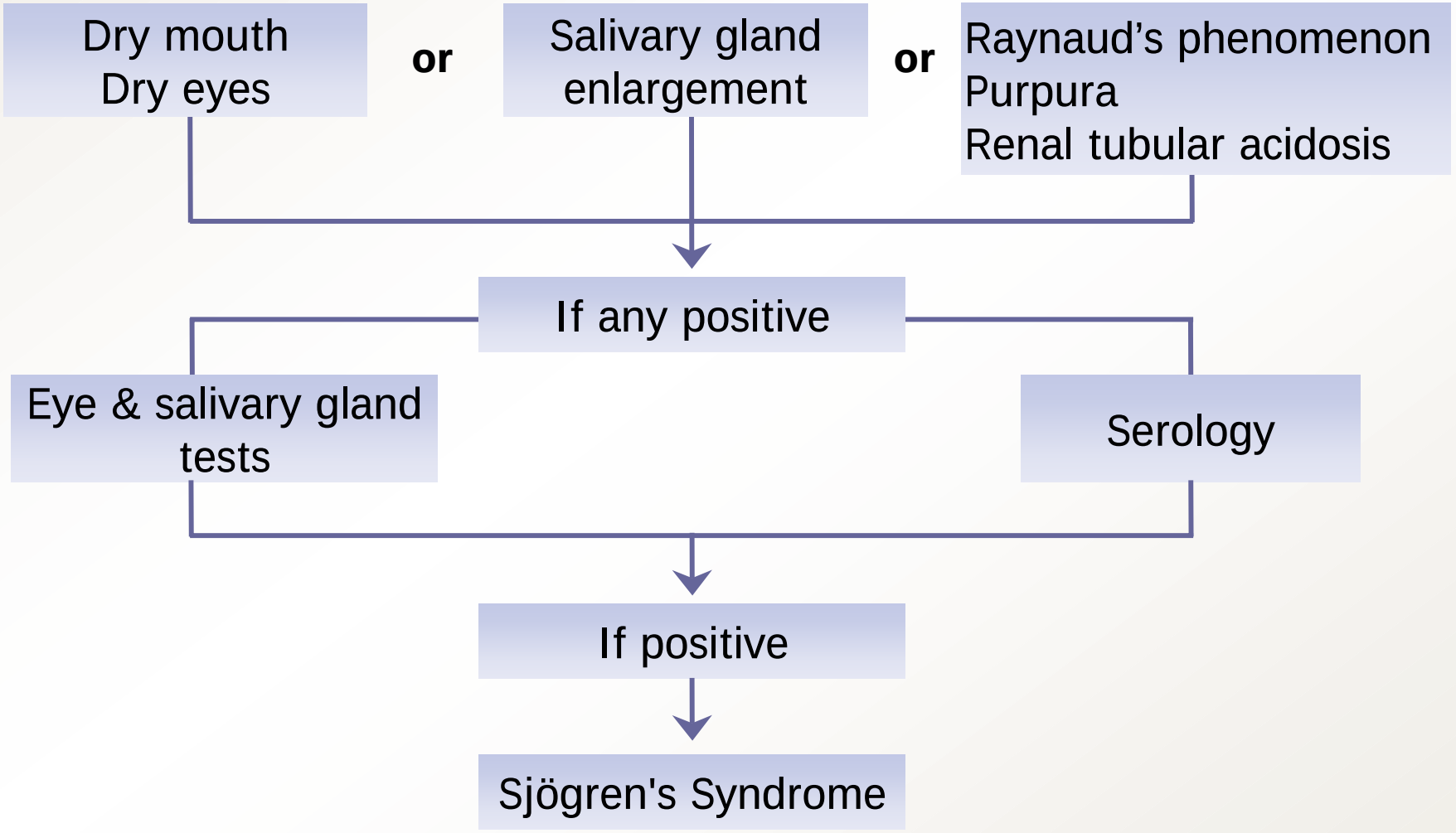
- Antibodies to Ro(SSA) or La(SSB) or both

Rules for classification: In patients without any potentially associated disease the presence of any four of the six items is indicative of definitive primary Sjogren's syndrome. In patients with a potentially associated disease (for instance another connective tissue disease) item-1 or item-2 plus any two from items 3, 4, 5 is indicative of secondary Sjogren's syndrome.

Exclusion criteria : prior head and neck irradiation, pre-existing lymphoma, acquired immunodeficiency disease (AIDS), hepatitis C infection, sarcoidosis, graft-versus-host disease, sialoadenosis, use of neuroleptic, anti-depressant, anti-hypertensive or parasympatholytic drugs.

Sjögren's Syndrome – Autoimmune Epithelitis

Algorithm for the diagnosis



Diseases mimicking clinically Sjögren's Syndrome

- HIV, HCV infection
- Sarcoidosis
- Amyloidosis
- Lipoproteinemia IV & V
- Chronic graft-versus-host disease
- Lymphoproliferative disorders

Sjögren's Syndrome

Differential Diagnosis with HIV Infection

HIV Infection and Sicca Syndrome	Sjögren's Syndrome	Sarcoidosis
Predominant in young males	Predominant in middle-aged women	Invariable
Lack of autoantibodies to Ro/SS-A and/or La/SS-B	Presence of autoantibodies	Lack of autoantibodies to Ro/SS-A and/or La/SS-B
Lymphoid infiltrates of salivary glands by CD8+ lymphocytes	Lymphoid infiltrates of salivary glands by CD4+ lymphocytes	Granulomas in salivary glands
Association with HLA-DR5	Association with HLA-DR3 and –DRw52	Unknown

Primary Sjögren's Syndrome

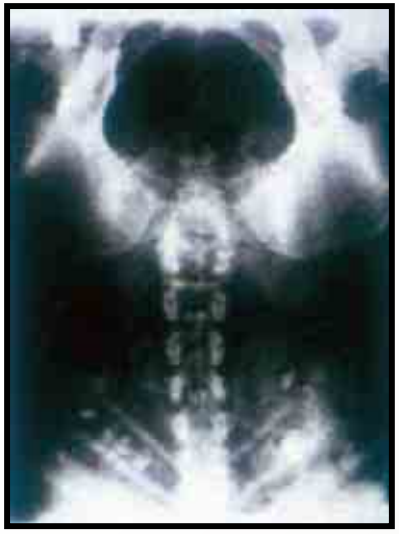
Systemic manifestations	Frequency (%)
Arthralgia/arthritis	60
Raynaud's phenomenon	30
Purpura/Vasculitis	15 (1)
Lung involvement	10 (25)
Kidney involvement	8 (25)
Liver involvement	5
Muscle involvement	1

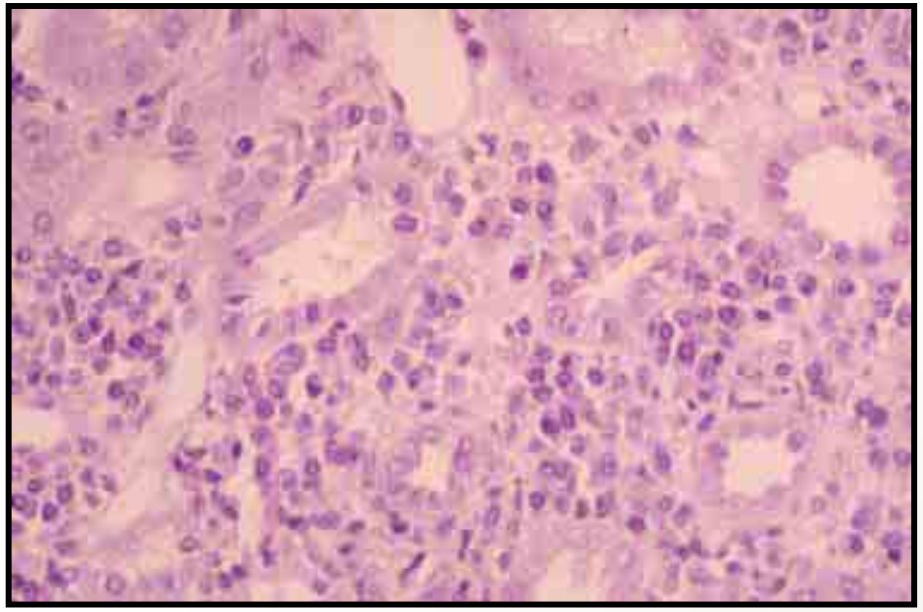
Skopouli et al., Semin Arthritis Rheum. 2000, 29:296

Primary Sjögren's Syndrome

Renal Involvement

- Interstitial nephritis (25%)
  - Asymptomatic-subclinical
  - Proximal tubular acidosis
  - Distal tubular acidosis
  - Nephrocalcinosis
- Glomerulonephritis (2.5%)
  - Membranoproliferative
  - Membranous
  - Messangioproliferative

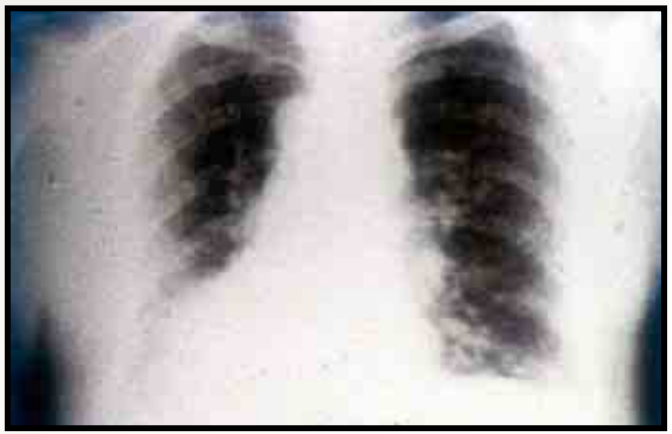




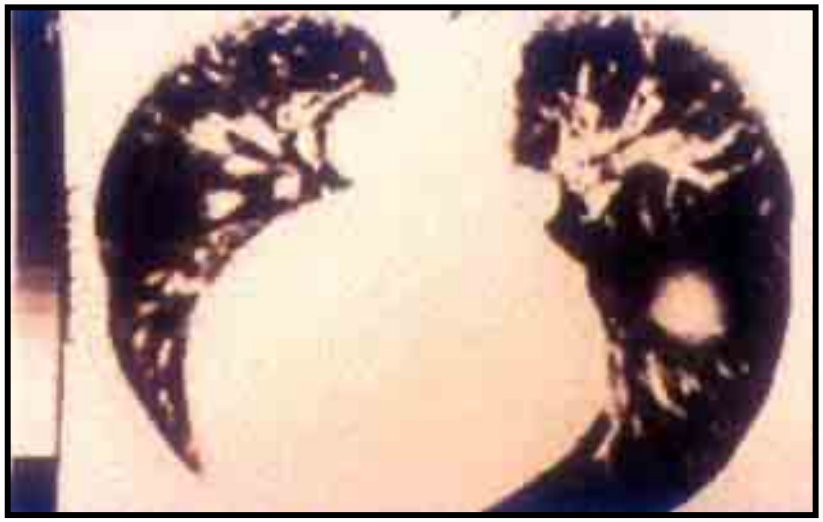
Systemic manifestations	N *(n=10)*	GMN *(n=10)*	Statistical significance
Age (mean SD)	37±12	46±7	P=0.063
Years after disease onset	2±3	8±6	P=0.001
Cryoglobulins	20	80	P=0.023

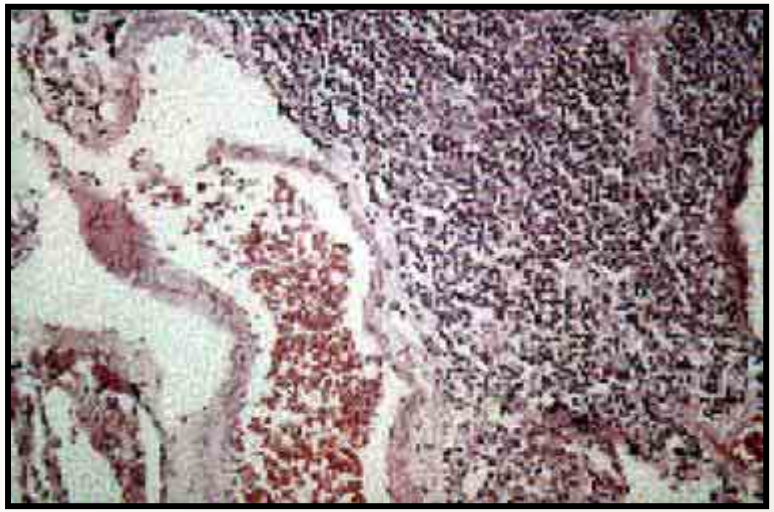
Primary Sjögren's Syndrome

Pulmonary Involvement



Pulmonary function		Patients	Controls
FEV..L	%pred	96±16	111±13
$MEF_{50}Lsec^{-1}$	%pred	72±25	103±17
$MEF_{20}Lsec^{-1}$	%pred	50±18	98±20
DLCO	%pred	85±18	95±22
PaO_2	mmHg	84±13	ND

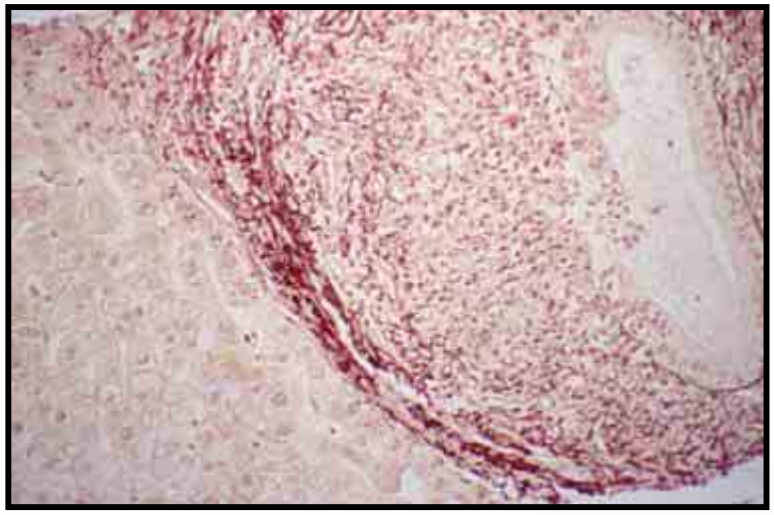




Primary Sjögren's Syndrome

Liver Involvement

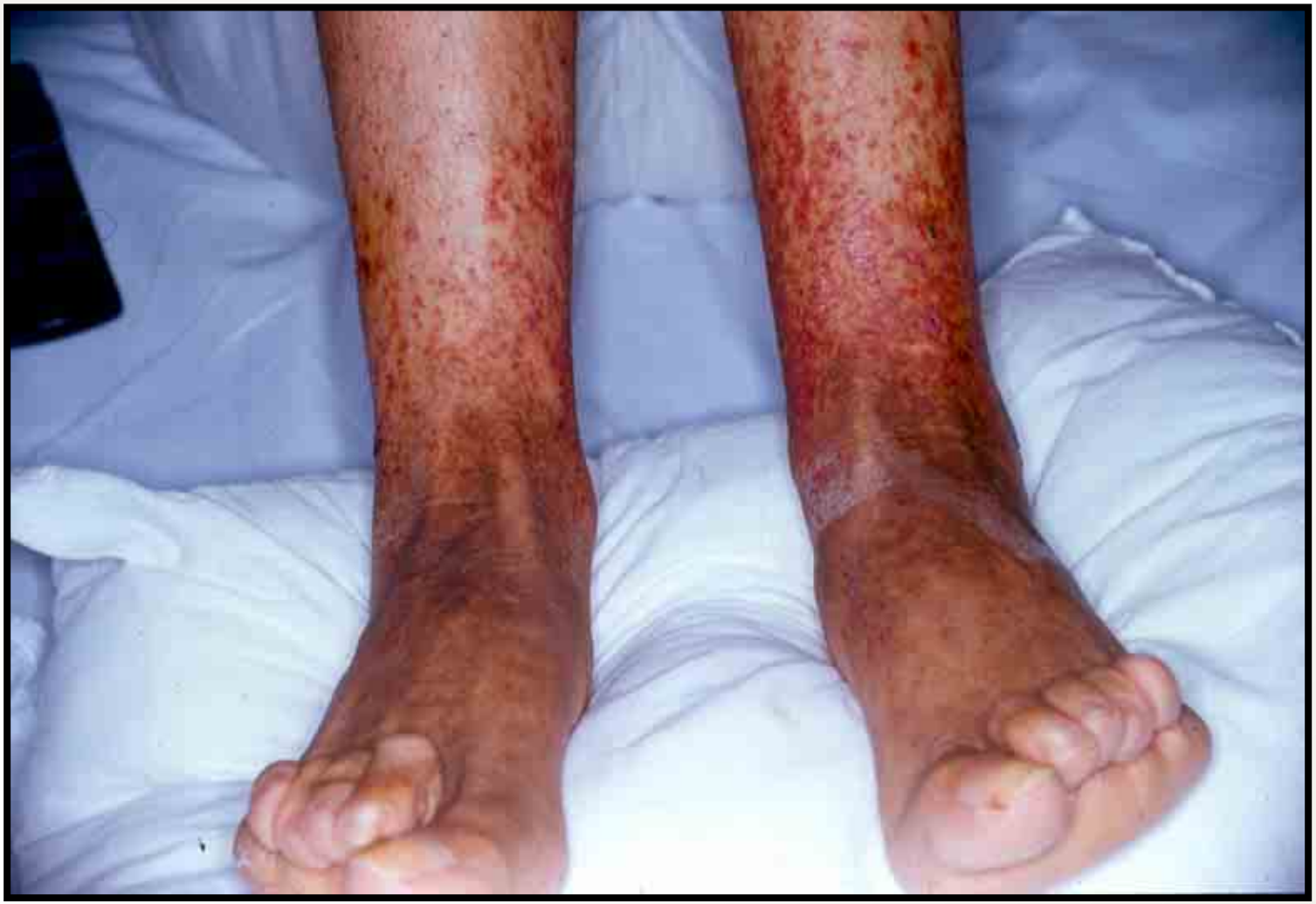
Number of patients	300
Clinical symptoms & signs of liver involvement	2%
↑ Liver enzymes	5%
Antimitochondrial antibodies (AMA)	7%



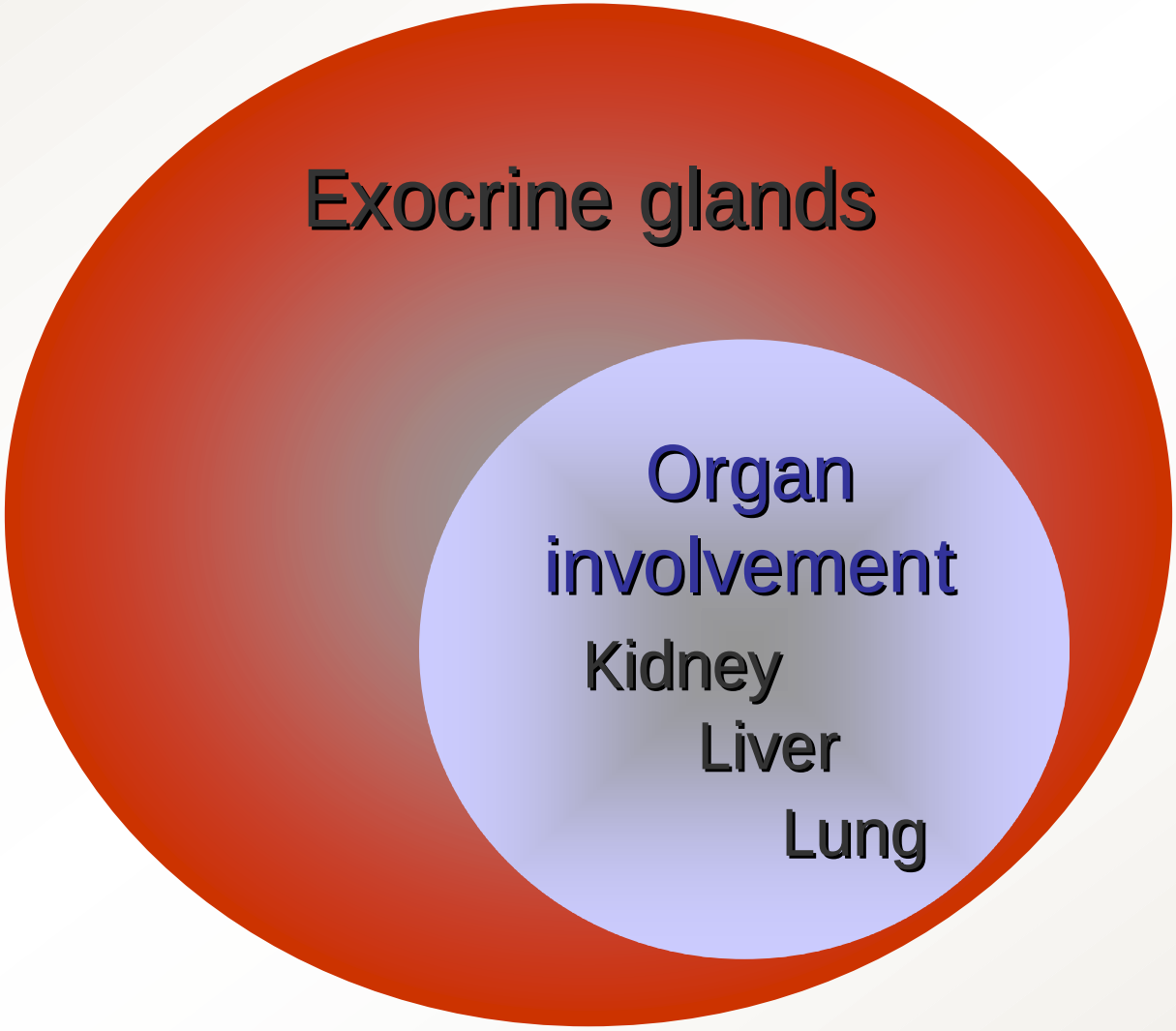
	Patients (percent)	
	AMA(+),20	AMA(-),250
Clinical symptoms & signs of liver involvement	20	0.3
↑ Liver enzymes		
• AST	41	15
• ALT	50	15
• ALP	64	0
Liver histology		
• Primary billiary chirrosis	82	0
• Chronic active hepatitis	0	0.3
• Viral hepatitis	0	1

Primary Sjögren's Syndrome

Purpura



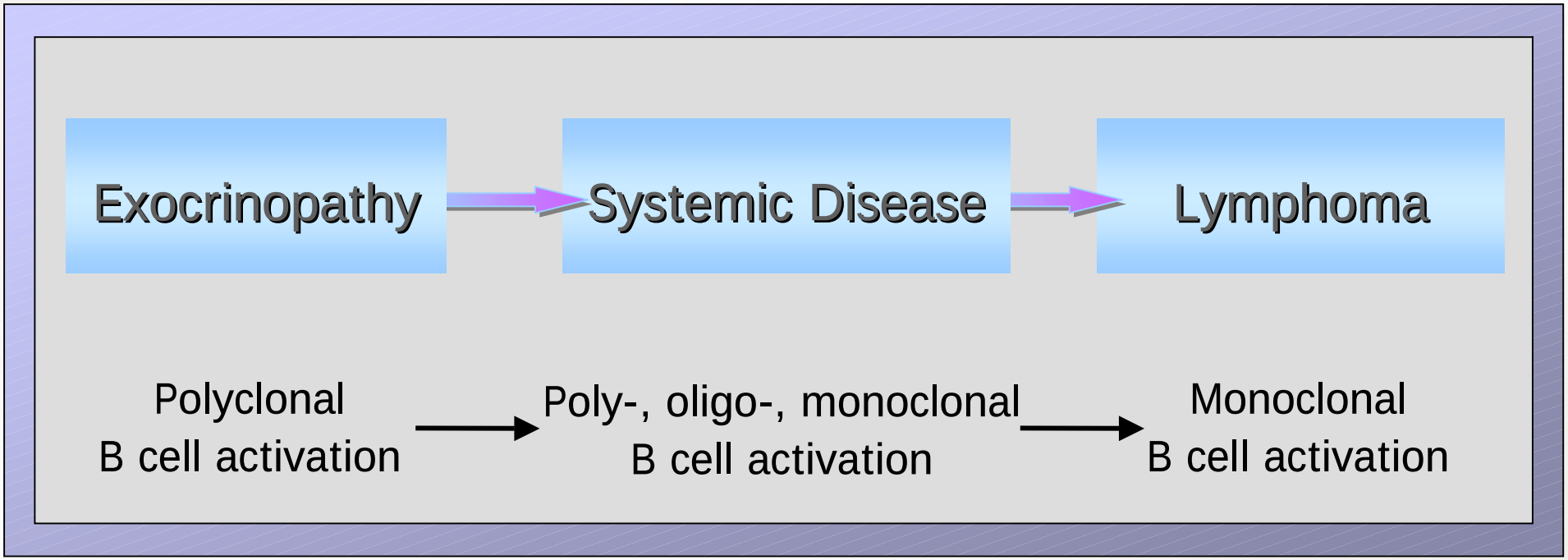
Sjögren's Syndrome



Autoimmune Epithelitis

Sjögren's Syndrome – Autoimmune Epithelitis

Evolution



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Primary Sjögren's Syndrome

Clinical evolution, morbidity and mortality

Study Characteristics

- 261 patients with primary SS
  - 1981-1995
  - mean follow-up time 3.6 years
- Evolution of the clinical picture and laboratory profile
- Incidence and predictors for systemic disease
- Impact of SS on overall survival

Skopouli et al., Semin Arthritis Rheum 2000; 29: 296

Primary Sjögren's Syndrome

Clinical evolution, morbidity and mortality

(261 patients)

- Time interval from the first symptoms to diagnosis:
  - mean: 6 years (*interquartile range:2-8 years*)
- Follow-up from the time of diagnosis
  - mean: 3.6 years (*interquartile range: 2-5 years*)
- Total reported duration of symptoms
  - mean: 9.5 years (*interquartile range: 5-12 years*)

Skopouli et al., Semin Arthritis Rheum 2000; 29: 296

Primary Sjögren's Syndrome

Manifestations referred as first symptoms and at diagnosis (261 patients)

	first symptoms	at diagnosis
	patients (%)	
Dry eyes	46.5	95
Dry mouth	41.5	90
Parotid gland enlargement	16.2	49
Arthralgia/arthritis	33.8	70
Raynaud's phenomenon	19.2	41
Dry cough	3	30
Dyspareunia	3.9	29
Purpura	1	10

Skopouli et al., Semin Arthritis Rheum 2000; 29: 296

Primary Sjögren's Syndrome

Clinical manifestations at diagnosis and at the end of the follow-up (261 patients)

	Diagnosis	End of follow-up
	patients (%)	
Arthralgia/arthritis	70	75
Raynaud's phenomenon	41	48
Purpura	10	11
Pulmonary involvement (small airway disease)	19	23
Primary biliary cirrhosis	4	4
Renal involvement		
interstitial	7	9
glomerulonephritis	0.4	2
Peripheral Neuropathy	1	2
Lymphoproliferative disorders	2	4

Skopouli et al., Semin Arthritis Rheum 2000; 29: 296

Primary Sjögren's Syndrome

Laboratory findings at diagnosis and at the end of the follow-up (261 patients)

	Diagnosis	End of follow-up
	patients (%)	
Rheumatoid factor	58	61
ANA	83	89
a-Ro/SSA	53	56
a- La/SSB	28	30
C3<50 mg/dl	1	2
C4<20 mg/dl	15	17
Cryogrlobulins		
Polyclonal	3	5
Monoclonal	5	9

Skopouli et al., Semin Arthritis Rheum 2000; 29: 296

Primary Sjögren's Syndrome

Glandular manifestations are present at the time of diagnosis

Systemic manifestations

- Arthritis
- Raynaud’s phenomenon
- Interstitial nephritis
- Liver involvement

Serologic profile

Did not change during follow-up

Skopouli et al., Semin Arthritis Rheum 2000; 29: 296

Primary Sjögren's Syndrome

Predictors of various outcomes at time of diagnosis

Outcome	Predictor	P-value	Relative Risk
Lymphoproliferative disease	Low C4 levels	0.016	7.5
	Monoclonal cryoglobulins	0.0012	7.9
	Palpable purpura	0.015	5.0
Glomerulonephritis	Low C4 levels	0.015	8.6
	Monoclonal cryoglobulins	0.03	6.5
	Palpable purpura	0.0024	16.3
Death	low C4 levels	0.014	4.9

Cox regression analysis

Skopouli et al., Semin Arthritis Rheum 2000; 29: 296

Primary Sjögren's Syndrome

Milestones of lymphoproliferation

- 1964: Description of the first cases with lymphoma *(Bunim & Talal)*
- 1978: Increased risk of lymphoma in SS *(Kassan et al)*
- 1979: Lymphoma in SS in a B-cell lymphoma *(Zulman et al)*
- 1989-1991: Monoclonal expansion of B-cell takes place in the affected exocrine glands (Fieshlander et al, Moutsopoulos et al)
- 1998 - : Prediction models of poor outcome in large patient cohorts

Primary Sjögren's Syndrome

Limitations for studying lymphoma

- Low incidence of SS *(0.5 – 1.4%)*
- Risk of lymphoma *(6.4 cases/1000 per year)*

ARTHRITIS & RHEUMATISM
Vol. 42, No. 8, August 1999, pp 1765–1772
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MALIGNANT LYMPHOMA IN PRIMARY SJÖGREN'S SYNDROME

A Multicenter, Retrospective, Clinical Study by the European Concerted Action on Sjögren's Syndrome

MICHALIS VOULGARELIS, URANIA G. DAFNI, DAVID A. ISENBERG, HARALAMPOS M. MOUTSOPOULOS, and the MEMBERS OF THE EUROPEAN CONCERTED ACTION ON SJÖGREN'S SYNDROME

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- **University College, London, UK :** D.A. Isenberg, N. Sutcliffe
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  - **Centre Hospitalier Universitaire de Brest, France** : P. Youinou
  - **University Hospital MAS, Malmo, Sweden** : E. Theander, R. Manthorpe

Primary Sjögren's Syndrome

Malignant Lymphoma (n=33)

Demographic characteristics	
Age (years)	58 (range 33-82)
Race	Caucasians
Gender	♀/♂ : 29/4
Median time SS to lymphoma diagnosis	7.5 years

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Malignant Lymphoma (n=33)

Sjögren's syndrome diagnostic criteria	%
Ocular symptoms	93
Oral symptoms	94
Ocular signs *(Schirmer's and/or Rose Bengal tests)*	96
Oral signs *(Unstimulated parotid FR and/or parotid scintigraphy)*	85
Minor salivary gland biopsy	97
Autoantibodies:	
ANA	91
RF	82
anti-Ro/La	69

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Malignant Lymphoma

Salivary gland involvement	%
Major salivary gland	91
Parotid gland	86
Bilateral	84
Permanent	28
Submandibular gland	17
Lacrimal gland	7

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Malignant Lymphoma (n=33)

Systemic manifestations	%
Arthralias/ Arthritis	75
Fatigue	68
Raynaud's phenomenon	49
Cutaneous vasculitis	33
Lung involvement	31
Low grade fever	25
Peripheral nerve involvement	24
Thyroid involvement	21
Kidney involvement	18
Liver involvement	6

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Malignant Lymphoma

Histological classification (WHO-REAL)

Grade		%
High:	Immunoblastic	24
	MALT	
Intermediate:	Follicular, large cell	6
	Diffuse, large	
Low:	Small lymphocytic	70
	Lymphoplasmacytic	
	Mixed follicular monocytoid B-cell	
	MALT	

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Clinical characteristics of lymphoma

		%
Performance status (ECOGScale)	0-1	82
	2-3	18
B-symptoms		24
Location	Nodal	18
	Extranodal	36
	Both	45
Mass size (>7cm)		16

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Clinical characteristics of lymphoma

Nodal involvement

Lymphadenopathy	%
Peripheral	86
cervical	
supraclavicular	
axillary	
Abdominal	29
Mediastinal	38
Hilar	43

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Clinical characteristics of lymphoma

Extranodal involvement

Extranodal site	%
Salivary gland	58
Stomach	13
Nasopharynx	6
Skin	6
Lung	6
Liver	3
Bone marrow	3
Lacrimal gland	3

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Malignant Lymphoma (n=33)

Laboratory findings	
Anemia	48%
Lymphopenia	78%
Cryoglobulinemia	50%
Hypogammaglobulinemia	10%

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Lymphoma – Causes of death

(9/33 patients)

Histological classification	Causes related to:		Unrelated
	lymphoma	treatment	
Low	1	0	4
High/intermediate	3	1	0

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

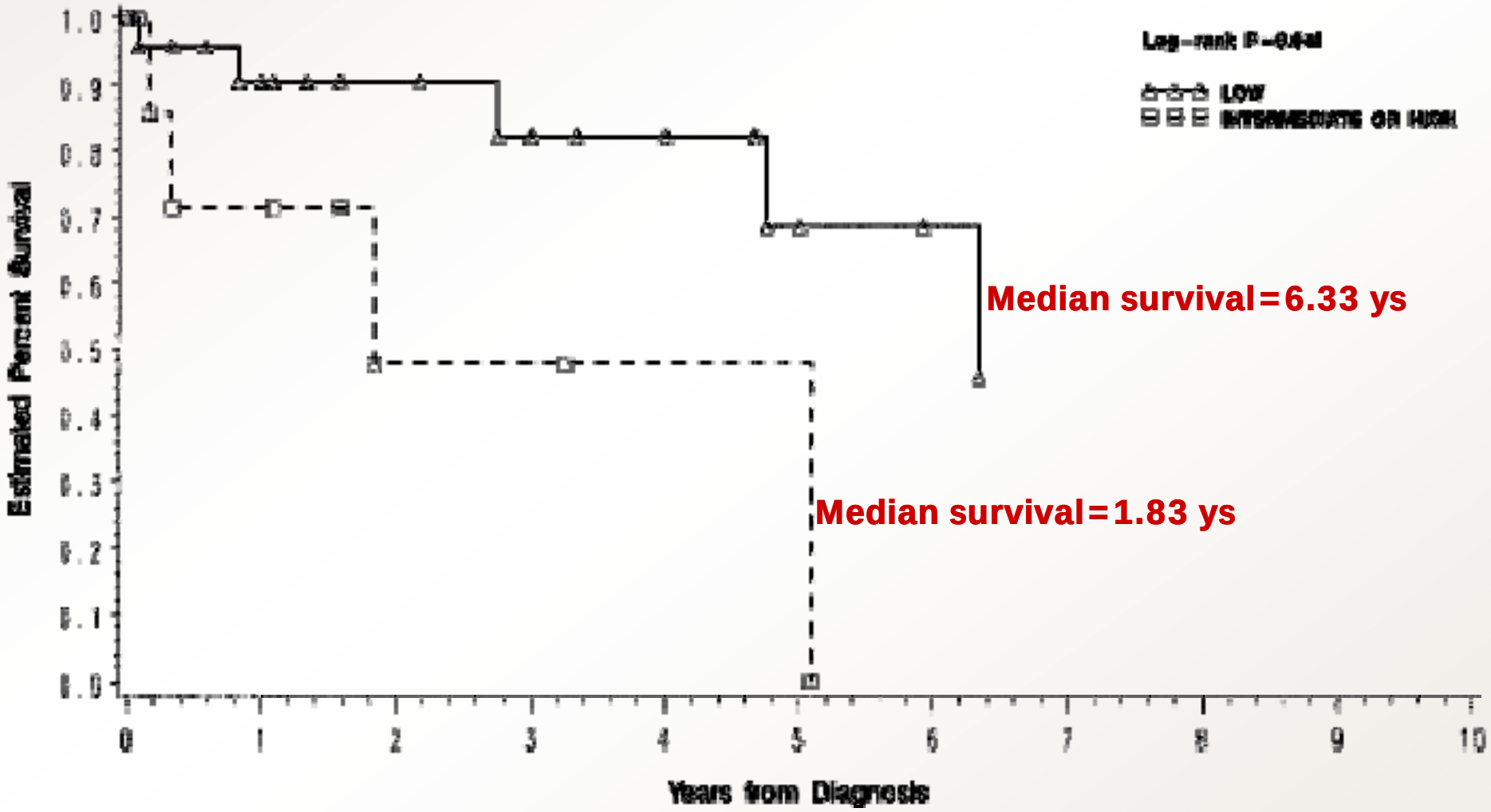
Lymphoma – Factors of increased death risk

Variable	Risk ratio	p-value
B-symptoms	9.2	0.017
Mass size>7cm	7.7	0.046
Histologic grade (*high/intermediate*)	4.1	0.06

Voulgarelis et al., Arthritis Rheum. 1999;42:1765

Primary Sjögren's Syndrome

Lymphoma



Voulgarelis et al., Arthritis Rheum. 1999;42:1765

ARTHRITIS & RHEUMATISM
Vol. 46, No. 3, March 2002, pp 741–747
DOI 10.1002/art.10221
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Long-Term Risk of Mortality and Lymphoproliferative Disease and Predictive Classification of Primary Sjögren's Syndrome

John P. A. Ioannidis,[1] Vassilios A. Vassiliou,[2] and Haralampos M. Moutsopoulos[2]

Primary Sjögren's Syndrome

Study Characteristics

Aim: Determination of incidence and predictors of adverse long-term outcomes in Sjögren's Syndrome

- 723 consecutive patients with primary Sjögren's syndrome
- 4384 person-years
- Determination of mortality rate
- Determination of lymphoproliferative disease rate
- Development of a rational predictive classification for the syndrome

Ioannidis et al., Arthritis Rheum. 2002;46:741

Primary Sjögren's Syndrome

Long-term outcome

- 38 Lymphoproliferative disorders (4%)
- 39 Deaths
- Mortality ratio: 1.15 *(95% CI 0.86-1.73)*
- Probability for lymphoma development:
  - 2.6% at 5 years
  - 3.9% at 10 years

Ioannidis et al., Arthritis Rheum. 2002;46:741

Primary Sjögren's Syndrome

Long-term outcome

- 7 out of 39 deaths was attributable to lymphoma
- All patients who developed lymphoma resulting in death had either:
  - Low C4 levels or
  - Palpable purpura at the first study visit

Ioannidis et al., Arthritis Rheum. 2002;46:741

Primary Sjögren's Syndrome

Outcome of patients with SS/Lymphoma

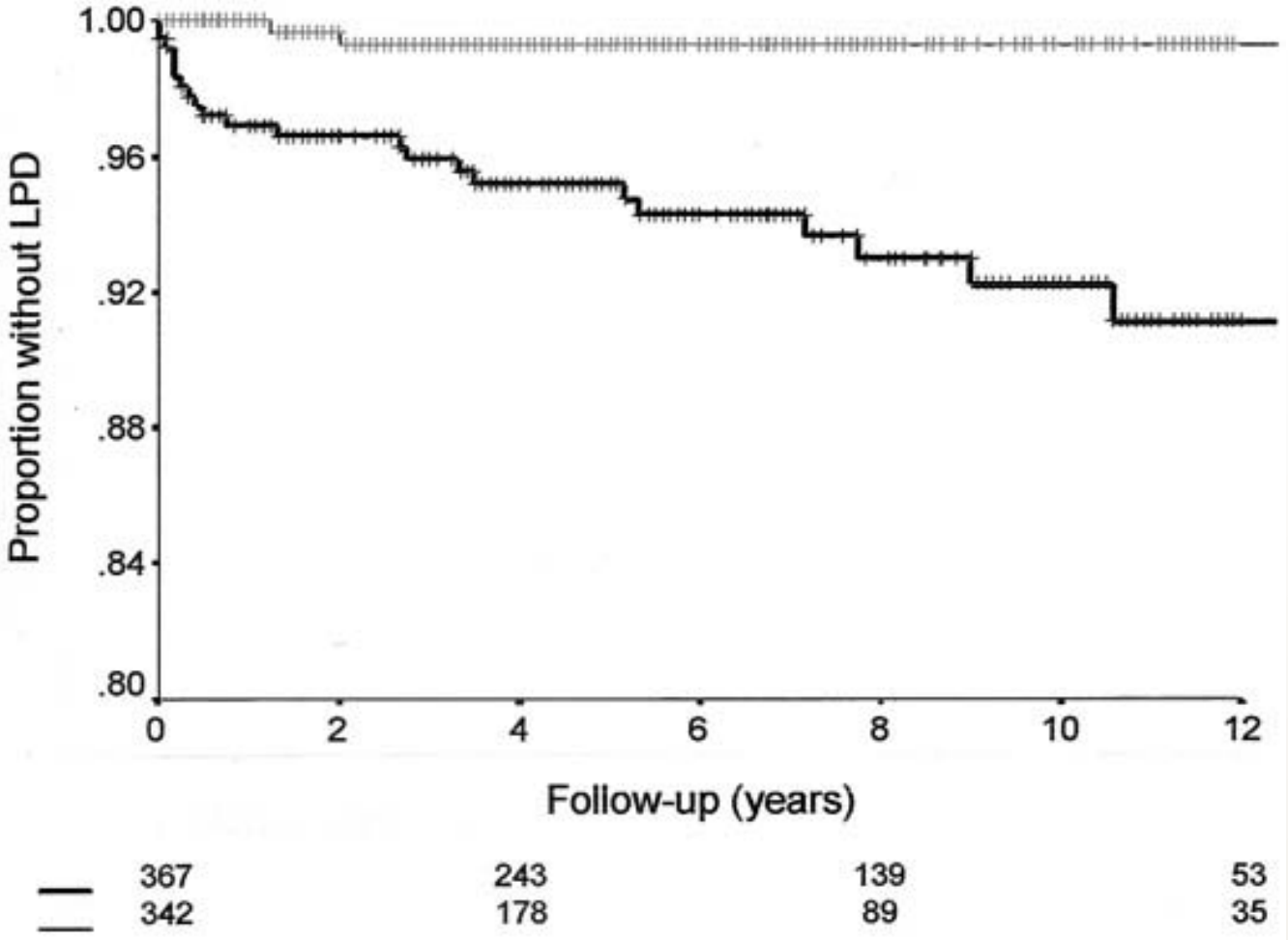
The lymphoproliferative disease was independently predicted by:

- Parotid gland enlargement (Hazard ratio: 5.21)
- Palpable purpura (Hazard ratio: 4.16)
- Low C4 levels (Hazard ratio: 2.40)

Ioannidis et al., Arthritis Rheum. 2002;46:741

Primary Sjögren's Syndrome

Probability of lymphoma development in patients with and without risk factors



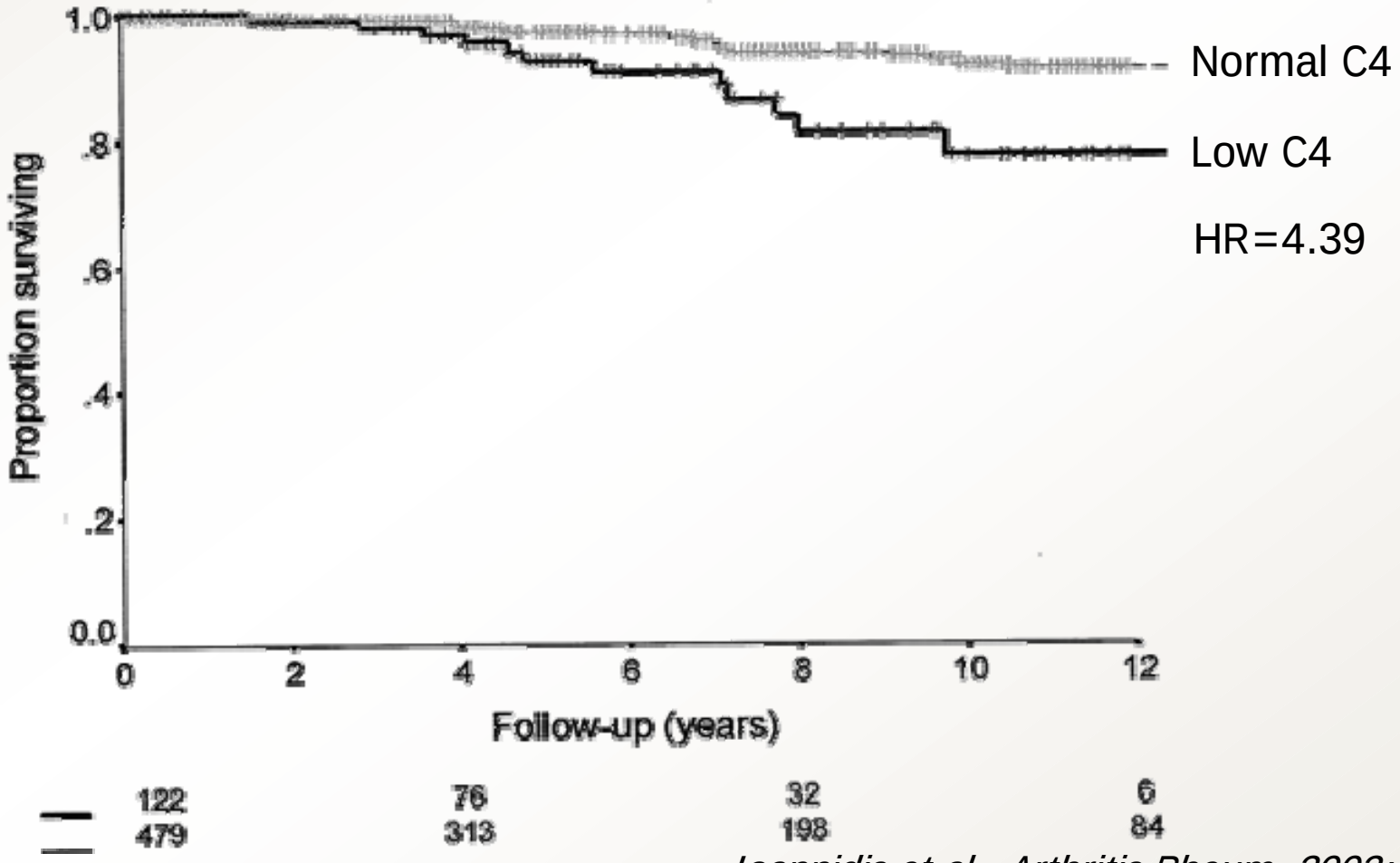
No risk factors

PGE or
Palpable purpura or
Low C4

Ioannidis et al., Arthritis Rheum. 2002;46:741

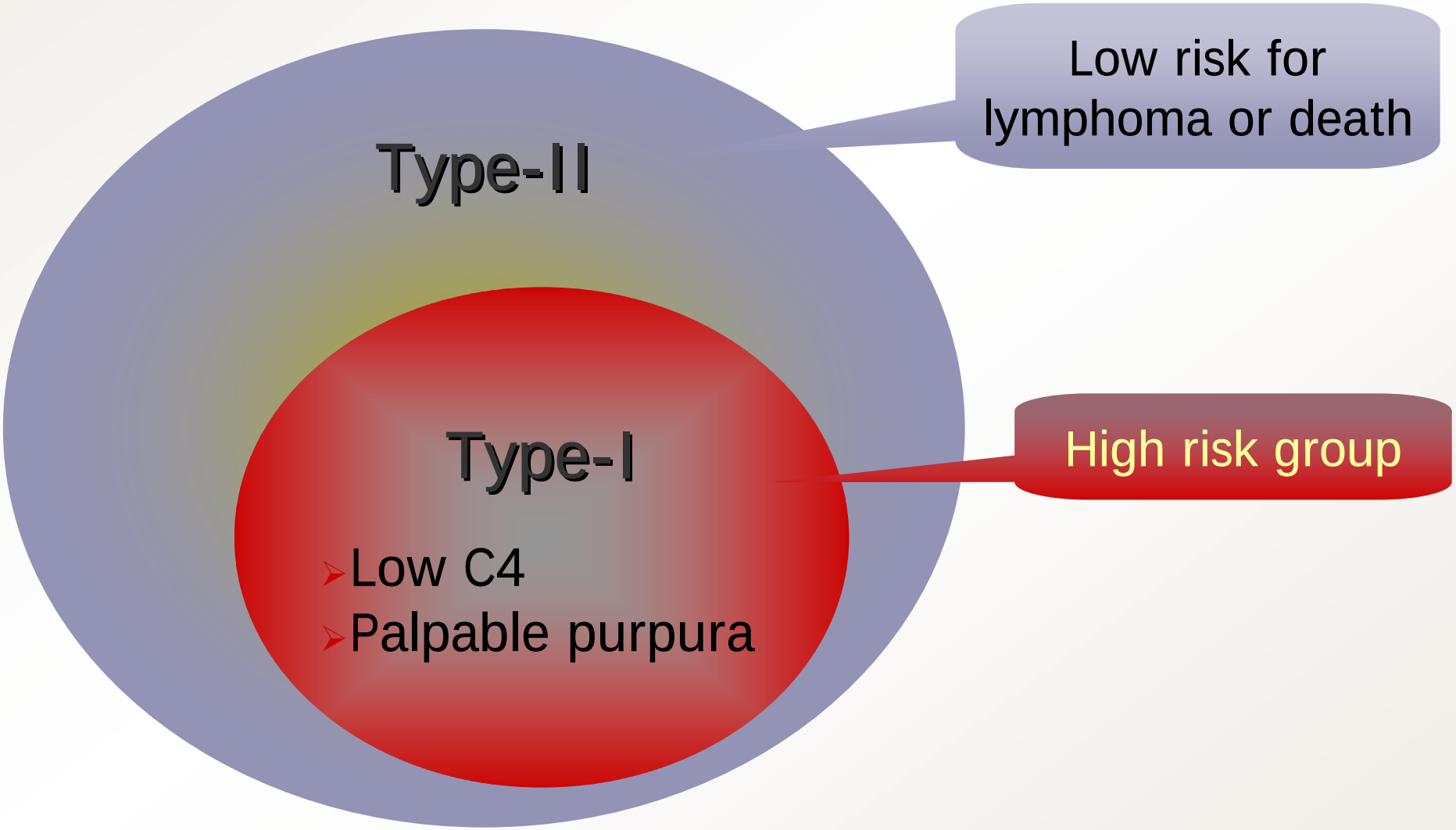
Primary Sjögren's Syndrome

The mortality rate was signifficantly higher in patients with low C4 levels



Ioannidis et al., Arthritis Rheum. 2002;46:741

Sjögren's Syndrome - Autoimmune Epithelitis



Sjögren's syndrome

Therapy

- Collaboration
  - Rheumatology
  - Ophthalmology
  - Oral medicine – Dentistry
  - Other medical specialties
- Empirical - symptomatic

Sjögren's syndrome – Therapy

Glandular manifestations

- Stimulation
- Replacement
- Support
- Immunomodulation?

Sjögren's syndrome – Therapy

Treatment of xerostomia

- Oral hygiene to prevent dental caries
- Early diagnosis and treatment of oral candidiasis
- Saliva substitutes
- Systemic stimulation of glandular secretions

Sjögren's syndrome – Therapy

Treatment of xerophthalmia

- General measures and replacement therapy
- Protective bicarbonate buffer solutions
- Stimulators of tear production
  - Local : Cyclosporine A
  - Systemic: Pilocarpine, Cimeviline
- Operative procedures

Sjögren's Syndrome-Therapy

Keratoconjuctivitis sicca - Xerophthalmia

Pilocarpine hydrochloride

Contra-indications

- Uncontrolled hypertension
- Heart failure – arrhythmias
- GI ulcers – chololithiasis
- Pregnancy

Sjögren's syndrome – Therapy

Systemic stimulation of glandular secretions

Pilocarpine tablets for the treatment of dry mouth and eyes of Sjogren's Syndrome: Randomized, placebo-controlled, fixed-dose, multicenter trial

Vivino et al, Arch Intern Med 1999, 159:174

Sjögren's syndrome

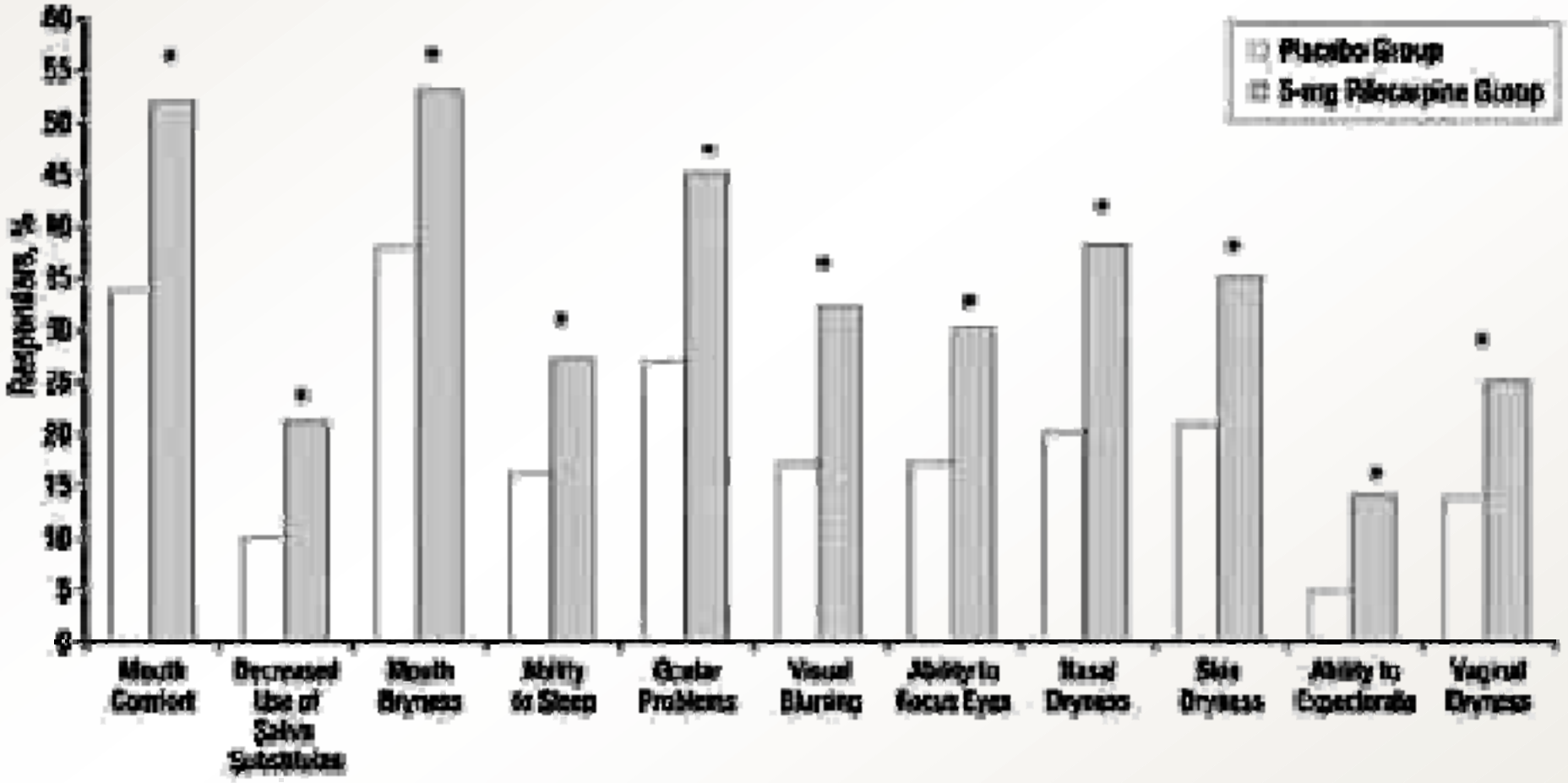
Patient Disposition

Status	Placebo *(n=125)*	Pilocarpine *2.5mg (n=121)*	Pilocarpine *5mg (n=127)*
	% positive		
Completed	90	84	87
Discontinued	10	16	13
Adverse reactions	6	7	7

Vivino et al, Arch Intern Med 1999, 159:174

Sjögren's syndrome – Therapy

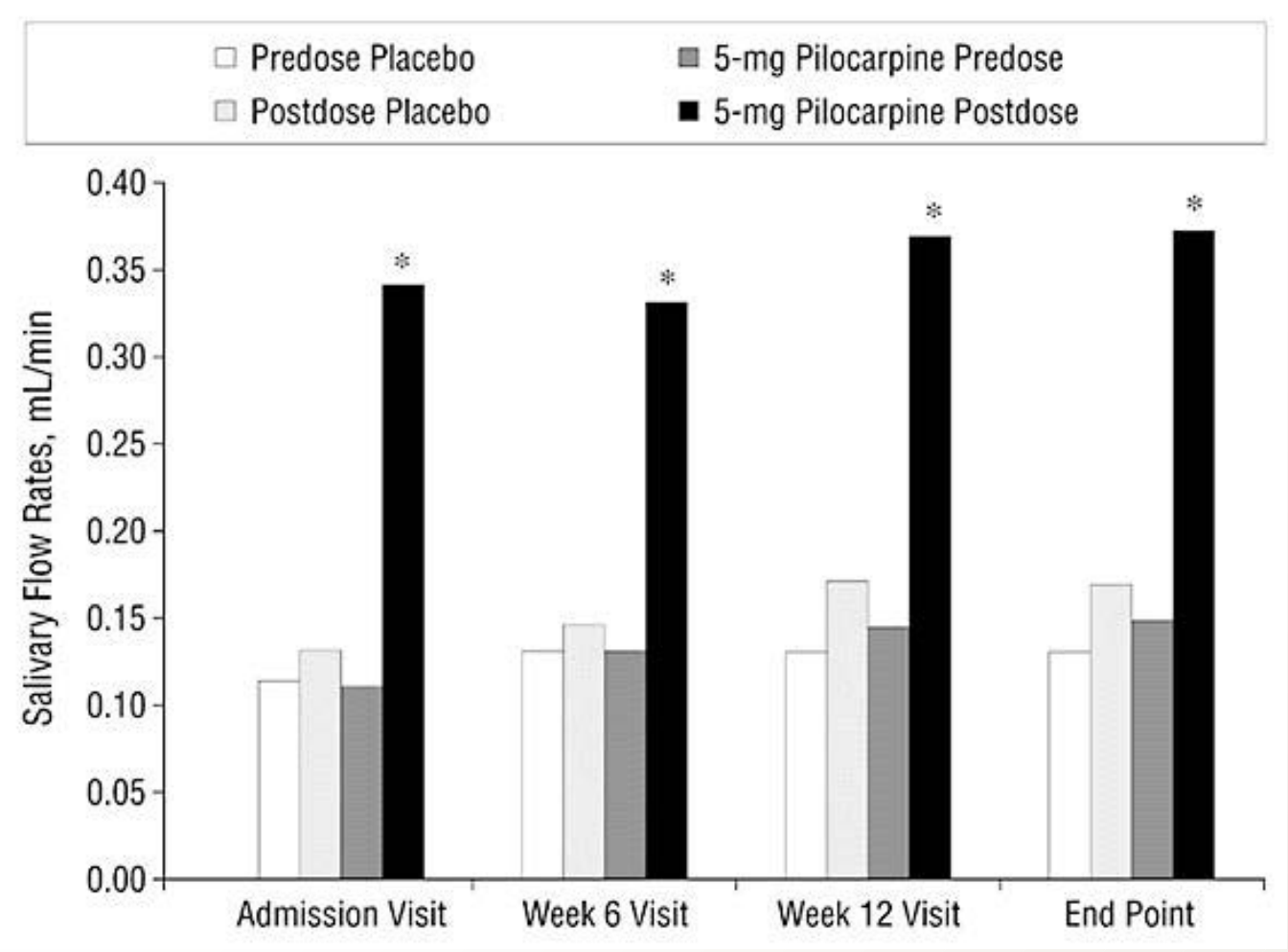
Pilocarpine treatment



Vivino et al, Arch Intern Med 1999, 159:174

Sjögren's syndrome – Therapy

Pilocarpine treatment



Vivino et al, Arch Intern Med 1999, 159:174

Sjögren's syndrome

Incidence of Adverse Reactions

Adverse reactions	Placebo	Pilocarpine		Overall P
		2.5mg	*5mg*	
	n=125	*n=121*	*n=127*	
		% patients		
Sweating	7	11	43	0.001
Headache	25	21	16	0.20
Flu syndrome	9	13	14	0.38
Nausea	9	12	12	0.62
Urinary frequency	2	11	10	0.01

Vivino et al, Arch Intern Med 1999, 159:174

Sjögren's syndrome – Therapy

Parotid gland Enlargement

- self-limited
- tender – persistent
  - Local moist heat
  - Antibiotic Therapy
  - NSAID
  - R/O lymphoma

Sjögren's Syndrome-Therapy

Sicca Manifestations

Immunomodulation:

- Methotrexate

  (Clin Exp Rheumatol 1996, 4:555)

- Nandrolone decanoate

  (Clin Exp Rheumatol 1988, 6:53)

- Cyclosporine A

  (Ann Rheum Dis 1986, 45:732)

- Infliximab

  (Arthritis Rheum 2001, 44:2371)

Sjögren's syndrome - Therapy

Musculoskeletal manifestations

- Arthralgias – non erosive arthritis
  - Hydroxychloroquine (*200mg daily*)
  - Methotrexate (*0,2mg/kg body weight/week*)
- Raynaud's phenomenon
  - avoidance of physical or emotional stress
  - nifedipine (*5-10mg/x3 daily*)

Sjögren's Syndrome-Therapy

Parenchymal organ involvement

Lungs, Kidneys, Liver

- Slow process
- Usually does not lead to organ failure

Skopouli et al., Semin Arthritis Rheum. 2000, 29:296

- Lack of controlled therapeutic trials
- Corticosteroids ineffective-dangerous?

Sjögren's Syndrome-Therapy

Systemic Vasculitis

- Corticosteroids
- Cyclophosphamide
- Plasmapheresis

Sjögren's Syndrome -Therapy

Aggressive B-cell non-Hodgkin's lymphomas

Combined B-cell depletion therapy and CHOP

AIMS: To evaluate...

- the efficacy of CHOP plus rituximab
  - 6 patients with Diffuse Large B-cell Lymphoma
  - 9 patients treated with CHOP alone
- Patients' outcome
- Clinical and serological picture of SS patients that received combination treatment

Sjögren's Syndrome

Aggressive B-cell non-Hodgkin's lymphomas

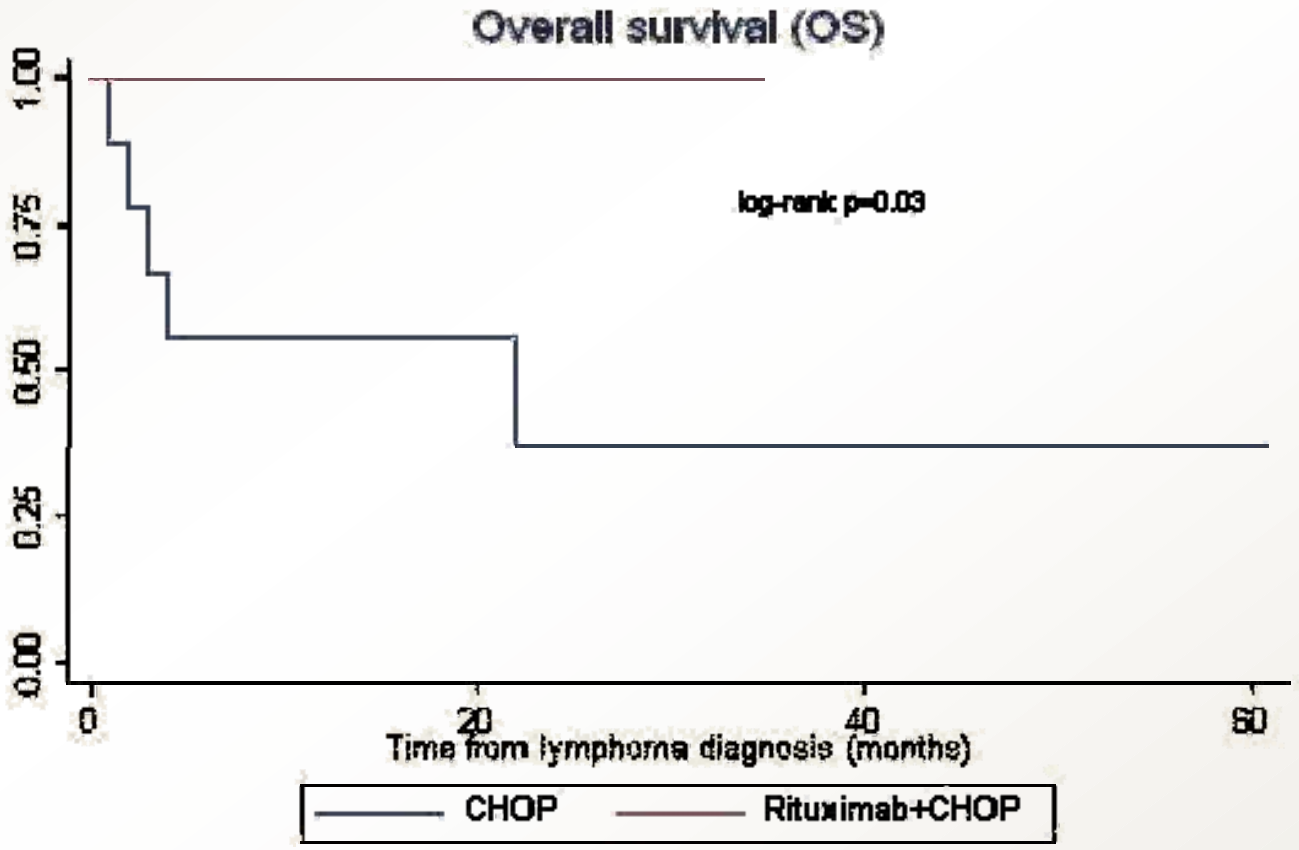
Main clinical, serological and histopathological features at diagnosis

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (yr)	62	37	51	45	74	54
Type of lymphoma	Diffuse large B cell	Nodal marginal zone	Diffuse large B cell	Nodal marginal zone	Diffuse large B cell	Diffuse large B cell
B symptoms	–	+	–	–	–	+
Ann Arbor stage	IV	II	IV	II	II	IV
Bone marrow involvement	+	–	+	–	–	+
$ß_2$-microglobulin (mg/l)*	8.9	5	8.2	12	4.6	7.4
Extranodal involvement	Salivary glands	Salivary glands	Lung, Salivary glands	–	–	Salivary glands

Sjögren's Syndrome lymphomas

Combined B-cell depletion therapy and CHOP

Overall survival

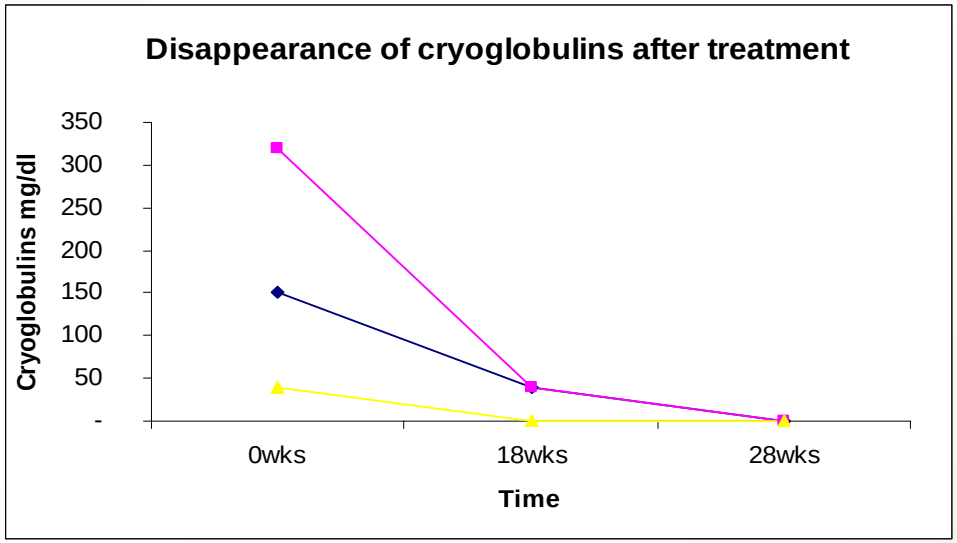


Sjögren's Syndrome lymphomas

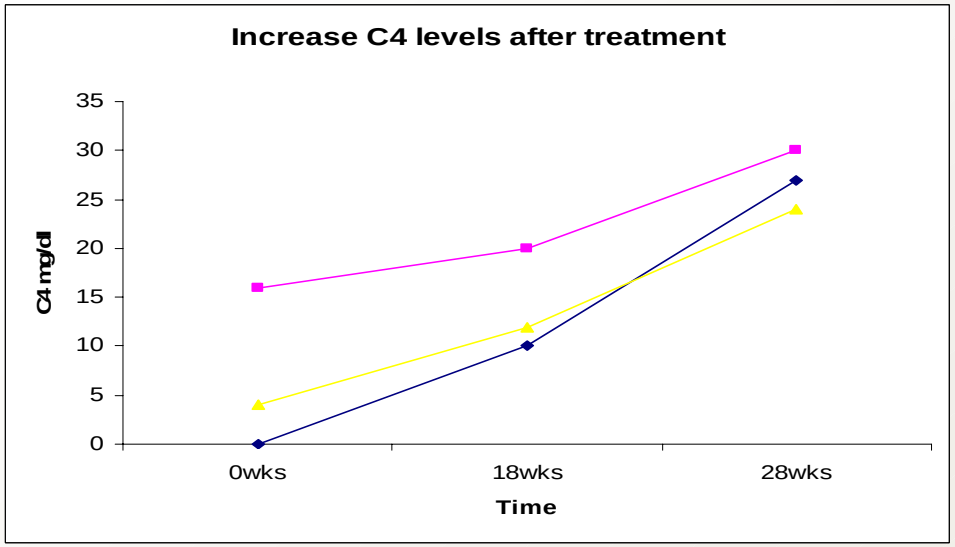
Combined B-cell depletion therapy and CHOP

Outcome

- Reduction of serum cryoglobulins



- Normalization of C4 levels during treatment



Sjögren's Syndrome lymphomas

Combined B-cell depletion therapy and CHOP

Outcome

- Extraglandular manifestations vanish by the end of treatment
  - Peripheral neuropathy (2 patients)
  - Cutaneous vasculitis (3 patients)
- Sicca symptoms persist

Sjögren's Syndrome lymphomas

Combined B-cell depletion therapy and CHOP

Conclusions

- Combination treatment R-CHOP is superior to standard CHOP
- Minimal toxicities
  - fever & chills *(2 patients)*
  - alopecia *(6 patients)*
  - grade III neutropenia *(5 patients)*
  - neutropenic fever *(2 patients)*
- Sustained response