# Rheumatology & Immunology

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# IgG4-RELATED DISEASES

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## Introduction 00:01:28

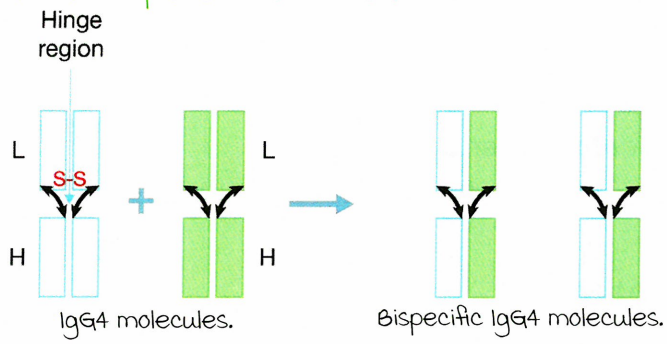
IgG is the most abundant antibody.
The least prominent in IgG is IgG4 (<5%).

**IgG4 :**

- Characterised by lack of compliment binding.
- It is an anti inflammatory molecule which blocks the binding of IgG1 to C1q.
- It activates myofibroblasts → Activates PDGF and TGF-β → Fibrosis.

Fab arm exchange (FAE) :

- The heavy chain and light chain pairs are exchanged resulting in a bispecific IgG4 molecule with 2 antigen binding sites → Sequesters the antigens.
- Hence no immune complexes are formed.




**New definition :**

- IgG4 diseases are a set of diseases which contain tumor like lesions characterised by IgG4 containing lymphoplasmacytic cells.
- They have a tendency for fibrosis (Storiform fibrosis) + obliterative phlebitis + mild eosinophilia.
- The reason for increase in IgG4 is still unknown.

Note : Chronic antigenic stimulation, mainly galactin-3 leads to increased IgG production but IgG4 have been produced in excess, leads to fibrosis.

Diseases which have been renamed as IgG4-related are :

1. Type 1 autoimmune pancreatitis.
2. Mickulicz disease.
3. Primary sclerosing cholangitis.
4. Retroperitoneal fibrosis.
5. Reidels thyroiditis.
6. Lymphocytic hypophysitis.

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Other diseases which have been renamed :

Mikulicz's disease (affecting the salivary and lacrimal glands)
Küttner's tumor (affecting the submandibular glands)
Riedel's thyroiditis
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Lymphomatoid granulomatosis, grade 1 (commonly affecting the lungs)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues/organs)
Lymphoplasmacytic sclerosing pancreatitis/autoimmune pancreatitis
Inflammatory pseudotumor (orbits, lungs, kidneys, and other organs)
Mediastinal fibrosis
Retroperitoneal fibrosis
Sclerosing mesenteritis
Periaortitis/periarteritis
Inflammatory aortic aneurysm
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits

## Clinical manifestations 00:23:35

### Presentation :

- Multiorgan immune mediated condition resembling inflammation or tumor.
- More common in males.
- Average age is >60 years.
- Subacute > chronic presentation.
- Background of atopy/allergy.
- Constitutional symptoms : Fatigue and weight loss.

### Major manifestations :

1. Type I autoimmune pancreatitis (m/c).
2. Salivary gland involvement.
3. Lacrimal gland involvement.
4. Retroperitoneal fibrosis.

### Minor manifestations :

1. Orbit.
2. Central nervous system.
3. Lung.
4. Kidney.
5. Bile duct.
6. Aorta.

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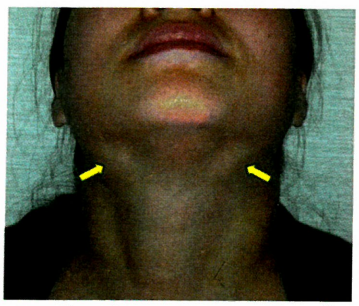
Salivary gland :

- m/c gland to be involved : Submandibular gland.
- Symmetric painless asymptomatic enlargement.
- Very minimal sicca symptoms.

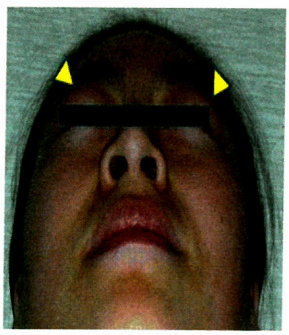
| IgG4-related disease | Sjogren syndrome. |
|---|---|
| Submandibular gland. | Parotid gland. |
| Significant gland enlargement. | No significant enlargement. |
| Sicca symptoms not present. | Sicca symptoms present. |
| Symmetric painless nodules. | Asymmetric painful nodules. |
| Highly responsive to steroids. | Sicca symptoms are not responsive to steroids. |

Lacrimal gland :

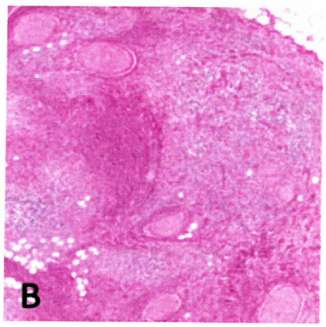
- Symmetric painless asymmetric enlargement.
- Biopsy : Storiform fibrosis (Swirling pattern/cart wheel pattern).



Non tender enlargement of left submandibular gland.



Lacrimal gland enlargement.




Swirling pattern in biopsy.

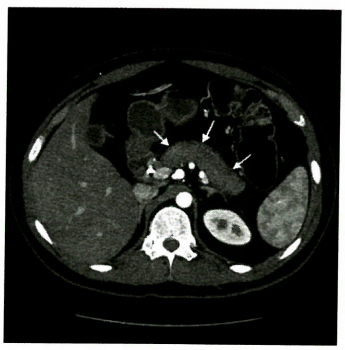
Retroperitoneal fibrosis : Leads to bilateral obstructive uropathy.

Autoimmune pancreatitis :

m/c manifestation.

Presentation :

- Mild abdominal symptoms initially but presents as obstructive jaundice.
- Type 3c diabetes mellitus.
- Exocrine insufficiency.



Sausage appearance of pancreas in CT.

Investigations :

- Diffuse enlargement of pancreas with irregular narrowing of the pancreatic duct on ERCP.
- Sausage appearance of pancreas with feathery border on CT.

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Vascular :

- Immune complex small vessel vasculitis characterised by purpura.
- m/c vasculitic manifestation : Aortitis, spares the branches.
- Paravertebral mass is also seen.

Orbit :

- Inflammatory pseudotumor presenting as a painful mass.
- Produces upper respiratory tract symptoms.

CNS :

- Lymphocytic hypophysitis : Post partum ↑ in ICT (Stalk effect).
- Pachymeningitis without brain parenchymal involvement.

Bile duct :

Primary sclerosing cholangitis characterised by fibrotic lesion of intra and extra hepatic bile duct.

Lung :

- Features similar to sarcoidosis.
- Non specific interstitial pneumonia.
- Thickening of bronchovascular bundle.

Kidney :

- Tubulointerstitial nephritis responsive to steroids.
- membranous glomerulonephropathy with low complements.

Note :

- Serum IgG4 is increased in 60% of cases and normal in 40%.
- IgG4/IgG ratio > 40% is of high value in diagnosis.

## Diagnosis

00:48:21

The criteria used now is the 2020 revised comprehensive diagnostic criteria for IgG4-RD.

1. Clinical and radiological feature :

≥1 organs show diffuse or localized swelling, mass and nodule characteristic of IgG4-RD.

In single organ involvement, lymph node swelling is omitted.

2. Serological diagnosis : Serum IgG4 levels are more then 135 mg/dL.

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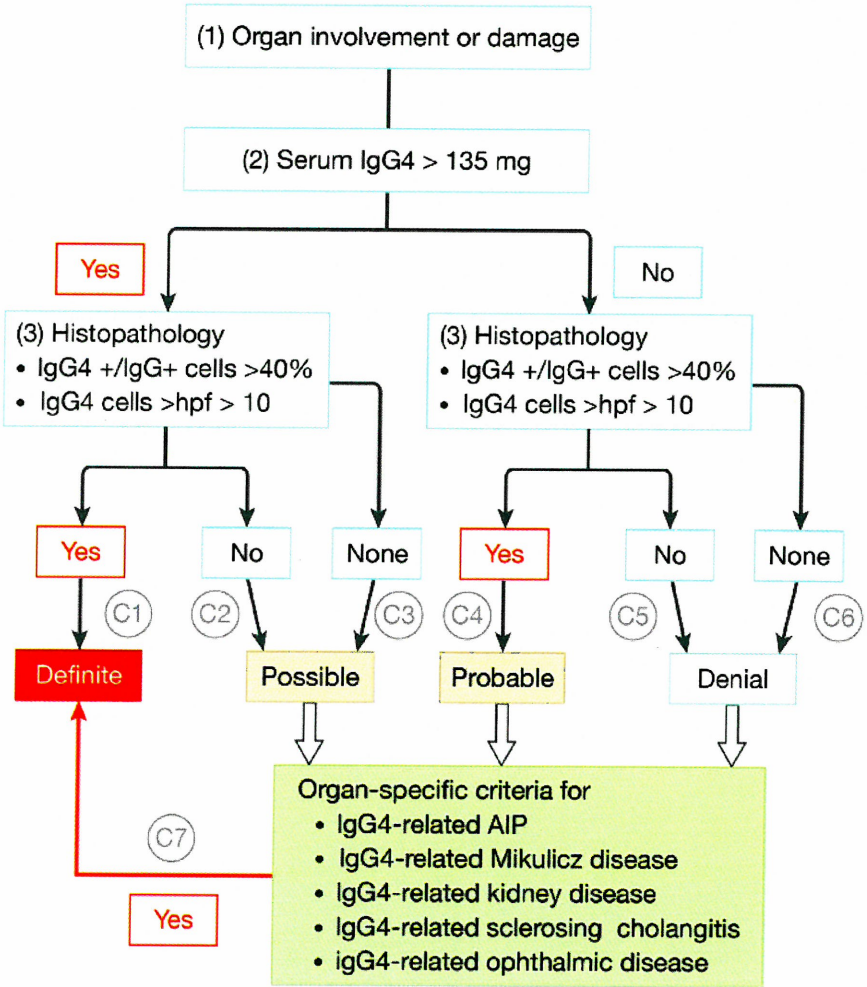
3. Pathological diagnosis :

Positivity of 2 or more of the following 3 criterias :

- Dense lymphocyte and plasma cell infiltration with fibrosis.
- Ratio of IgG4-positive plasma cells/IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells >10 per high power field.
- Dense lymphocyte and plasma cell infiltration with fibrosis.

**Diagnosis :**

- Definite : 1 + 2+ 3.
- Probable : 1 + 3.
- Possible : 1 + 2.




Diagnostic algorithm for IgG-RD.

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## Treatment

00:49:40

Steroids are the first line of treatment.

Dose :

- 1 mg/kg full dose for 4 weeks
- Minimal dose to be achieved in 8 to 12 weeks.
- Excellent response within 2 weeks.

Relapses :

- Seen in 40 to 50% cases.
- Treated by : Rituximab 375 mg/$m^2$ x 4 doses.

# SJOGREN'S SYNDROME

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## Overview

00:02:07

2nd most common multisystem autoimmune CTD.
International sjogrens day → 1st july.

### Classification

1. 1° sjogren
2. 2° sjogren :
   - Rheumatoid arthritis (MC) > SLE.
   - Inflammatory muscle disease.
   - Granulomatosis with polyangitis.

OR

1. Glandular sjogren.
2. Extraglandular sjogren (50%) :
   - Almost 15 % of extraglandular are severe.

## Glandular sjogren

00:02:07

Autoimmune lymphocytic exocrinopathy → Periductal and perivascular inflammation ( T+ B cell mediated [CD4 T cell > B cells], Th1 > Th17 immune response) → Activation of ductal epthelium → Immune destruction & immune inhibition (Anti MR-3 antibodies).

Only endocrine gland involved → Thyroid gland (Autoimmune thyroiditis).

### Epidemiology

- 40- 60 years.
- Female > male.
- F : M = 9 : 1.

Clinical hallmark :

- Dry eye (Keratoconjunctivitis sicca).
- Xerostomia.
- Salivary gland enlargement :

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- Bilateral, painless symmetric firm enlargement.
- Caused by IL-18 positive macrophages.
- Parotid & submandibular gland involvement.

## Classification criteria

2016 American College Of Rheumatology /European League Against Rheumatism Classification Criteria :

**TABLE 78.1 2016 American College of Rheumatology/ European League Against Rheumatism Classification Criteria for Sjögren's Syndrome**

| Item | Score |
|---|---|
| Histopathology showing focal lymphocytic sialadenitis with a focus score ≥ 1 per 4 $mm^2$ | 3 |
| The presence of anti-Ro/SS-A antibodies | 3 |
| SICCA ocular staining score ≥5 using lissamine green and fluorescein dye (or Rose Bengal score ≥4 by the van Bijsterveld scoring system) | 1 |
| Schirmer's test ≤5 mm per 5 minutes in at least one eye | 1 |
| Unstimulated whole salivary flow of less than 0.1 mL per minute | 1 |
| **Rules for Classification** | |
| Patients may be classified as primary Sjögren's syndrome if they display at least one symptom of ocular or oral dryness and a total score of 4 or greater when the weights from the five criteria items above are summed. | |
| **Exclusion Criteria** | |
| History of head and neck radiation treatment<br>Active hepatitis C infection (with confirmation by PCR)<br>AIDS<br>Sarcoidosis<br>Amyloidosis<br>Graft vs. host disease (GVHD)<br>IgG4-related disease (IgG4-RD) | |

*AIDS*, Acquired immunodeficiency syndrome; *SICCA*, Sjogren's International Collaborative Clinical Alliance.

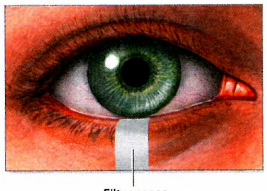
Genetic and environmental factors :

- HLA DR3 > DR2.
- T+ B cell mediated (CD4 T cell > B cells) , Th1 > Th17 immune response.
- IL-18 positive macrophages and associated salivary gland enlargement.
- No role for viral infections (CMV = Salivary gland virus).
- Anti M3/ Anti alpha fodrin (non specific) produced.

## Diagnosis

Schirmer test :

- Detects deficient tear production in Sjogrens syndorme.
- Cut off value : <5 mm in 5 mins.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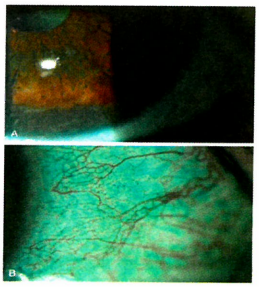
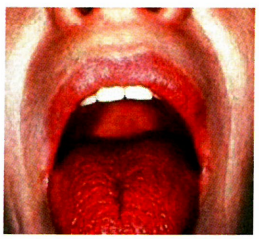
Slit lamp examination :

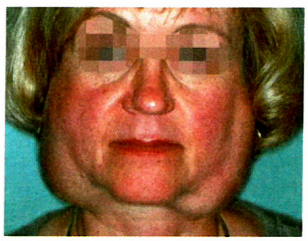
- Lissamine green & Fluoroscein dyes are used.
- Lissamine green : Stains epithelilal surfaces with mucin deficiency.
- Fluoroscein dyes :
  - Expose devitalised epithelium/ epithelial defects.
  - Tear film break up time : <10 secs (Lipid layer/ aqueous layer issues can also cause, hence nonspecific finding).



**Dry mouth/ Xerostomia :**

- more specific than dry eye.
- Features :
  - Altered taste.
  - Dental caries.
  - Oral thrush.
  - Deep red tongue.
  - Bilateral parotid enlargement : 1° sjogren.





- 25 % have chronic symmetrical painless swelling of salivary glands.
- Aymmetrical gland enlargement with palpable nodules : Lymphoma (marginal zone B cell [extranodal] lymphoma).
- Recurrent episodes of acute parotitis due to duct blockade : Childhood & adolescent Sjogren.

## Exrtraglandular sjogren

00:28:29

Most common symptom → Fatigue.

Predictors for extraglandular manifestations :

- Severe in 15 % cases.
- Fatigue.

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- Anti RO (SS-A) & Anti La (SS-B) → Only in primary, Earlier onset, longer duration of extraglandular manifestations, poor prognosis, increases the risk for lymphoma, persistent salivary gland enlargement.
- Rheumatoid factor.
- Cryoglobulinemia (Cryoglobulins & low C3, C4).

Anti Ro/La in SLE → 2° Sjogren in SLE :

- Good prognosis (decreased nephritis & vasculitis).
- Neonatal lupus with congenital heart block.
- Subacute cutaneous lupus (Photo sensitive non scarring lupus).

## Extraglandular manifestations

**TABLE 361-1 Prevalence of Extraglandular Manifestations in Primary Sjögren's Syndrome**

| CLINICAL MANIFESTATION | PERCENT | REMARKS |
|---|---|---|
| **Nonspecific** | | |
| Fatigability/myalgias | 25 | Fibromyalgia |
| Arthralgias/arthritis | 60 | Usually nonerosive, leading to Jaccoud's arthropathy |
| Raynaud's phenomenon | 37 | In one-third of patients, precedes sicca manifestations |
| **Periepithelial** | | |
| Lung involvement | 14 | Small airway disease/lymphocyte interstitial pneumonitis |
| Kidney involvement | 9 | Interstitial kidney disease is usually asymptomatic |
| Liver involvement | 6 | Primary biliary cirrhosis stage I |
| **Immune complex–mediated** | | |
| Small vessel vasculitis | 9 | Purpura, urticarial lesions |
| Peripheral neuropathy | 2 | Polyneuropathy, either sensory or sensorimotor |
| Glomerulonephritis | 2 | Membranoproliferative |
| **Lymphoma** | | |
| Lymphoma | 6 | Glandular MALT[a] lymphoma is most common |

[a]Mucosa-associated lymphoid tissue.

Arthralgia/arthritis :

- Similar to SLE.
- 2nd most common extraglandular manifestation.
- Bilateral symmetrical non erosive small joint UL polyarthritis.
- Deformities (due to laxity of ligaments) : Jacouds arthropathy.

Raynauds phenomenon :

- Precede sicca symptoms in 1/3rd.
- Produce critical limb ischemia.

Vasculitis :

- Small vessel cutaneous non thrombocytopenic palpable purpura.

Cryoglobulinemia :

- Ischemic ulcers.
- Vascultitis with ulcers + MPGN + Neuropathy.

Head to foot :

1. Neurological :
   - Central : MS like lesions.
   - Peripheral : Ganglionopathy (Asymmetrical, post column, sensory ataxia : truncal ataxia).

2. Lungs :
   - Non specific interstitial pneumonia : Reticulonodular infiltrates on x ray, ground glass opacities on CT.
   - Lymphocytic interstitial pneumonia (LIP) : Subtype of NSIP classically seen in sjogren and HIV (Thin walled cysts, GGO, Centrilobular nodules).

3. Liver :
   - Hepatitis C (Sjogren, Porphyria cutanea tarda, Cryoglobulinemia type 2/3, lichen planus).

4. Biliary system → Primary biliary cirrhosis.

5. Kidney :
   - Mainly tubulointerstitial involvement (Distal RTA → Hypokalemic paralysis).
   - Glomerular involvement → MPGN → Cryoglobulinemia.

## Diagnosis

- Persistent parotid enlargement.
- Purpura.
- Cryoglobulinemia.
- Leukopenia.
- Low C4 levels.
- High Ro/La TITRES.
- Lymphadenopathy.

These features point towards high chances of lymphoma (Extranodal marginal zone lymphoma : maltoma).

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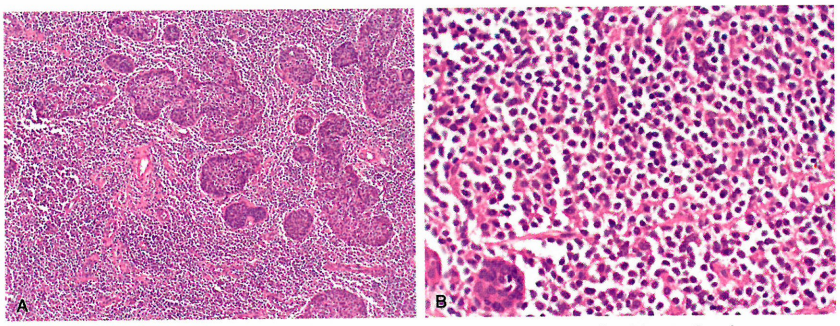



• **Fig. 78.5** Mucosa-associated lymphoid tissue (MALT) lymphoma in a woman with painless swelling of a submandibular gland. (A) Hematoxylin-eosin (H&E) staining at 10× demonstrating a dense infiltrate of malignant B cells surrounding the ductal epithelium. (B) Infiltrating malignant B cells at higher power (×40).

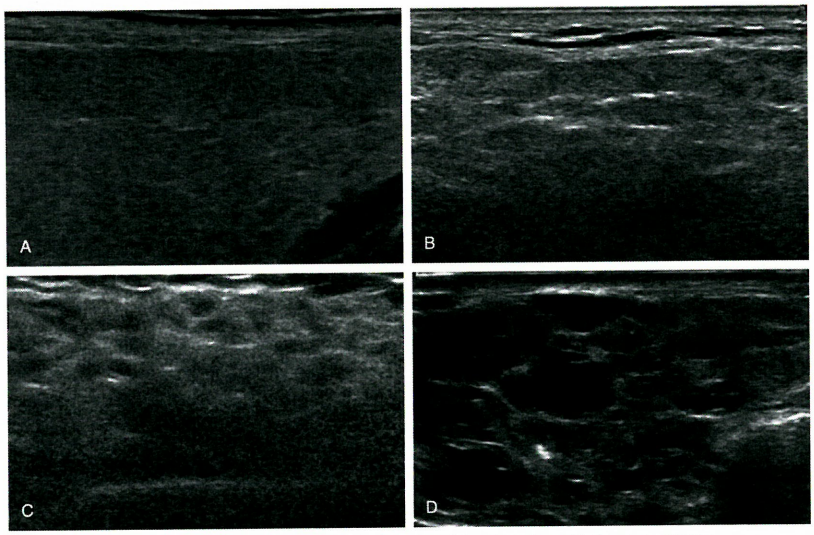
## Antibodies

00:51:24

- ANA positivity in sjogren → 85 %.
  - most common pattern : Speckled (Connective tissue disorder likely, non specific).
- Anti Ro (50%) & Anti La (33%) :
  - No role in secondary.
  - Anti La by itself has no value.
- Low complement suggest cryoglobulinemia.
- SLE with Ro/La suggests good prognosis.

### Diagnostic modalities

- Sialography : Unstimulated salivary flow rate less than 1.5 ml/15 minutes.
- Labial biopsy is the gold standard (Focal lymphocytic sialadenitis).
- Ultrasonography :




• **Fig. 78.7** Ultrasonography of the parotid glands in primary Sjögren's syndrome. (A) Normal parotid gland with homogeneous echogenicity. (B) Mild abnormalities, including hyperechogenic linear reflectors and indistinct hypoechoic lesions. (C) Multiple distinct ovoid hypoechoic lesions, occupying at least 50% of the glandular surface area. (D) Advanced abnormalities, including multiple ovoid hypoechoic lesions, larger anechoic lesions likely representing cysts, and punctate hyperechogenic lesions representing calcifications. (Image Courtesy Alan N. Baer, MD, Division of Rheumatology, Department of Medicine, Johns Hopkins University.)

- Histopathology :

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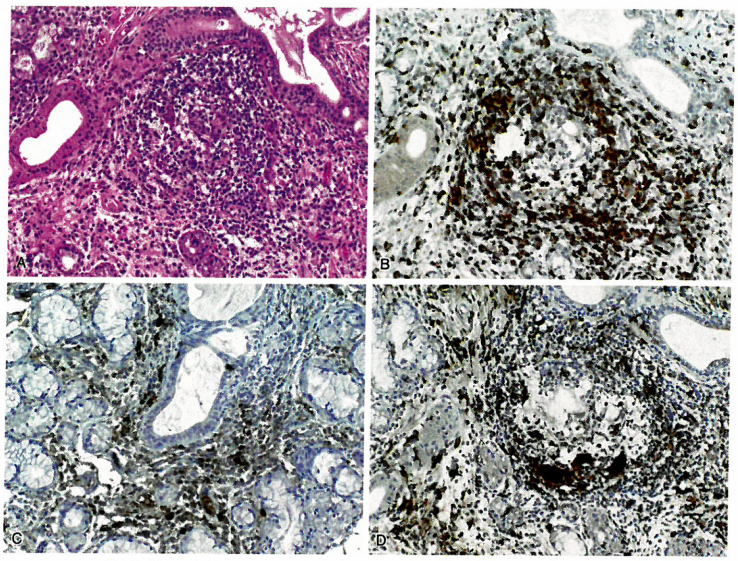

• **Fig. 78.1** Histopathology of the labial salivary glands in primary Sjögren's syndrome. (A) Hematoxylin-eosin (×20). (B) Anti-CD3 staining of T cells (×20). (C) Anti-CD21 staining of B cells (×20). (D) Anti-CD68 staining of macrophages (×20). Mononuclear cells aggregate in foci throughout the glands (A). In this biopsy, most of the mononuclear cells are T cells (B), with fewer numbers of B cells (C) and macrophages (D).

Differential diagnosis :

- Salivary gland enlargement + ILD + Uveitis + hilar adenopathy : Sarcoidosis.
- Gland enlargement + storifirm fibrosis + plasmacytic infiltrate + Autoimmune pancreatitis : IgG4 related disease.

## Management

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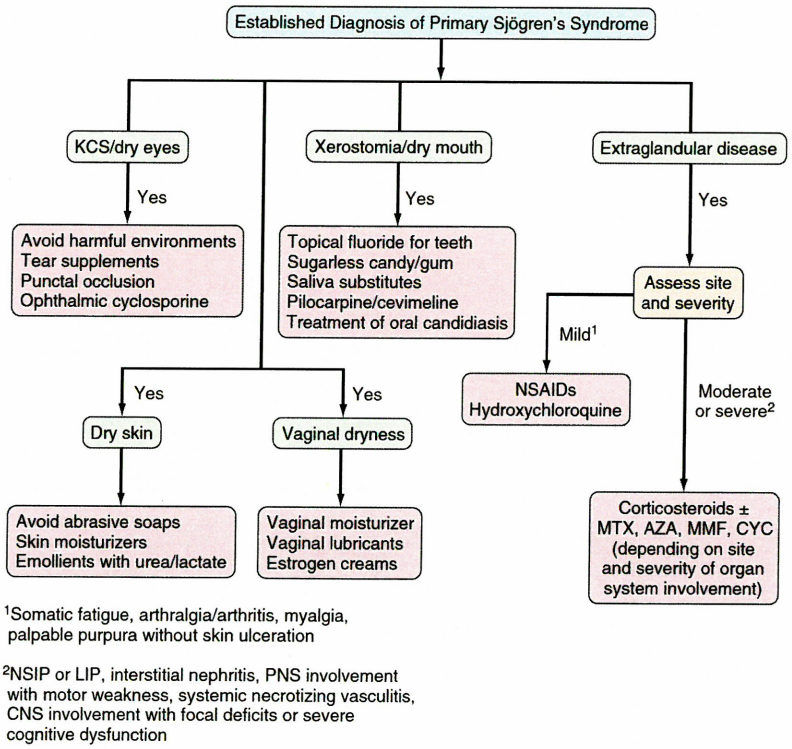


[1]Somatic fatigue, arthralgia/arthritis, myalgia, palpable purpura without skin ulceration

[2]NSIP or LIP, interstitial nephritis, PNS involvement with motor weakness, systemic necrotizing vasculitis, CNS involvement with focal deficits or severe cognitive dysfunction

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- Glandular symptoms with fatigue or athralgia mostly managed by low dose Steroids + NSAID + HCQ.
- Severe symptoms require Steroids + Cyclophosphamide/ oral MMF.
- Also look for anemia of chronic disease.

Outcomes :

- Accelerated atherosclerosis & association with thrombosis are not commonly seen in Sjogren.