National University of Athens
Greece

Renal involvement in Sjögren Disease

Andreas V Goules, MD
Rheumatologist
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Dept. of Pathophysiology
Medical School

Disclosures

- Novartis
- GSK
- BMS
- Servier
- Amgen
- Abbvie

Outline

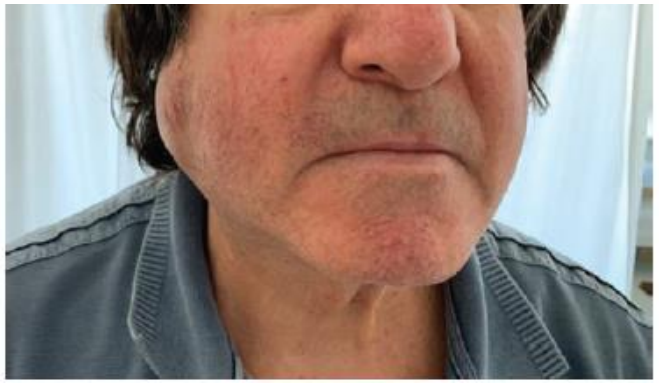
- Immunopathology and general features of SjD
- Interstitial nephritis in SjD
- Glomerulopathy in SjD

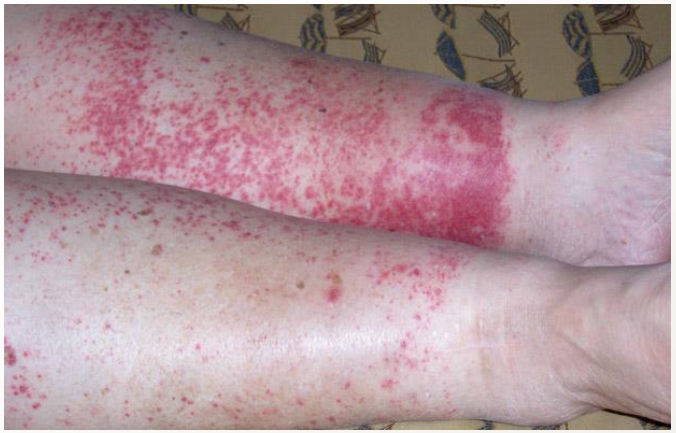
Outline

- **Immunopathology and general features of SjD**
- Interstitial nephritis in SjD
- Glomerulopathy in SjD

Sjögren Disease
Epidemiology

- Prevalence
  - ~0.1% of general population
- Incidence (annual)
  - ~3/100.000 person-years
- Sex
  - ♀/♂ : >15/1
- 4^{th}-5^{th} decade of life
- Slowly progressive





Goules et al. Autoimmun Rev 2016
Chatzis et al. J Clin Med 2020
Hammit et al. Clin Exp Rheumatol 2020
Gabriel et al. Arthritis Res Ther 2009
Izmilrt et al Arthrits Care Res 2019
François et al Nature Rev Nephrol 2015

Sjögren Disease
General Features

- Systemic autoimmunity
  - Isolated (primary)
  - Accompany other diseases (associated)
  - Humoral
  - Cellular

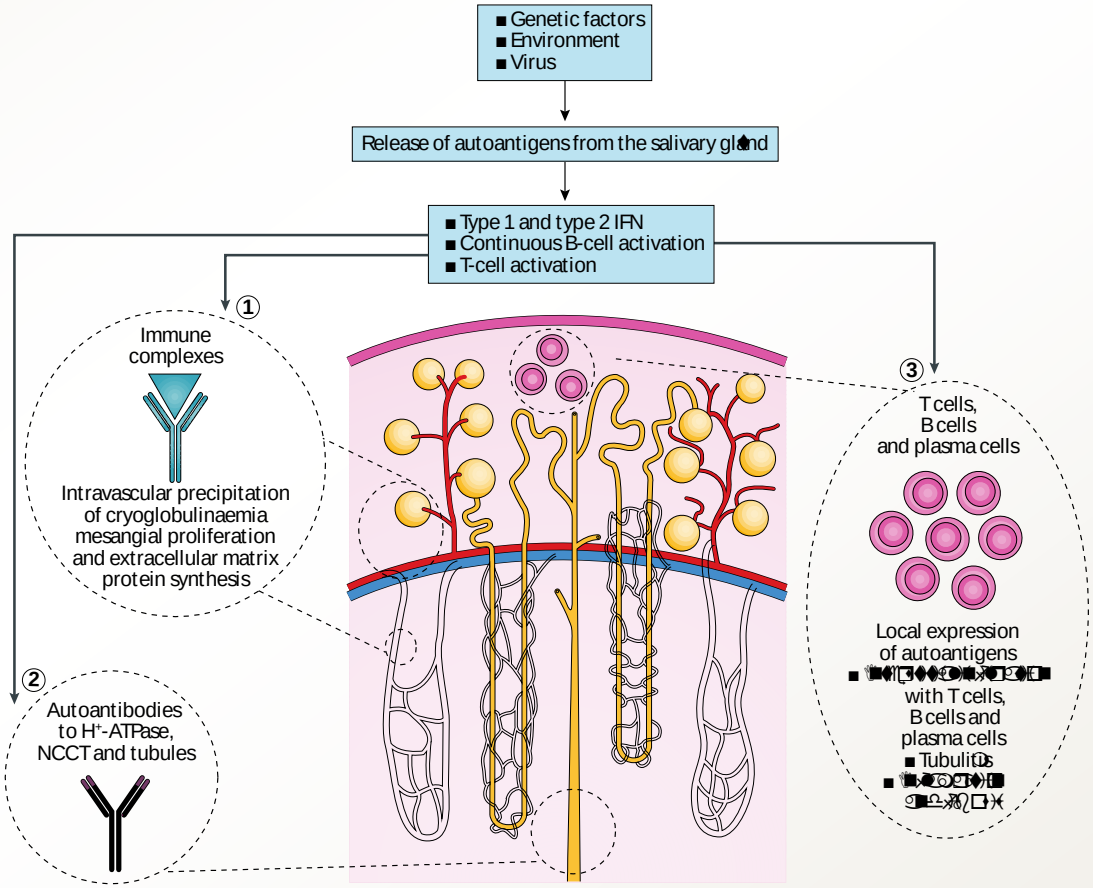
- Wide clinical spectrum
  - organ-specific
  - systemic
  - lymphoma

Goules et al. Autoimmun Rev 2016, François et al Nature Rev Nephrol 2015

Sjögren Disease
Immunopathology

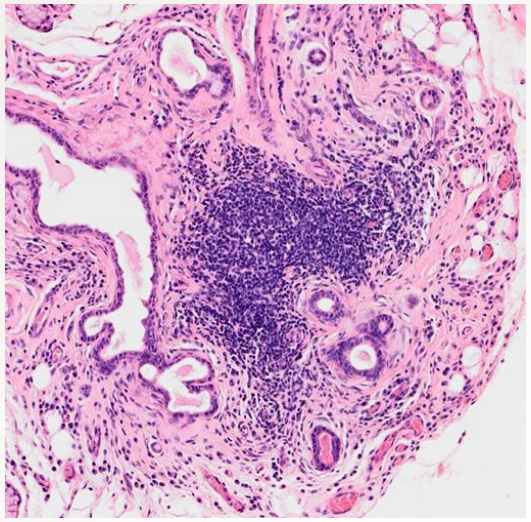
- Lymphocytic infiltration of the affected epithelial structures

- B cell hyperactivity- autoantibodies

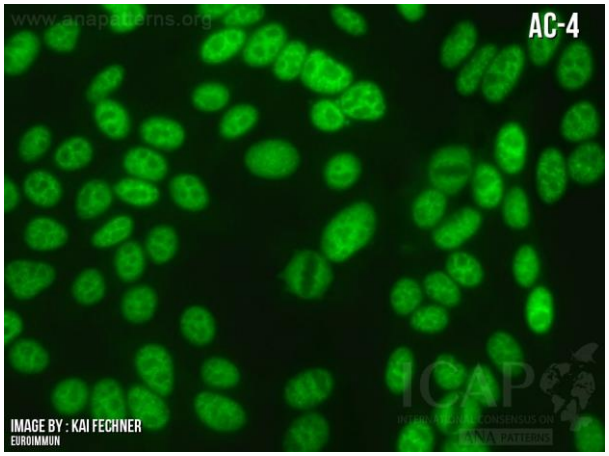


Moutsopoulos et al. Clin Immunol immunopathol 1994,
Goules et al. Autoimmun Rev 2016, François et al Nature Rev Nephrol 2015

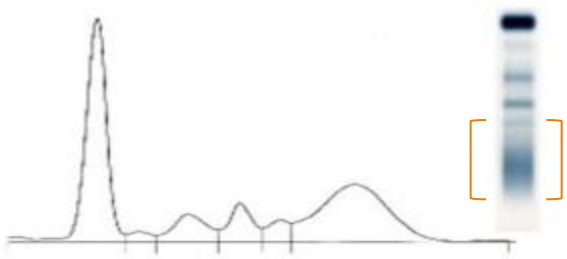
Sjögren Disease
Immunopathology



Periductal infiltration by activated T and B cells



Fine tiny speckled pattern across nucleoplasm compatible with anti-Ro/SSA and anti-La/SSB



Goules et al. Autoimmun Rev 2016,Goules et al. Clin Immunol 2017, François et al Nature Rev Nephrol 2015, Hhttps://www.anapatterns.org

Sjögren Disease
Clinical Manifestations

Glandular

- Oral dryness
- Ocular dryness
- Salivary gland enlargement
- Other type of dryness
  - Skin
  - Nasal
  - Pharynx
  - Xerotrachea
  - Vagina

Extra-glandular/systemic

Non-specific

- Arthralgias/arthritis
- Fatigue
- Limb pain
- Raynaud's phenomenon

Peri-epithelial

- Bronchitis/bronchiolitis
- PBC
- Interstitial nephritis

Extra-epithelial (immune complex mediated)

- Palpable purpura
- Glomerulonephritis
- Peripheral neuropathy

Mavragani et al. CMAJ 2014, Goules et al. Autoimmun Rev 2016

Sjögren Disease
Clinical Manifestations

Peri-epithelial

- Early during disease course
- Stable for many years
- Low prevalence of end stage-organ failure
- T cells predominate within MSLG biopsy lesions

Extra-epithelial

- Late during disease course
- Evolve if left untreated
- May lead to end-stage organ failure
- Risk factors for NHLs
- B cells predominate within MSLG biopsy lesions

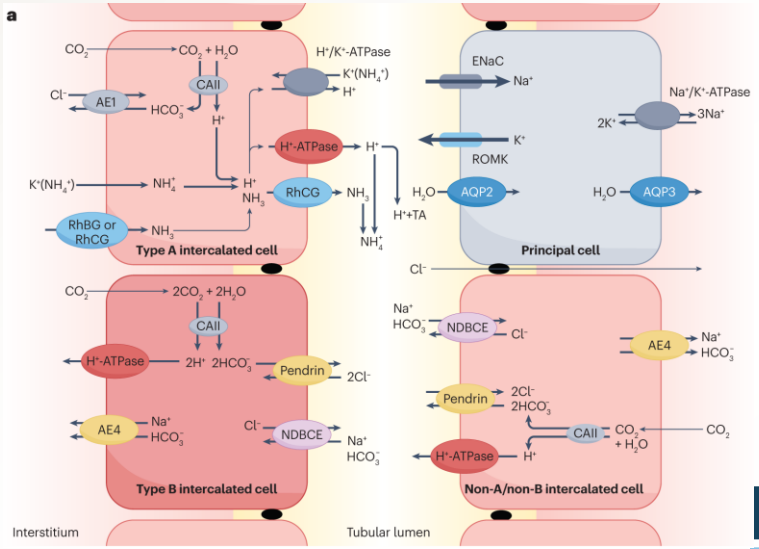
Goules et al. Autoimmun Rev 2016

Outline

- Immunopathology and general features of SjD
- **Interstitial nephritis in SjD**
- Glomerulopathy in SjD

Sjögren Disease

Kidney Disease: the tubular system



Proximal RTA:

Finding	Mechanism
Acidosis	- NHE3 - NBCe1 - Carbonic anhydrase II
Hypokalemia	- Acidosis → Sodium wasting → Hyperaldosteronism - Bicarbonaturia → Increased distal sodium → Potassium wasting
Glycosuria	- Proximal tubule dysfunction
Uricosuria	- Proximal tubule dysfunction
Aminoaciduria	- Proximal tubule dysfunction
Diabetes insipidus	- AQP2

Distal RTA:

Finding	Mechanism
Acidosis	- H+/ATPase (Type A IC cells) - H+/K+/ATPase
Hypocitraturia	- NaDC1 (Proximal) (stimulated by acidosis)
Hypercalciuria	- Reduced calcium reabsorption (stimulated by acidosis)
Hypokalemia	- Hyperaldosteronism - Increased distal sodium delivery
Diabetes insipidus	- AQP2

Kashoor et al. Kidney Research and Clinical Practice. 2019,
Wagner et al. Nat Rev Nephrol 2023, Hall et al. Nat Rev Nephrol 2025

Sjögren Disease
Kidney Disease: interstitial nephritis

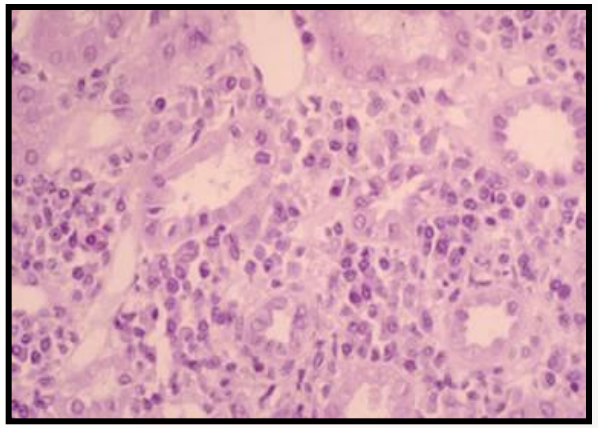
Interstitial nephritis (25%-30%)

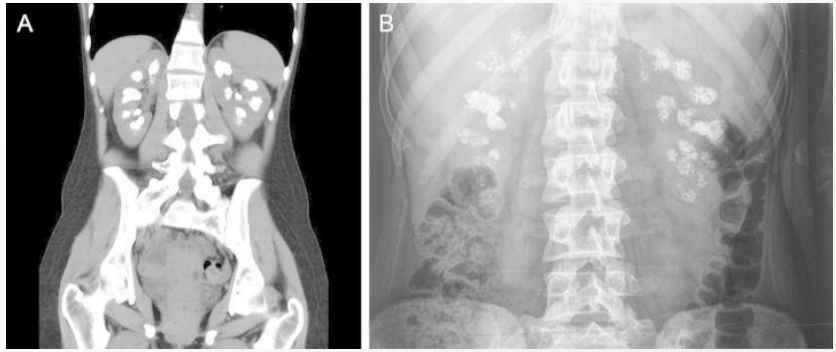
- Urinary concentrating defects
- Incomplete dRTA (subclinical)
- Nephrolithiasis/nephrocalcinosis

common

- Complete dRTA
- Proximal renal tubular acidosis (pRTA)
- Arginine vasopressin resistance (diabetes insipidus)
- Hypokalemia
- Chronic kidney disease

rare





Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Gharbi et al. Clin Kideny J 2014, Bossini et al. Nephrol. Dial. Transplant. 2001, Maripuri et al Clin. J. Am. Soc. Nephrol. 2009, Ren et al. J Rheumatol 2008, François et al Nature Rev Nephrol 2015

Sjögren Disease
Kidney Disease: interstitial nephritis

Distal renal tubular acidosis

- Incomplete dRTA (subclinical)
  - Normal serum HCO_3 levels and blood pH
  - Serum potassium > 3.8mEq/L
  - ***Persistently elevated urinary (fasting morning) pH>5.5***
  - ***Hypocitraturia, hypercalciuria, alkaline urinary pH*** → Nephrolithiasis/nephrocalcinosis
  - NH_4Cl loading or furosemide/fludrocortisone (F+F) test

- Complete dRTA
  - ***Hyperchloremic metabolic acidosis with normal serum anion gap*** and increased urinary anion gap
  - ***Hypokalemia***
  - Serum HCO_3 levels: <16 mEq/L
  - Hypocitraturia, hypercalciouria, alkaline urinary pH → Nephrolithiasis/nephrocalcinosis

Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Gharbi et al. Clin Kideny J 2014, Bossini et al. Nephrol. Dial. Transplant. 2001, Maripuri et al Clin. J. Am. Soc. Nephrol. 2009, Ren et al. J Rheumatol 2008, François et al Nature Rev Nephrol 2015

Sjögren Disease
Kidney Disease: interstitial nephritis

Other clinical manifestations

- Proximal RTA (established)
  - Hyperchloremic metabolic acidosis with normal serum anion gap and increased urinary anion gap
  - Low normal potassium levels or mild hypokalemia
  - Serum HCO_3 levels: <14-20 mEq/L
  - Urinary pH<5.3
  - Glycosuria, aminociduria
  - No nephrolithiasis
  - Intravenous infusion of sodium bicarbonate test

- Arginine vasopressin resistance (diabetes insipidus)
  - Polyuria, polydipsia

Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Gharbi et al. Clin Kideny J 2014, Bossini et al. Nephrol. Dial. Transplant. 2001, Maripuri et al Clin. J. Am. Soc. Nephrol. 2009, Ren et al. J Rheumatol 2008, François et al Nature Rev Nephrol 2015

Sjögren Disease

Kidney Disease: interstitial nephritis

A 45 year old female:

- Bilateral parotid and submandibular enlargement
- Low fasting morning urine specific gravity
- Microscopic hematuria and proteinouria
- Slightly impaired renal function

Differential diagnosis?

Sjögren Disease
Kidney Disease: interstitial nephritis
Differential diagnosis

IgG4RD

- Acute or chronic kidney injury
- Mass lesions
- Plasma rich infitrate
- Storiform fibrosis
- Proteinuria (often)
- Hematuria (rare)
- Sterile pyuria (rare)
- No nephrolithiasis
- Urinaly concetrating defects (occassionaly)
- Response to steroids

SjD

- Distal RTA or chronic kidney injury or hypokalaemia or nephrolithiasis
- Mass lesions-MALTs (rare)
- Lymphocytic infiltrate
- Proteinuria (occasionally)
- Hematuria (occasionally)
- Sterile pyuria (occasionally)
- Nephrolithiasis
- Urinary concentrating defects (common)
- Ocassionally response to steroids

Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Gharbi et al. Clin Kideny J 2014, Bossini et al. Nephrol. Dial. Transplant. 2001, Maripuri et al Clin. J. Am. Soc. Nephrol. 2009, Ren et al. J Rheumatol 2008, François et al Nature Rev Nephrol 2015, Saeki Kidney Int 2014, Buglioni et al. Kidney Int Rep 2024

Sjögren Disease
Kidney Disease: interstitial nephritis

RTA treatment

- Goal: i) ***alkali treatment*** to achieve HCO_3 serum level>22mEq/L, ii) ***prevention of stone formation***
- Distal RTA: 1-2mEq/L $NaHCO_3$ → divided in 4 doses (1/2 teaspoon baking soda x 4 or 3tbs $NaHCO_3$ x 4) (titration)
- Proximal RTA: 10-15mEq/L $NaHCO_3$ → plus thiazide/amiloride or spironolactone
- Hypokalemia: potassium bicarbonate or citrate plus spironolactone
- Citrate: <500mg/d → 30mEq potassium citrate (titration)

Immunosuppression (IS)?

- Prednisone ± MMF or AZA or Rx

Kidder et al Nephrol Dial Transplant. 2015, Maripuri et al. Clin J Am Soc Nephrol. 2009, Jasiek et al. Rheumatology (Oxford). 2017, Evans et al BMC Musculoskelet Disord. 2016, Shen et al. Am J Nephrol. 2017, Goules et al Clin Exp Rheumatol. 2019, Jeon et al. Sci Rep 2025, Narvaez et al. Clin Exp Rheumatol. 2020, Jain et al. Rheumatol Int 2018

Sjögren Disease
Kidney Disease: interstitial nephritis

Immunosuppression (IS)?

- 9 case series
- Heterogeneity regarding regimen, duration, follow up, renal status, renal disease duration
- No controls patients
- Outcome: mean eGFR change or >20% GFR improvement
- Confounders

Group	Treated TIN only patients	Untreated TIN only patients	Outcome	Confounders
Maripuri et al.	• 15 patients • mainly prednisone, (range 30-60mg/d) for median duration of 30w	0 patients	• >20% eGFR gain responders: 9	No information
Jasiek et al.	• 64 patients • prednisone median (range 5-80mg/d) for at least for 6 months plus rituximab, AZA or MMF	8 patients	• Mean GFR change 7.5ml/min/1.73m^2 • pre=35, post=42.5 (at 12 month follow up)	No information
Shen et al.	• 56 patients • Prednisone, mean dose 25.5mg/d for more than 3 months	0 patients	• Mean GFR change: 2.72±19.11 ml/min/1.73m^2 (at 12 month follow up) • Pre=64.86±30.45 ml/min/1.73m^2	ACEi, ARB

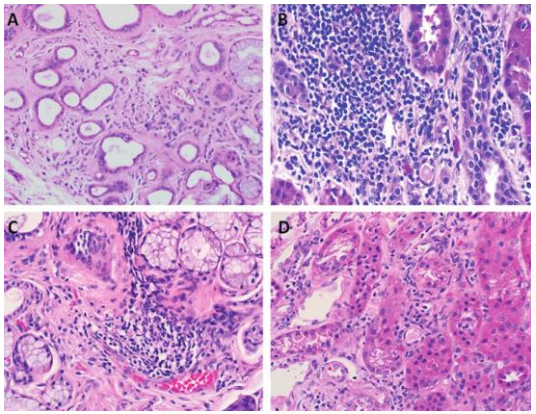
Kidder et al Nephrol Dial Transplant. 2015, Maripuri et al. Clin J Am Soc Nephrol. 2009, Jasiek et al. Rheumatology (Oxford). 2017, Evans et al BMC Musculoskelet Disord. 2016, Shen et al. Am J Nephrol. 2017, Goules et al Clin Exp Rheumatol. 2019, Jeon et al. Sci Rep 2025, Narvaez et al. Clin Exp Rheumatol. 2020, Jain et al. Rheumatol Int 2018

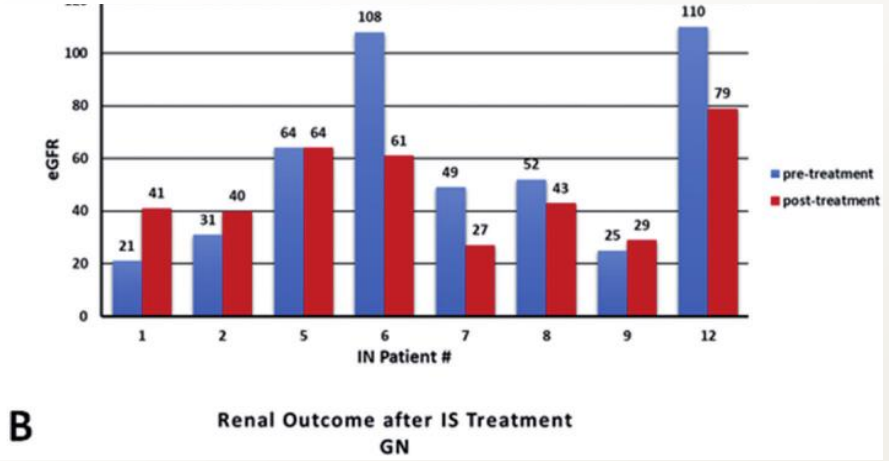
Sjögren Disease
Kidney Disease: interstitial nephritis

<u>Immunosuppression (IS)</u>

- IS does not seem to improve renal function (prednisone, MMF, AZA, Rx)

- Consider IS: AKI attributed to no other cause with or without tubulitis





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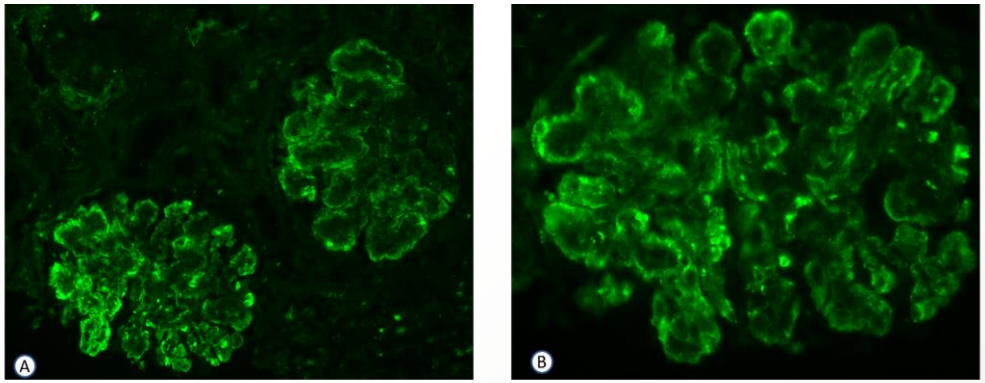
Outline

- Immunopathology and general features of SjD
- Interstitial nephritis in SjD
- **Glomerulopathy in SjD**

Sjögren Disease
Kidney Disease: glomerulonephritis

<u>Glomerulonephritis (2%)</u>

- Clinical presentation
  - Nephritic syndrome
  - Nephrotic range proteinuria
  - Cryoglobulinemic manifestations
- Histopathology (LM)
  - Membranoproliferative
  - Membranous
  - Mesangioproliferative



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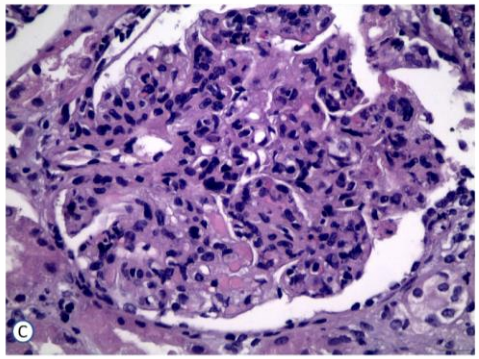
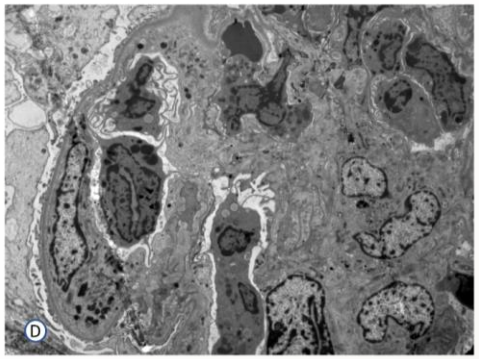
Sjögren Disease
Kidney Disease: glomerulonephritis

Evaluation

- Serology (HIV, HBV, HCV)
- Serum cryoglobulins (type II IgMk), RF, C4
- Autoantibody profile
- Lymphoma work up



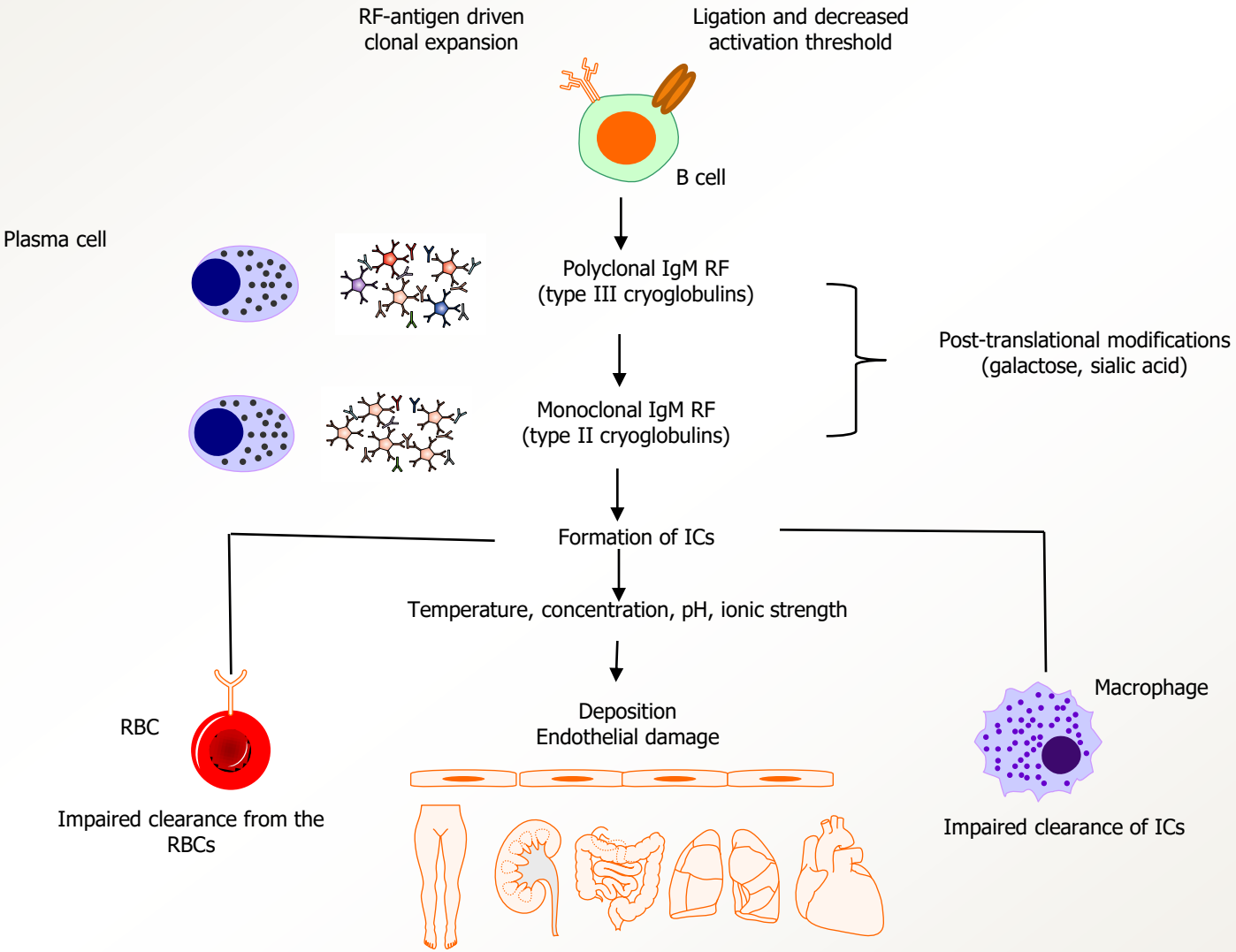


Differential diagnosis

- Viral infections
- Lupus
- NHL lymphomas

Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Kidder D et al Nephrol Dial Transplant. 2015, Bossini et al. Nephrol. Dial. Transplant. 2001, Maripuri et al Clin. J. Am. Soc. Nephrol. 2009, ,Goules et al. Sjogren's Disease. The Rose and Mackay textbook of autoimmune diseases 2025

Sjögren Disease
Kidney Disease: cryoglobulinemia



Cacoub et al. N Engl J Med. 2024

Sjögren Disease
Kidney Disease: glomerulonephritis
Differential diagnosis

- Overlapping clinical phenotype between lupus and SjD
- SjD patients with disease onset<40 years old may switch to lupus
- Lupus patients may suffer from associated SjD
- Lupus patients may develop usually type III cryoglobulins

Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Goules et al Frontiers Immunology 2020, Manoussakis et al. Arthritis Rheum 2004, Bolleto et al Semin Arthritis Rheum 2020, Alani et al. Scand J Rheumatol 2018

Sjögren Disease
Kidney Disease: glomerulonephritis
Differential diagnosis

SjD

- LM: mesangial, membranous membranoproliferative with ***intraluminal hyaline thrombi***
- IF: predominantly ***IgM deposits*** along with C3 and C1q deposition
- EM: subendothelial and endomembranous deposits with ***cylinder or microtubular shape***
- ***Type II IgMk*** cryoglobulins
- Steroids + Rx ± belimumab
- Different autoantibody profile

Lupus

- LM: mesangial, membranous, proliferative, membranoproliferative
- IF: ***full house pattern*** with IgG, IgM, IgA, C3, C1q deposits
- EM: mesangial, subendothelial and subepithelial deposits
- ***Cryo (-) or type III IgG*** cryoglobulins
- Steroids + MMF/CYC + belimumab
- Different autoantibody profile

Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Bolleto et al Semin Arthritis Rheum 2020

Sjögren Disease
Kidney Disease: glomerulonephritis

Treatment

- ***Steroids (0.5-1mg/Kg) ± Rx*** or CYC
- Plasmapheresis (limited role)
  - Hyperviscocity syndrome
  - High cryocrit (>10%)
  - Life threatening or rare conditions
  - Before or 3-4 days after Rx
  - 3 sessions/weekly x 3 weeks/FFPs
- Refractory cases
  - ***Steroids+Rx ± belimumab*** or CYC

Monitoring

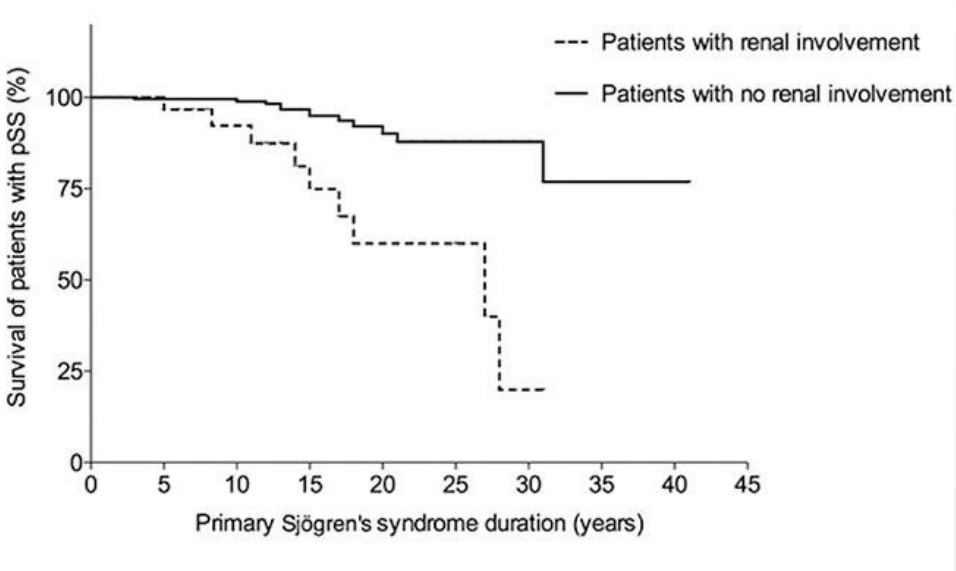
- Urinalysis: proteinuria, active urine sediement
- Serum creatinine and eGRF
- Cryoglobulins, RF, C4

Goules et al. Medicine 2000, Goules et al. Arthritis Rheum 2013, Goules et al. Clin Exp Rheumatol 2018, Roccatello et al. Nat Rev Dis Primer 2018, Ramos-Casals et al. Lancet 2012, Sneller et al. Arhtiris Rheum 2012, De Vita S et al. Arthritis Rheum 2012, Terrier et al. Blood 2012, De Vita S et al. Clin Exp Rheum 2014, Mariette et al. Ann Rheum Dis 2013, Marriette et al JCI insights 2022

Sjögren Disease
Kidney disease: outcome

Clinically significant renal involvement

- Impaired renal function, renal colics, urinary pH>7.0, proteinuria>500mg/d, active urine sediment
- 35/715 (4.9%): 13 (37%) IN only, 17 GN (49%) only, 5 (14%) both
- Outcome (252 person-years): 9 (25%) died, 11 (31%) developed CKD/GFR<50ml/min (4 hemodialysis), 9 developed lympoma (25%) (mainly GN)
- 5-year overall survival rate=85%



Goules et al. Arthritis Rheum 2013

Sjögren Disease
Kidney Disease

Conclusions

- Clincally significant renal involvement in SjD is NOT isignificant and has a variable prognosis
- All SjD patients should be initially screened for renal involevment
- Specific clinical manifetations imply kidney involvement in SjD
- Immunosuppression in IN should be reserved for selected cases
- SjD patients with glomerulonephritis are at high risk for lymphoma

Thank you for your attention