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Sjögren Syndrome

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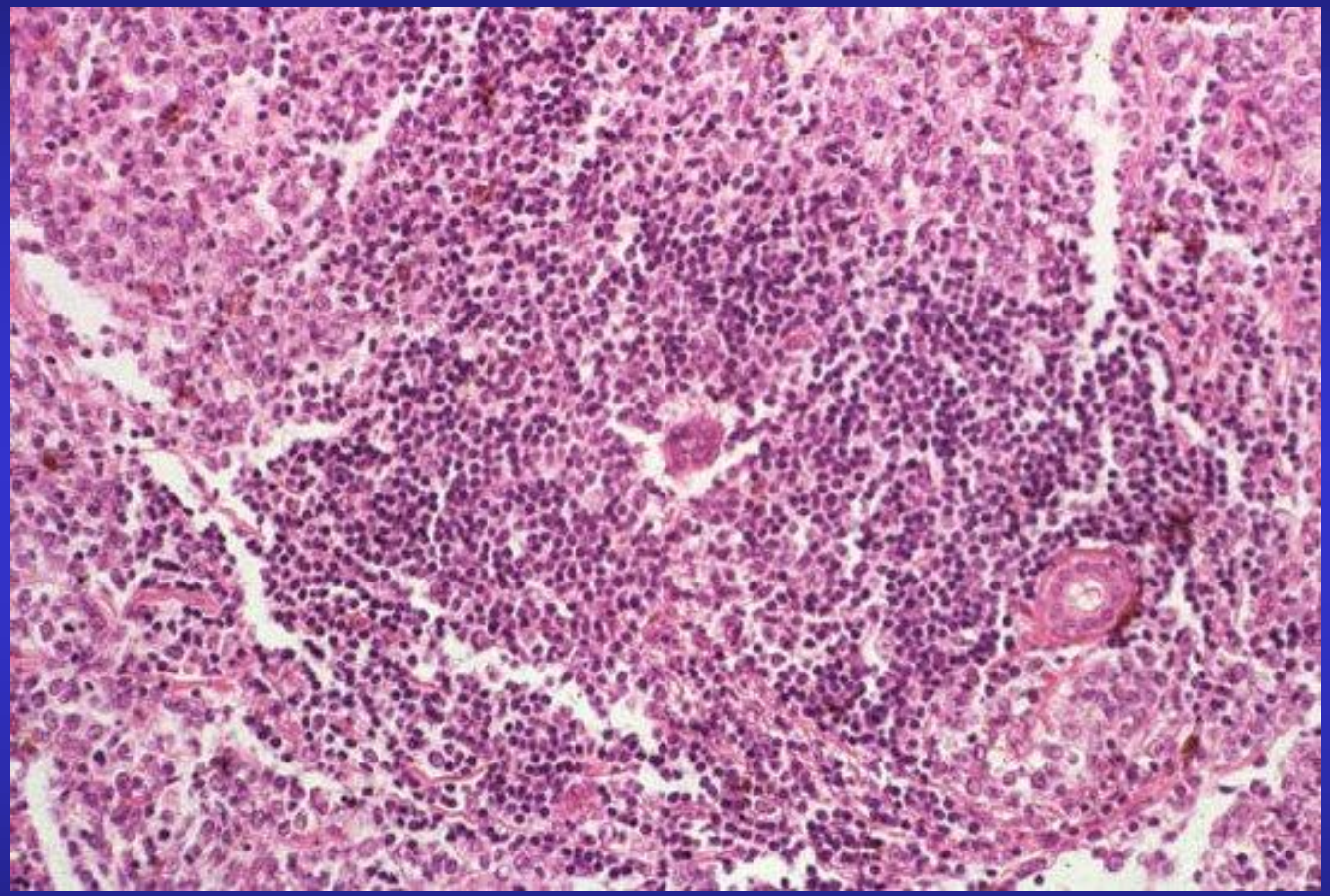
Definitions

• Common systemic autoimmune disease, with a female-to-male predominance of 9:1 and peak incidence at approximately 50 years of age.

• The hallmark of the disease is exocrinopathy, which often results in dryness of the mouth and eyes, fatigue, and joint pain.

Sjögren Syndrome (SS)– Histological Aspects



Clinical Aspects

- **D**ryness of the mouth and eyes, fatigue, and joint pain are present in more than 80% of the patients

- **Primary:** in isolation or in association with organ-specific autoimmune diseases, such as thyroiditis or primary biliary cirrhosis or cholangitis

- **Secondary:** in association with another systemic autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, or dermatomyositis.

Clinical Aspects

- The estimated prevalence is 0.3 to 1 per 1000 persons.

- The major diagnostic challenge relates to the fact that mouth and eye dryness, limb pain, and fatigue are very common in the general population and may be associated with fibromyalgia or other pain syndromes, whereas primary Sjögren's syndrome is relatively rare

Diagnosis and Evaluation

- A diagnosis of primary Sjögren's syndrome is often considered on the basis of the classic symptoms of mouth and eye dryness, fatigue, and pain.

- However, systemic complications sometimes provide the first clues to the disease.

- Patients presenting with such complications should routinely be queried about manifestations of primary Sjögren's syndrome and about the presence of other autoimmune diseases among family members.

Diagnosis and Evaluation

Table 1. 2017 ACR–EULAR Classification Criteria for Primary Sjögren's Syndrome.*

Item	Description	Score
Focus score of ≥1	A score determined by the number of mononuclear-cell infiltrates containing ≥50 inflammatory cells per 4 mm^2 of minor labial salivary gland obtained on biopsy	3
Presence of anti-SSA antibodies†	Measured in serum; only anti-Ro60 antibodies have to be considered; isolated anti-Ro52 antibodies are not specific for Sjögren's syndrome	3
SICCA ocular staining score of ≥5	A score determined by an ophthalmologist on the basis of examination with fluorescein and lissamine green staining; scores range from 0 to 12, with higher scores indicating greater severity	1
Schirmer test of ≤5 mm per 5 min	An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moisture on the paper	1
Unstimulated whole salivary flow of ≤0.1 ml per min	An assay for measuring the rate of salivary flow by collecting saliva in a tube for at least 5 min after the patient has swallowed	1
Total score		**9**

a diagnosis of primary Sjogren's syndrome is defined as a score of 4 or more, with at least one symptom of ocular or oral dryness or the presence of systemic manifestations suggestive of primary SS. † Positive serologic results for anti-SSB/La antibodies in the absence of anti-SSA/Ro antibodies is not specific and is no longer considered to be a criterion for the diagnosis.

Diagnosis and Evaluation

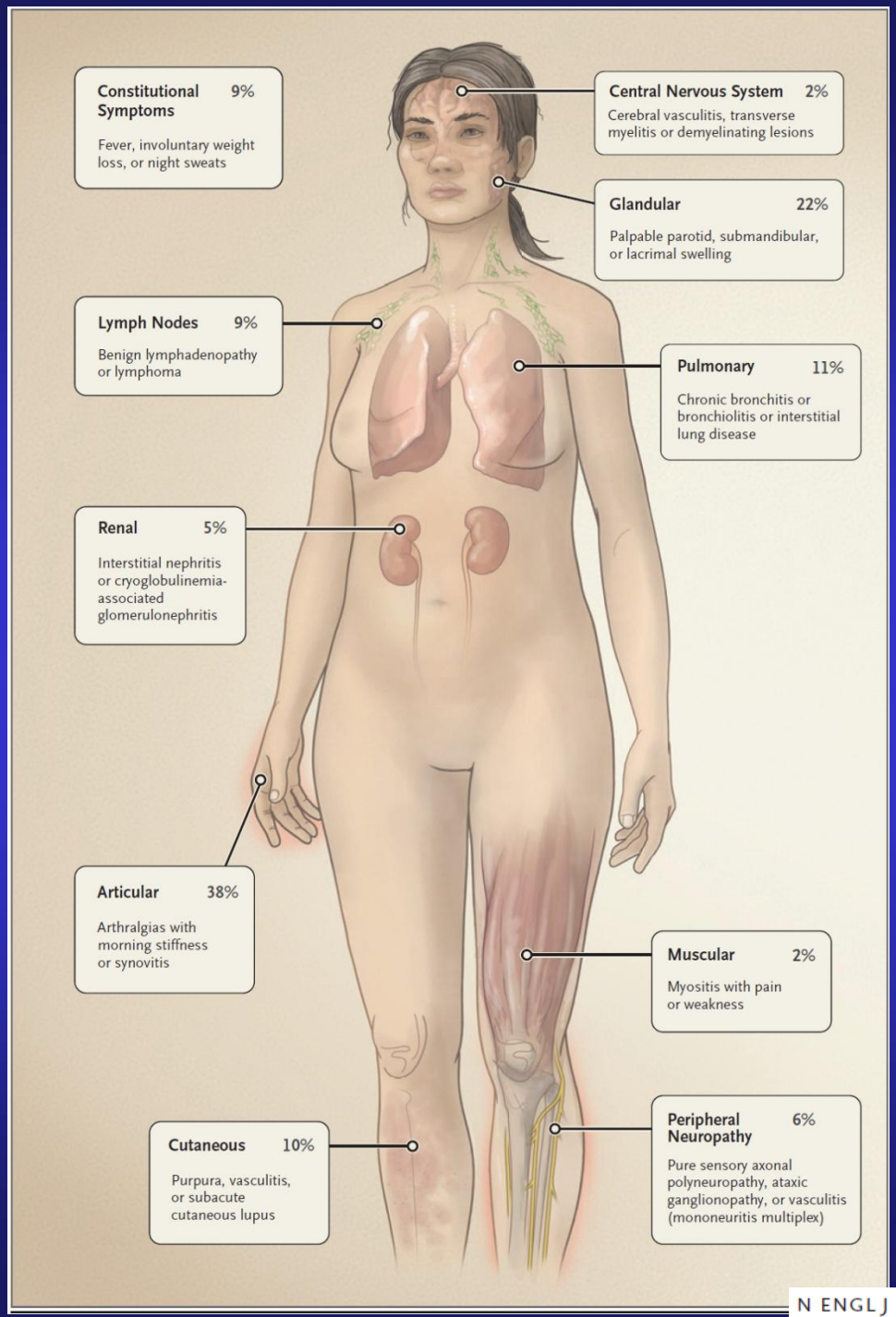
Exclusion criteria: active hepatitis C virus infection on polymerase-chain-reaction assay, radiotherapy of the cervical spine, sarcoidosis, graft-versus-host disease, receipt of anticholinergic drugs, and IgG4-related disease.

Systemic complications

- 30 to 40% of the patients with primary SS

- Lymphocytic infiltration of the epithelia of organs beyond the exocrine glands can cause interstitial nephritis, autoimmune primary biliary cholangitis, and obstructive bronchiolitis.

- Immune complex deposition can result in extraepithelial manifestations, such as palpable purpura, cryoglobulinemia-associated glomerulonephritis, interstitial pneumonitis, and peripheral neuropathy.


Constitutional Symptoms 9%
Fever, involuntary weight loss, or night sweats
Central Nervous System 2%
Cerebral vasculitis, transverse myelitis or demyelinating lesions
Glandular 22%
Palpable parotid, submandibular, or lacrimal swelling
Lymph Nodes 9%
Benign lymphadenopathy or lymphoma
Pulmonary 11%
Chronic bronchitis or bronchiolitis or interstitial lung disease
Renal 5%
Interstitial nephritis or cryoglobulinemia-associated glomerulonephritis
Articular 38%
Arthralgias with morning stiffness or synovitis
Muscular 2%
Myositis with pain or weakness
Cutaneous 10%
Purpura, vasculitis, or subacute cutaneous lupus
Peripheral Neuropathy 6%
Pure sensory axonal polyneuropathy, ataxic ganglionopathy, or vasculitis (mononeuritis multiplex)

Systemic complications

- Renal involvement in primary Sjögren's syndrome differs from that in SLE, since it is typically characterized by interstitial nephritis and associated with systemic acidosis, low levels of proteinuria, and progressive loss of renal function.

- Glomerulonephritis occurs more rarely in primary Sjögren's syndrome than in SLE and is most often associated with cryoglobulinemia.

Pathophysiological Features

- Activation of mucosal epithelial cells, possibly from viral stimulation.
- This process leads to the activation of the innate and adaptive immune systems with the secretion of autoantibodies.
- These autoantibodies constitute immune complexes that maintain and amplify the production of interferon alpha, resulting in a cycle of immune-system activation that leads to tissue damage.

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Pathophysiological Features

Data to support such models are derived from studies of innate immunity, genetics, and B-cell activation in primary Sjögren's syndrome.

The increased expression of genes related to interferon (either type I or type II) can be detected in salivary glands and blood in more than half the patients with this disease.7-11

Multiple viral agents have been hypothesized to have a role in the disease, although none have been shown to be causal.

Pathophysiological Features

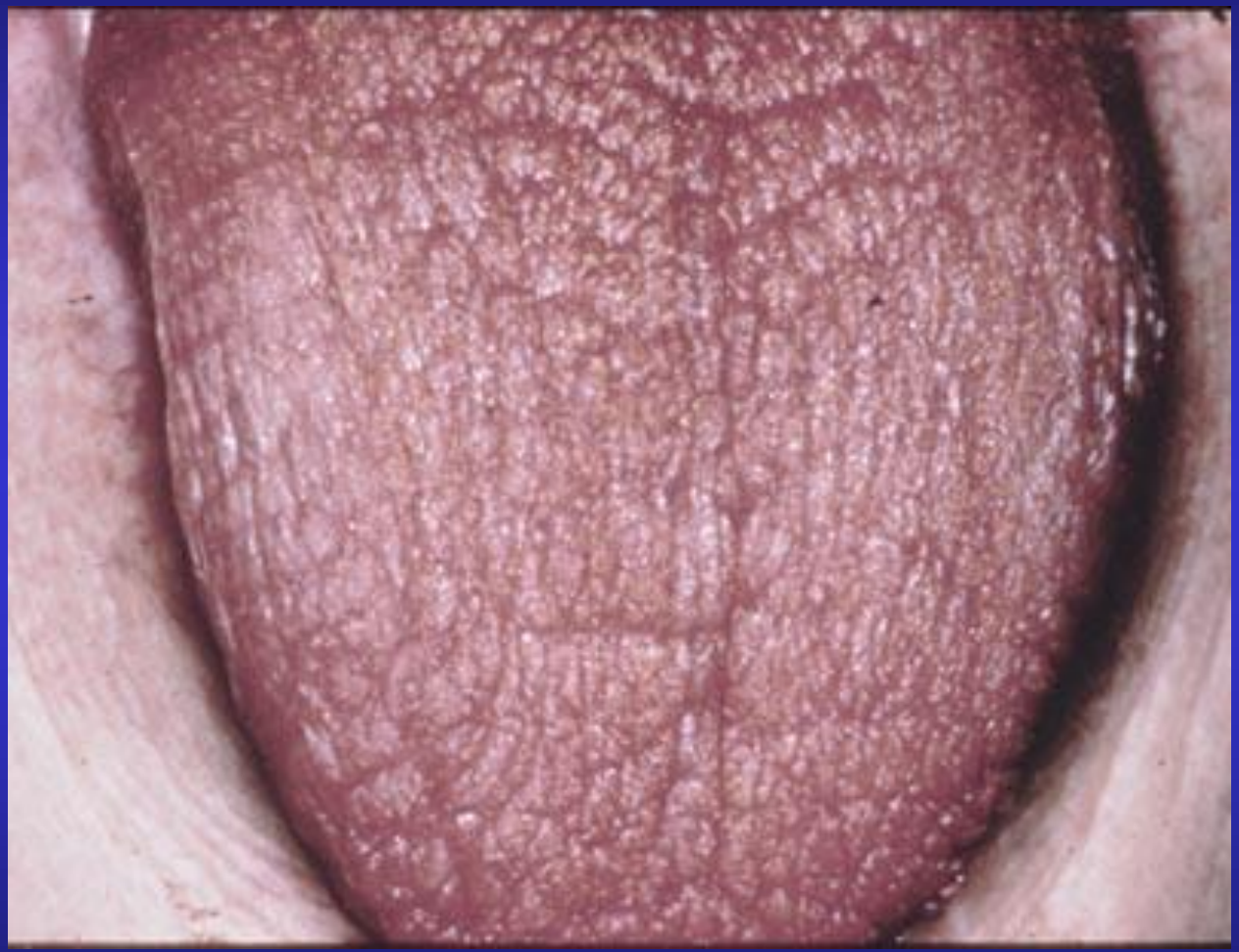
- Genome-wide association studies have shown associations between the syndrome and genes linked to interferon pathways.
- The presence of ectopic germinal centers in salivary glands highlights the B-cell activation that is characteristic of primary SS.
- Recent studies have suggested the presence of plasmablasts in the blood and plasma cells in the salivary glands and of activated CD8 T cells in the blood and glands.
- The level of B-cell activating factor of the tumor necrosis factor family (BAFF) is increased in primary SS, both in the serum and in salivary glands.

Early Symptoms of primary

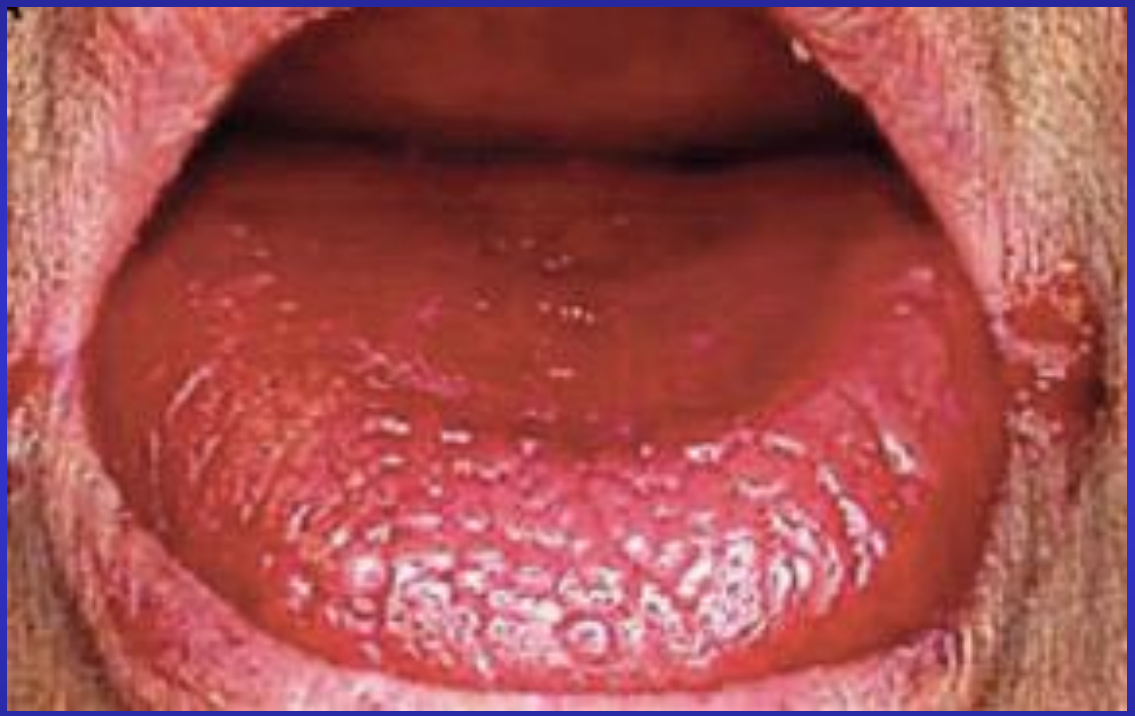
➢ Dry eye	47%
➢ Dry Mouth	43%
➢ Artralgia\Arthritis	28%
➢ Parotid gland swelling	24%
➢ Raynaud Phenomenon	21%
➢ Fever	10%
➢ Pulmomary involvement	2.5%
➢ Kidney involvement	2.5%

Red and Dry Eye

Dry Mouth



Dry Mouth



Salivary Gland Swelling

Unilateral	Bilateral
Neoplasias	Viral infections
Bacterial infections	Sjögren Syndrome
	Sarcoidosis
	Others:
	Diabetes
	Cirrhosis of the liver
	Chronic pancreatitis
	Acromegaly

Systemic Clinical Manifestations

➢ Lymphadenopathy	**15-20%**
➢ **Lung Involvement**	**10-20%**
➢ **Kidney involvement**	**10-15%**
➢ **Gut Involvement**	**10-15%**
➢ **Liver involvement**	**5-10%**
➢ **Vasculitis**	**5-10%**
➢ **Lymphoma**	**5-8%**
➢ **Peripheral neuropathy**	**2-5%**

Laboratory Testing

- Anti-SSA antibodies (often associated with anti-SSB) are present in two thirds of patients
- Rheumatoid factor is present in approximately half of the patients
- Anti-dsDNA are typically absent

Diagnostic work-up

- Biopsy of minor salivary glands is typically recommended for establishing a diagnosis of primary SS in the absence of anti-SSA antibodies

- Schirmer's test of ocular dryness and determination of the unstimulated salivary flow rate to assess oral dryness

- Ultrasonography of the major salivary glands may reveal multiple hypoechoic or anechoic areas in the four main salivary glands (parotid and submandibular glands) and may be helpful in diagnosis or longitudinal assessment, although such evaluation is not formally included among the classification criteria

Management and follow-up

• The risk of B-cell lymphoma is 15 to 20 times as high among patients with primary SS as in the general population, attributed to the chronic B-cell activation in this condition

•Mostly B-cell non-Hodgkin's lymphomas, with a predominance of the lowgrade, marginal-zone histologic type.

•Lymphomas often develop in organs in which primary SS is active, such as the salivary glands, and thus are primarily mucosa-associated lymphoid tissue (MALT) lymphomas

Table 2. Risk Factors for the Development of Lymphoma in Patients with Primary Sjögren's Syndrome.*

Risk Factor
Recurrent swelling of parotid glands
Splenomegaly, lymphadenopathy, or both
Purpura
Score of >5 on the ESSDAI†
Rheumatoid factor
Cryoglobulinemia
Low C4 level
CD4 T-cell lymphocytopenia
Presence of ectopic germinal centers
Focus score of >3‡
Germinal mutations in *TNFAIP3*

Therapeutic Approaches

Manifestation	Therapy
Ocular	
Xerophthalmia	Artificial tears: preserved/non-preserved
Blepharitis	Punctual occlusion
Iritis/uveitis	Topical ciclosporin
	Topical androgen (in trial)
	Topical purinogenic receptor agonist (in trial)
	Topical (non-preserved) steroids
	Autologous serum tears
	Lid scrubs for blepharitis
	Bandage contact lens
Oral	
Xerostomia	Mechanical stimulation
Periodontal	Regular oral hygiene
Gingitivis	Topical fluoride
Oral candidosis	Artificial saliva and lubricants
	Secretagogues, including pilocarpine, cevimeline
	Anhydrous maltose lozenge
	Interferon alfa (in trial)
	Therapy for oral candidosis
	Diet modification
	Gene therapies (preclinical)

Therapeutic Approaches

Joint/muscle	
Arthralgia/myalgia	NSAIDs
Arthritis/myositis	Antimalarial drugs
	Disease-modifying anti-arthritic drugs, including methotrexate, azathioprine, leflunomide
	TNF inhibitors
	Anti-CD20 (in trial)
Cutaneous	
Raynaud's syndrome	Corticosteroids (topical and systemic)
Hyperglobulinaemia purpura	Tacrolimus (topical)
Mixed cryoglobulinemia	Antimalarials
Erythema multiforme	Disease-modifying anti-arthritic drugs for vasculitis
Erythema annulare	Cytotoxic agents
Necrotising vasculitis	
Vitiligo, xerosis, alopecia	
Amyloid anetoderma	
Embolic and thrombotic lesions due to procoagulants	
Ears, nose, throat	
Sinusitis	Moisturing agents
Oesophageal reflux	Antibiotics and antifungal agents
Tracheal reflux	Proton-pump inhibitors
Parotid/submandibular swelling	Gastric motility agents
	Diet modification
Hearing loss	Steroids and disease-modifying anti-arthritic drugs

Therapeutic Approaches

- Benefit of muscarinic agonists (pilocarpine hydrochloride and cevimeline hydrochloride) for the treatment of oral dryness and, to a lesser extent, ocular dryness

- The use of topical cyclosporine eyedrops (0.05% or 0.1% concentration) has been shown to result in better tear production than placebo and in improvement in symptom scores among patients with moderate or severe ocular dryness and inflammation

- Ocular glucocorticoid drops are not recommended in such patients, since they are not very effective and are associated with adverse effects

Therapeutic Approaches

• Regular dental examinations and oral hygiene are crucial for reducing the risks of caries and periodontal disease associated with xerostomia

•Few biologic agents have been rigorously studied in primary SS, and none have shown significant efficacy in multiple studies.

•Randomized, controlled trials of infliximab and etanercept showed no significant improvement in a composite primary outcome on a visual-analogue scale of joint pain, fatigue, and dryness

•Rituximab may be useful for the treatment of some systemic manifestations. Data are limited with respect to the effectiveness of this drug for the prevention of lymphoma in the presence of risk factors for lymphoma.