Pathogenesis of Sjögren's syndrome

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Document Version: 5.0
Last Major Updated Date: Apr 17, 2012

The "Clinical Question":

Based on our current understanding of pathogenesis of Sjogren's syndrome (SS), why have clinical trials with biologic agents not yielded more significant changes in the patient's symptoms of oral or ocular discomfort?

Sjogren's syndrome has both **"benign"** and **"systemic"** manifestations. The benign manifestation of oral and ocular pain, as well as myalgia, fatigue, and brain fog are considered by patients as the leading causes of their "disability."

However, these "benign" symptoms do not correlate well with our acute phase markers of the innate and acquired immune system. Further, they have not responded significantly to clinical trials of cytokine inhibition, even when markers of extraglandular inflammation (as measured by ESSDAI) have improved. This suggests that we have not yet identified critical pathogenetic pathways responsible for these "benign" symptoms. New developments in the interaction of the immune system and the central nervous in the Ophthalmology research literature are now reviewed in this chapter. The identification of animal models and new neurokines may provide new directions to therapy.

Synopisis:

Primary Sjogren's Syndrome is estimated to be the second most common systemic autoimmune disorder with incidence lower than rheumatoid arthritis, but similar to Systemic Lupus Erythematosus. Lymphocytic infiltration into lacrimal and salivary glands leads to xerostomia (dry mouth) and keratoconjunivitis sicca (dry eyes), respectively.

- A third of patients develop systemic complications including skin, arthritic, renal, pulmonary and neurological manifestations.
- Approximately 5% may develop lymphoma, that has over a 20-fold greater incidence than other autoimmune disorders.

Both **genetic** and **non-genetic** (e.g., environmental and epigenetic) **factors** play a role in initiation of pathogenesis and disease progression.

- *Genetic factors* have implicated both the innate and acquired immune system.
- *Environmental factors* remain poorly understood, and there is a renewed interest in viruses such as Epstein-Barr based on genome sequencing and microRNA expression in the affected glands.

Salivary and lacrimal gland epithelial cells, as well as the local vascular adhesive molecules, play important roles in the early steps of lymphocyte homing and inflammation. The innate immune system has been demonstrated to have an important role, notably through the activation of Toll receptors and the type I interferon system.

In addition, mechanisms of T-cell and B-cell activation have shown the importance of the TNF family cytokine B-cell activating factor (BAFF).

The role of local autoantibodies such as anti-SS A/SS-B and the their ability to activate the innate immune through Toll receptors indicate the interaction of acquired and innate immune pathways. Subsequent T-cell activation leads to a complex pattern of cytokines derived from Th1 and NK-like cells. Neuroendocrine interactions are being explored as the basis of ocular and oral pain that patients consider a main cause of disability, but they do not correlate closely with our normal markers of systemic inflammatory response.

Pathogenesis of Sjögren's Syndrome

INTRODUCTION —
There is much to suggest that Sjögren's Syndrome (SS) is, like many connective tissue diseases, an autoimmune disorder. Support for this hypothesis includes: (a) a female preponderance, (b) distinctive HLA associations, (c) familial clustering with other autoimmune processes, (d) the presence of autoantibodies, and (e) the existence of shared clinical features (e.g., arthritis, Raynaud phenomenon, serositis) with other autoimmune connective tissue diseases.

The innate immune system has been demonstrated to have an important role at the early stage of the disease, notable the activation of the type 1 interferon (IFN) system. In addition, mechanisms of B-cell activation in SS have become clearer and provided targets for trials of biologic therapy.

TNF family cytokine B-cell activating factor production is highly dependent on expression of type 1 and type 2 interferons. Subsequent T-cell activation involves IFN-γ secreting type 1 T-helper cells and a novel subclass of CD4+ NK-like cells. With the recognition of these complex interactions, novel roles of additional cytokines may provide targets for therapy.

In addition to inflammatory regulation by cytokines and chemokines, the important role of gene regulation at the level of histone acetylation and non-coding RNAs is emerging as a potential target. Among the most serious complications such as lymphoma arising in SS, new data shows a role for another member of the TNF receptor family A20. Several excellent recent reviews of SS pathogenesis have appeared in the last year[1, 2].

The close relationship of primary SS and Systemic Lupus Erythematosus (SLE) has led to the suggestion that primary SS likely

shares common pathogenetic features with SLE [1]. If it is considered that SLE consists of several subgroups that are each characterized by particular autoantibodies and HLA-DR alleles, then SS has close similarities to one of these SLE subsets (i.e., HLA-DR3, anti-SSA antibody-positive). In this regard, SS might be loosely considered a subset of SLE, characterized by particular homing receptors that allow lymphocytic infiltrates into particular extranodal sites, such as salivary and lacrimal glands. Thus, the features of SS include ocular and oral dryness, as well as increased frequency of lymphoproliferative disorders including an elevated risk of lymphoma [1].

Due to the relative ease and safety of biopsying the target organ of inflammation (e.g., the salivary or lacrimal gland, or conjunctiva), SS provides a prototype for understanding the interaction of immune and neuro-endocrine systems. With availability of techniques of molecular biology to analyze the plethora of proteins (proteomics) of small tissue samples and fluids, it should be possible to correlate the changes in tissue with those in blood and draining fluids (i.e., tears and saliva) in order to assess prognosis and to provide biomarkers for response to therapy.

Although features of dry eyes, dry mouth and systemic manifestations such as vasculitis remain well understood, the vague symptoms of muscle pain, mild cognitive defects and (fibromyalgia-like) fatigue remain poorly characterized at a molecular level. Treatment for these common symptoms will depend on further understanding of pathogenesis. The interaction of the glandular inflammation, afferent innervation of:

- the midbrain (lacrimal and salivary nuclei of the Vth cranial nerve),
- projection to the cortical centers for sensing dryness/pain, and
- the efferent pathways back to the glands to initiate secretory function

have been termed *"the functional circuit"* by Stern and co-workers [3-6].

Although we have learned a great deal about the cytokines within the inflamed glands, the knowledge of other neurokines and their relation to cortical function remain to be elucidated more fully[7-9].

Mikulicz's disease (MD) has been considered a subtype of Sjögren's syndrome (SS) based on histopathological similarities. However, it is now recognized that MD is an IgG4-related disorder, distinguishable

from SS, and called an IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS)[10].

Regarding immunological aspects, it is generally accepted that CD4+ T helper (Th) cells play a crucial role in the pathogenesis of SS. IgG4-related disease (IgG4-RD) is a systemic disease characterized by the elevation of serum IgG4 and infiltration of IgG4-positive plasma cells in multiple target organs, including the pancreas, kidney, biliary tract and salivary glands.

Our current understanding of the pathogenesis of SS is reviewed here. The clinical manifestations, diagnosis, and treatment and prognosis of this disorder are discussed separately.
The reader is directed to these four **UpToDate.com** links for more information:

(1) **"Clinical manifestations of Sjögren's syndrome: Exocrine gland disease"**
http://www.uptodate.com/contents/clinical-manifestations-of-sjogrens-syndrome-exocrine-gland-disease

(2) **"Clinical manifestations of Sjögren's syndrome: Extraglandular disease and prognosis"**
http://www.uptodate.com/contents/search?search=%22Clinical+manifestations+of+Sjögren%27s+syndrome%3A+Extraglandular+disease+and+prognosis%22+&x=0&y=0

(3) **"Classification and diagnosis of Sjögren's syndrome"**
http://www.uptodate.com/contents/search?search=%22Classification+and+diagnosis+of+Sjögren%27s+syndrome%22+&x=0&y=0

(4) **"Treatment of Sjögren's syndrome"**
http://www.uptodate.com/contents/search?search=%22Treatment+of+Sjögren%27s+syndrome%22&x=0&y=0

OVERVIEW OF PATHOGENESIS —
An overview of pathogenesis is given prior to discussion of specific steps, and there have been several excellent recent reviews [2][10]. An overlap of a subset of Systemic Lupus Erythematosus (SLE) and SS is evident in their:

- clinical manifestations,
- laboratory abnormalities (i.e., ANA and anti-SS-A antibody),
- genetics (HLA-DR3), and

- treatment.

Further, the gene signatures in both SLE and SS include a predominant type I interferon expression of mRNA expression [11-14]. Thus, it might be humorously expressed that SS is really SLE with homing receptors to particular sites such as salivary and lacrimal glands, as well as to other sites that characterize extraglandular involvement in SS. The pathogenesis of SLE is discussed in detail elsewhere. For further information, please refer to the **UpToDate.com** link:

"Epidemiology and pathogenesis of systemic lupus erythematosus"
http://www.uptodate.com/contents/search?search=%22Epidemiology+and+pathogenesis+of+systemic+lupus+erythematosus%22&x=0&y=0

The overlap of SS and SLE includes many features, but the most distinct features of SS are lymphocytic infiltrative, and those of SLE appear antibody-mediated (immune complex leading to complement activation).

Thus, we see a somewhat **distinct pattern of pathogenesis in SS** in comparison to SLE.

- The lung disease in SS tends to be interstitial pneumonitis rather than pleurisy, and
- The renal disease is interstitial nephritis rather than glomerulonephritis.

Thus, the damage seen in SLE tends to be antibody mediated, while that in SS tends towards lymphocytic infiltrative. In this regard, SS is a "lymphocyte"-aggressive disorder that starts with lymphocytic infiltration into lacrimal and salivary glands where lymphocytes are not normally found. Thus, it should not be surprising that SS patients have a highly increased frequency of lymphoma, the ultimate outcome in a "lymphocyte" infiltrative disorder. For more information, please refer to the **UpToDate.com** link on:

"Clinical manifestations of Sjögren's syndrome: Extraglandular disease and prognosis", section on 'Lymphoma'
http://www.uptodate.com/contents/search?search=%22Clinical+manifestations+of+Sjögren%27s+syndrome%3A+Extraglandular+disease+and+prognosis%22%2C+section+on+%27Lymphoma%27&x=0&y=0

The pathogenesis of SS includes multiple different steps:

a) ***genetic and gender predispostion***;
b) ***non-genetic factors*** including environmental factors such as viral infection, and epigenetic factors that modulate gene expression including histone acetylation, non-coding RNA's and microRNA's
c) ***alteration of local vascular endothelial cells*** in the target organs, including upregulated expression (HLA-DR, chemokines and their receptor) to promote homing of lymphocytes and their migration into the gland.
d) ***activation of innate and acquired pathways*** by lymphocytes within the glandular tissues or extraglandular sites leading to cytokine release and production of autoantibodies
e) ***apoptosis of glandular cells and dysfunction of residual glandular function*** due to cytokines and metalloproteinases
f) ***alteration of the afferent signaling pathways*** from the gland to the regions of the brain that regulate salivatary and lacrimal function.
g) ***alteration of the efferent signaling pathways*** from the brain to the gland to initiate glandular function
h) ***alteration of the cortical regions*** that give rise to the cognitive sense "dryness" and oral/ocular discomfort

The clinical-pathology correlation of a patient's sensation of **dry eyes** consists of several components [43-45]. The patient's description of increased work of blinking refers to the increased viscosity of the lid traversing the globe. As a consequence of lymphoid infiltration into the lacrimal glands, there is a decrease in aqueous tear production due to partial destruction of the glands and due to the dcereased secretory ability of the residual glands as a result of local cytokine production.

- Only about 50-percent of the acini/ducts are destroyed on biopsy in patients with significantly dry eyes or mouth, so the residual glands are functionally impaired.

The patients also describe **pain in the eye** [46]. Dryness of the cornea may cause exfoliation of the superficial corneal epithelium leaving corneal erosions, resulting in considerable ocular discomfort, which is chronic in nature, because of the characteristics of SS [47]. The cornea is the tissue most densely innervated in the body and receives sensory and autonomic nerves fibers that are located primarily in the epithelial layer and are supplied by the long ciliary nerves, derived from the trigeminal nerve (cranial nerve V).

There are **two types of nerve fibers in the corneal epithelium:**
(1) the *myelinated A-delta fibers* that run parallel to the corneal surface within the basal cell layer, and
(2) the *unmyelinated C fibers* that turn upward from the epithelial plexus toward the surface [47].

A-delta fibers are large-diameter, straight nerves that respond primarily to mechanical stimuli, whereas C fibers are small-diameter, beaded nerves that respond to thermal and chemical stimuli.

The stimulus triggering the activation of these cells activates neural mechanisms responsible for perception of acute pain, with consequent behavioral adaptation aimed to give protection from the irritating stimulus. The persistent C fiber input can easily lead to the summation (wind-up) of stimuli, resulting in augmented responses of the spinal trigeminal nuclei neurons and final central sensitization [48,49].

It will also activate the *parasympathetic innervation* of the lacrimal glands and conjunctival goblet cells resulting in their increased secretion. However, in chronic inflammatory conditions such as SS, summation of peripheral input may occur, since C fiber activity starts to dominate the A-delta fiber activity, resulting in an active inhibition of the parasympathetic system at the central level of the peri-aqueductal grey area of the limbic system [50,51]. This results in further peripheral sympathetic and/or parasympathetic dysfunction in SS.

However, a key observation about the chronic eye pain in SS patients has recently been emphasized by Rosethal et al. [8] As the clinical course progresses, the SS patient's symptoms have relatively poor correlation with objective findings on ocular exam. Indeed (and interestingly), he has found that in chronic eye pain patients with SS, the pain is only partially reduced by local anesthesia. He has attributed this residual pain to a "nocioceptive phantom pain" that can be mapped by functional MRI to a particular region of the brain cortex[7].

Genetic factors —
A familial tendency to SS has been well documented, including the occurrence of a variety of autoimmune disorders in relatives of patients with this disorder. Using California criteria, "definite" or "probable" SS occurred in 4.4 percent in first-degree relatives in one

series, all of whom were female and older than the probands [59]. Family members are also more likely to have autoantibodies.

In one report, for example, the following observations were noted in families of anti-Ro/SSA positive patients with primary SS or SLE [60]:

- *Twenty-one percent of first-degree relatives and 11 percent of second-degree relatives had detectable levels of anti-Ro/SSA antibodies*. The frequency increased to 41 percent in relatives considered to have clinical or serologic evidence of autoimmune disease. The comparable value in relatives from healthy families was 6 percent.
- *Anti-La/SSB antibodies were infrequent* in the relatives.

The best genetic marker for SS appears to lie within the MHC complex. In Caucasians, primary SS is associated with an increased frequency of HLA DR3 (DRB1*03) [61,62], in particular with the extended haplotype HLA-DR3, B8, DQ-2, and the C4A null gene. This haplotype is found in approximately 50-percent of cases, but also in 20- to 25-percent of the healthy Caucasian population [56].

Genetic factors are more closely associated with autoantibody production than with the disease itself. Thus, if patients producing anti-Ro or anti-La antibodies are considered, the frequency of HLA-DR3 in Caucasians rises to 60- to 90-percent [63].

There is, however, considerable heterogeneity in the HLA-DR association across different ethnic groups.

- Greek and Israeli patients show a link to DR5 as opposed to DR3 [64],

while different haplotypes are also seen in:

- Japanese (DRB1*0405-DRB4*0101-DQA1*0301-DQB1*0401),
- Chinese (DRB1*0803-DQA1*0103-DQB1*0601), and
- Spanish (DRB1*15) patients [65,66].

These differences could be explained if the true association lies with HLA-DQA1 that is itself in linkage disequilibrium with both DR3 and DR5. Structural analysis has lent some support to this hypothesis. One series, for example, found that all 106 subjects with Sjögren's syndrome or systemic lupus erythematosus who produced anti-Ro antibodies had glutamine at position 34 of DQA1 and/or leucine at position 26 of DQB1 [67].

Although the incidence of having one "risk" allele out of four is high due to chance alone, there seems to be a gene dose effect with an increasing risk of producing anti-Ro antibodies in association with a greater number of such DQA and DQB alleles [67-69].

Genes other than those of the HLA loci may also be associated with an increased risk of disease. Genetic polymorphisms associated in SS are summarized in **Table 1**, as summarized in the excellent recent review by Nocturne et al [1]. Several of these with particular interest include:

- *IL-10 promoter polymorphisms* —IL-10 has strong sequence homology to EBV encoded protein BCRF! and thus may provide a link between between EBV infection and initiation/progression of SS

  Please refer to the **UpToDate.com** link on:

  "Role of cytokines in the immune system"

  http://www.uptodate.com/contents/search?search=%22Role+of+cytokines+in+the+immune+system%22.%29&x=0&y=0

- *MHC region*—HLA-DR and extended haplotype which are involved in antigen presentation by T-cells and B-cells;
- *Homing Receptor (Chemokine receptor 5)*: CXCR5 which influences B-cell follicle organization;
- *CTLA-4* — Two common haplotypes of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) gene may be associated with an increased risk of developing primary SS and with serologic and extraglandular features [71];
- *IRF5 gene* — An association between a common interferon regulatory factor-5 (IRF5) gene polymorphism and primary SS was noted in a single study of 212 patients and 162 healthy blood donors in France [72];
- *TNP1*—an inhibitor of TNF signaling vi interference with A20, that is important in lymphagenesis risk in SS[1];
- *MBL2*—a pattern recognition receptor that may augment Toll receptor signaling from the phagosome.

Finally, it is worth mentioning…

Microchimerism, the persistence of some cells derived from another individual, has been suggested to be important in the pathogenesis of SS and some systemic disorders that share features with murine chronic graft versus host disease. This phenomenon has been the subject of much debate in systemic sclerosis (scleroderma).

Please refer to the **UpToDate.com** link:

"Pathogenesis of systemic sclerosis (scleroderma)", section on 'Graft versus host disease or microchimerism'

http://www.uptodate.com/contents/search?search=graft+versus+host+disease+or+microchimerism+&x=0&y=0

A possible role for microchimerism in patients with primary SS was suggested by a preliminary report finding of DNA sequences derived from the Y chromosome in biopsy material from labial salivary glands of 36-percent of patients with SS, but in none of 10 patients with other disorders [120]. However subsequent studies have not supported the initial observations for a significant role of microchemerism in SS[11].

Non-Genetic Factors including Viral infection —
A role for viruses in the pathogenesis of SS is suggested by a number of observations [73].

- *Certain viruses, particularly the ubiquitous herpes viruses Epstein-Barr virus (EBV), frequently infect the salivary glands.* It is the pathogenetic agent of infectious mononucleosis and EBV is spread to non-infected individuals via the saliva. Primary EBV infections progress to lifelong latent infection with periodic reactivation. The site of latency for EBV is in the salivary gland.

- *EBV has the ability to induce strong immune responses* by T-cells and activate B-cell production of autoantibodies.

- *The Ro and La antigens*, targets of autoantibody production in SS, are involved, and were first identified as "chaperones" for viral RNA after infection with either adenovirus or EBV

  Please refer to the **UpToDate.com** link:

  "Clinical significance of anti-Ro/SSA and anti-La/SSB antibodies"

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- *At least three viruses, human T-lymphotropic virus (HTLV) type I, HIV, and hepatitis C*, are known to be associated with clinical syndromes that share many features of SS.

Epstein-Barr virus —
Initial interest focused on three viruses:
(1) *EBV*,
(2) *cytomegalovirus*; and
(3) *human herpesvirus-6 (HHV-6)* [74].

Studies are complicated by the high level of infection within the general population, and data from serologic studies has been conflicting. Some reports have found raised antibody titers to all three viruses in SS [75,76], while other workers have noted no increase compared to the normal population [77,78].

Similarly, although genetic material from EBV can be detected in SS salivary tissue by DNA hybridization [79] similar findings can also be seen in normal individuals.

Furthermore, even when EBV is detected in salivary tissue, less than 1-percent of cells are infected, and there may be a delay of many years between primary infection and the development of SS.

- A renewed interest in the role of *Epstein Barr virus (EBV)* has resurfaced with the recognition of several viral encoded microRNA's such as miR-146a and BART155) that can be detected in salivary gland biopsies of SS and stimulate the innate immune system [12].
  - In addition to the known site of infection and latency of EBV in salivary glands, new studies have also shown conserved intronic EBV sequences[13].
  - An elegant recent study by Steitz and coworkers (who first identified SS-A /SS-Bas a viral RNA transport molecules even before their association with SS) recently reported a genome wide survey showing at least 4 different EBV strains that may have latency or inserted introns that play a role in autoimmunity[13].

Other viruses with renewed interest in SS based on miRNA sequences include:

- *adenoviruses*,

- other *herpes viruses,* and
- *polyoma viruses*[14].

EBV encoded BCRF1 has strong sequence homology to IL-10 and encoded microRNAs detected in SS salivary gland[15, 16].

Because a causative link between these ubiquitous viruses and disease is difficult to prove, **attention has become focused on the detection of unusual virus genomes or atypical immune responses to virus by the host**.
As an example, a study of Chinese patients with SS found that genetic material from EBV was detectable, but differed from that of normal EBV in that the DNA contained an unusual genomic deletion [80]. It is therefore possible that the EBV in patients with SS differs structurally or antigenically from that in controls, or that some subjects have an HLA restricted inability to clear EBV infected cells, thereby predisposing these individuals to persistent infection [81].

Retroviruses —
Retroviruses are capable of disrupting the immune system by infecting immune cells, possibly leading to suppression, destruction, or stimulation of T-cells, increased production of antibodies, and development of malignancies such as lymphomas.

At least two retroviruses, **HIV and HTLV-I, are known to cause SS-like syndromes** [81,82]. Additional support for a role for HTLV-I came from a transgenic mouse model in which the tax gene had been inserted [87]. These animals developed a spontaneous sialadenitis characterized by focal proliferation of ductal epithelial cells within the major and minor salivary glands followed by lymphocytic infiltration.

Two groups initially reported the presence of HTLV-I genome in salivary gland tissue from patients with SS [83,84]. In both cases, only the tax gene was detectable with pol, gag, and env being apparently absent. It is possible that these results represented infection with a defective virus in which all genes other than tax had been deleted. This is an attractive theory, since it would explain the lack of easy vertical transmission that would be expected in complete virus infection.

There are other diseases in which defective HTLV-I proviruses are thought to play a role, such as mycosis fungoides and HTLV-I-associated T-cell leukemia. However, it is also possible that failure to detect other parts of the genome is due to technical factors associated

with PCR, or that the finding of tax itself is due to contamination artifact [56]. The fact that two independent groups found similar results makes the last two explanations less likely.

In both studies, no patient had serum antibodies to HTLV-I. This is in marked contrast to earlier reports from Japan and the United States, suggesting an increase in antibodies to HTLV-I in patients with SS [85,86]. It is unclear whether some subgroups of SS patients are able to produce antibodies to HTLV-I while others are not.

The general consensus for rheumatologists and SS patients is that no evidence for retroviruses as a causal agent in the routine type of SS described in this chapter and the anecdotal reports in the public press have caused great patient consternation. However in scientific honesty, it must be stated that the role of retroviruses remains to be elucidated.

Human endogenous retrovirus (HERV) and solitary long terminal repeats (LTRs) constitute 8% of the human genome. Although most HERV genes are partially deleted and not intact, HERV LTRs comprise features including promoters, enhancers, selective splicer sites and polyadenylation sites in order to regulate the expression of neighboring genes. Moreover, genetic instability, hypomethylation, transactivation and the antisense transcript of LTRs enhance the activity of LTRs and regulate the expression of their adjacent genes in human SS[17].

A subgroup of patients with HIV infection, for example, develop diffuse infiltrative lymphocytosis (DILS), in which patients exhibit xerostomia, keratoconjunctivitis sicca (KCS), and bilateral parotid swelling. This disorder differs from SS in that:
(a) The infiltrate in the salivary glands is predominantly CD8+ T-cells,
(b) Antibodies are seen less frequently,
(c) There is an excess of males (3:1), and,
(d) There are different HLA associations (HLA-DR5 and DR6) [88].

The pathology of the lymphocytic infiltrate and clinical associations have led to clear distinction of this variation of HIV (also called AIDS Related Salivary Gland Syndrome) from SS discussed in this section.

Hepatitis C virus —
Hepatitis C virus (HCV) is increasingly recognized as a cause of a SS-like syndrome [89,90]. A mild sialadenitis is common and a lymphocytic infiltrate can be detected in the glands [91]. Such patients may also

have type II mixed cryoglobulinemia and produce rheumatoid factor [92]; in comparison, antibodies to Ro and La are typically absent. Thus, rather than representing an etiologic factor for primary SS, HCV infection should be part of the differential diagnosis of sicca symptoms, especially in patients who lack anti-Ro or anti-La antibodies. It is important to recognize the presence of autoimmune disease in chronic HCV infection, since patients with concurrent autoimmune hepatitis may flare after therapy with interferon alpha [93].

Please refer to the **UpToDate.com**
"Principles of interferon therapy in liver disease and the induction of autoimmunity", section on 'Liver disease'
http://www.uptodate.com/contents/search?search=principles+of+interferon+therapy+in+liver+disease+and+the+induction+of+autoimmunity&x=0&y=0

Coxsackievirus —
Coxsackievirus infection may play a role in primary SS [94]. This was suggested by a study of minor salivary gland biopsies. Coxsackievirus RNA was identified in extracts of tissue in seven of eight patients with primary SS, but from none of those with secondary SS or from control tissues [95]. Immunohistochemical staining with a monoclonal antibody to a viral protein revealed reactivity in:

- 11 of 12 samples from patients with primary SS,
- 1 of 8 with secondary SS, and
- none of the controls.

A report from another center failed to confirm the report of coxsackie virus in SS tissue [96].

In summary, no single virus is clearly implicated in the pathogenesis of SS. Although virus can be detected in many patients, no virus has been present at high levels in target tissues. It is possible that low levels of virus-infected cells may be sufficient to break tolerance to autoantigens.

Autoantibodies —
SS is characterized by the presence of certain autoantibodies that by some criteria, are required for the diagnosis to be made, especially **Anti-Ro/SSA and anti-La/SSB**. Antibodies to acetylcholine receptors of salivary glands have been found and could account for decreased secretion from histologically normal glands. Antisalivary gland antibodies can be detected in some patients but they are infrequent and present at low titer, suggesting a secondary response to tissue already damaged by another process.

Antinuclear antibodies, as detected by immunofluorescence using Hep-2 cells, are present in 90 percent of patients and high titer rheumatoid factor is also frequently found. Some patients may have autoantibody production within exocrine glands. Ectopic lymphoid germinal centers in such patients contain antigen presenting dendritic cells, T-cells, and B lymphocytes and provide a conducive microenvironment [100].

Ro/SSA and La/SSB — Most interest in patients with SS has focused on the antibodies directed against nuclear proteins Ro/SSA and La/SSB. These antibodies can be detected in serum and may be produced locally in salivary glands [101].
See **UpToDate.com** link:

"Clinical significance of anti-Ro/SSA and anti-La/SSB antibodies"
http://www.uptodate.com/contents/search?search=%22Clinical+significance+of+anti-Ro%2FSSA+and+anti-La%2FSSB+antibodies%22&x=0&y=0

Perhaps the most carefully studied of these autoantigens is SSA Ro52, which belongs to the tripartite motif (TRIM) or RING-B-box-coiled-coil (RBCC) protein family, thus comprising an N-terminal RING, followed by a B-box and a coiled-coil region 34. Several different proteomic functions have been suggested for Ro52, including DNA binding, protein interactions and Zn(2+)-binding. Two structured parts of Ro52 have identified, corresponding to the RING-B-box and the coiled-coil regions, respectively.

Secondary structure analysis by circular dichroism (CD) spectroscopy indicated that the two subregions are independently structured. The entire RING-B-box region displayed Zn(2+)-dependent stabilization against proteolysis in the presence of Zn(2+), indicating functional Zn(2+)-binding sites in both the RING and the B-box. However, no stabilization with DNA was detected, irrespective of Zn(2+), thus suggesting that the RING-B-box region does not bind DNA. Immunologic analysis of the stable protein regions with sera from patients with Sjögren's syndrome shows that immunodominant epitopes to a large extent are localized in the structurally stable parts of Ro52. The results form a basis for further Ro52 functional studies on the proteome level.

- **Anti-Ro/SSA antibodies are found in over 70 to 90 percent patients with SS and about 35 to 50 percent of patients**

with lupus [102]. These antibodies are predominantly of the IgG1 subclass and recognize at least two proteins complexed with RNA: a 52 kD, 475 amino acid protein and a 60 kD 525 amino acid protein. Anti-52 kD antibodies are found more frequently in SS than RA or SLE, whereas anti-60 kD antibodies are more prevalent in SS associated with SLE [103]. Both antigens are located primarily in the nucleus, but expression in cytoplasm and on the cell surface also occurs.

A sicca syndrome and anti-Ro/SSA antibodies can also occur in primary biliary cirrhosis. The anti-Ro/SSA antibodies in this setting are directed against a smaller epitope on the 52 kD protein than in primary SS [104].

- **Anti-La/SSB antibodies are found in 50 percent of patients with SS.** These antibodies recognize a 47 kD phosphoprotein associated with newly synthesized RNA polymerase III transcripts. The gene encoding SSB is unusual in that it has two promoter sites, encoding for two different size mRNAs, and raising the possibility of gene switching under disease conditions [105].
- **Anti-centromere antibodies are found in a subset of SS patients lacking criteria for systemic sclerosis.** However, these patients do have a higher frequency of telangiectasias and Raynaud's.
- **The inclusion of anti-Ro/La antibodies in the current classification criteria strongly biases patient cohorts for research purposes**; ultimately, we must recognize that only about 60% of SS patients have these antibodies.

In vitro, antibodies to Ro are capable of mediating cytotoxicity against targets coated with Ro antigen [106]. There is, however, no direct evidence that antibodies to Ro or La are pathogenic in vivo. Although predominantly nuclear in location, cell surface expression with antibody binding has been demonstrated in an animal model [107]; expression is increased by exposure to ultraviolet light which may be relevant considering the photosensitive nature of skin lesions in SLE. There is also some evidence that the epithelial cells of salivary glands in SS express the La antigen as judged by binding of anti-La antibody to epithelial cells on histological sections from salivary gland biopsy [108]. These antigens could be exposed to circulating autoantibodies.

The most compelling evidence for a pathogenic role for autoantibodies in SS comes from patients with neonatal lupus, the most serious manifestation of which is complete heart block. Both anti-Ro and anti-La antibodies are found in 80 to 90-percent of mothers (some of whom have Sjögren's syndrome) of children with neonatal lupus, and almost all with complete heart block. Ro and La antigens are abundant in fetal heart tissue between 18 and 24 weeks. Maternal IgG anti-Ro and anti-La antibodies can cross the placenta and bind to fetal cardiac conducting tissue, resulting in autoimmune damage to the atrioventricular node and surrounding tissues.
See the **UptoDate.com** link:
"Neonatal lupus"
http://www.uptodate.com/contents/search?search=%22Neonatal+lupus%22&x=0&y=0

Anti-Muscarinic and Nicotinic Receptor Antibodies

The potential role of antibodies against the muscarinic (M) receptor for acetylcholine has been reviewed [39]. Although initially, it was difficult to demonstrate that these antibodies reacted with the extracellular domain of the human M3 receptor, subsequent reports suggested methods to detect such binding [40] and perhaps include SS in the spectrum of autoimmune disorders such as Grave's disease or myasthenia gravis where anti-receptor antibodies are pathogenetic. A modified assay using a cyclic sequence of the M3 receptor showed a higher specificity of anti-M3R antibodies in SS (67%) than in SLE patients (2%)[18]. T-cell epitopes of the M3R receptor have also been detected in SS patients and murine models[19]. It remains to be seen whether such antibodies in SS are primary or secondary phenomena.

Autoimmune autonomic ganglionopathy (AAG) is a disorder defined by antibodies to the nicotinic acetylcholine receptor of the autonomic ganglia. Song et al [20] reported two patients with chronically progressing dysautonomia and Sjögren's syndrome (SS).

Anti-alpha-fodrin —
Although no pathogenic role has yet been found for antibodies directed against alpha-fodrin (an actin-binding protein), their presence may be more sensitive and specific for Sjögren's syndrome than anti-Ro and/or anti-La antibodies.

As an example, anti-alpha-fodrin antibodies were found in

- 41 of 43 patients with primary Sjögren's syndrome,

- 5 of 8 with secondary Sjögren's syndrome,
- none of 21 patients with SLE, 14 with RA, or 15 healthy individuals [109].

Similar sensitivity, but slightly less specificity, has been noted in children with primary Sjögren's syndrome or SLE [110]. However, lower sensitivity and specificity have been reported by others with anti-alpha fodrin antibodies present in 16 of 56 (29 percent) patients with primary Sjögren's syndrome and in 25 of 53 (47 percent) of those with SLE without sicca symptoms [111]. Anti-alpha-fodrin antibodies of the IgA class appear to be less sensitive for primary and secondary disease (approximately 60 to 65 percent) [112].

Additional study of the clinical use of testing for anti-alpha-fodrin antibodies is needed to assess their role in diagnosis of Sjögren's syndrome. However, the most recent studies have suggested that IgG anti-fodrin antibodies are present in low titers and in a lower proportion of SS patients than initially reported in single center studies [113-115].

Anti-acetylcholine receptors —
In some patients with SS, autoantibodies directed against acetylcholine receptors may block neuroglandular transmission, thereby resulting in sicca symptoms [116,117]. These antibodies may be found in both primary and secondary SS.

In one study of 15 patients with SS, antibodies were found in 5 of 9 subjects with primary and 6 of 6 with secondary disease [118]. In animal models, these anti-M3 acetylcholine receptor antibodies decrease glandular secretion [116].

Islet cell autoantigen —
Islet cell autoantigen 69 (ICA69) is a protein that is present in salivary and lacrimal glands as well as pancreatic beta cells and tissue of the nervous system. In one study, elevated levels of autoantibodies to this protein were frequently found in the serum of patients with primary SS (8 of 9 patients), but not in patients with SLE (0 of 6) or in healthy controls (0 of 12) [119].

In a murine model of SS (the nonobese diabetic or NOD mouse), in which spontaneous lymphocytic infiltration of the lacrimal and salivary glands occurs, animals that did not express the ICA69 protein had a markedly slower progression of glandular lymphocytic infiltration than

wild-type or heterozygous ICA69 knockouts. Testing for anti-ICA69 antibodies is not recommended at this time. However, if larger studies confirm the differential presence in SS versus SLE, or other rheumatic disorders, testing for these antibodies may find a role in clinical practice.

PATHOLOGY OF THE SALIVARY GLAND INFILTRATE —
The principal pathological lesion of SS is a lymphocytic infiltration, which is common to all affected organs [52]. The salivary and lacrimal glands are the most frequently affected and also the most easily biopsied. The infiltrates consist of focal aggregates (50 or more cells) of lymphocytes, beginning around the ducts and spreading to involve the entire lobule (picture 1). Although some lobules are completely destroyed by this process, the overall architecture is preserved, with other lobules remaining intact and apparently normal. There is associated hyperplasia of salivary ductal epithelium that, together with the lymphocytic infiltrate, results in clinical enlargement of the gland. It is surprising that there is little progression of the focus score on serial biopsies of SS patients, even in those patients who subsequently develop lymphoma[21].

- **The initial steps in pathogenesis probably involve glandular, vascular endothelial cells, the glandular epithelial cells or their underlying stromal/dendritic cells** [22][17]. In an animal model of SS (eg, the nonobese diabetic - severe combined immunodeficient [NOD-SCID] mouse), changes of epithelial cells and local endothelial venules occur in the absence of functional lymphocytes [18], as well as elaboration of metalloproteinases. These changes are present in both male and female NOD mice [19]. However, dryness in the NOD-SCID mouse does not occur until T-lymphocytes occur in the gland. Important steps will include the upregulation of adhesion proteins and the elaboration of chemokines that promote trafficking of lymphocytes [20,21]. In addition to vascular and glandular cells, abnormalities of dendritic cells have been suggested as an important feature of organ specific lymphocytic localization [22] where dendritic cells are proposed to cause abnormal of retention of lymphocytes in the tissues. Thus, an infectious or inflammatory stimulus may lead to activation of innate immune system with characteristic damage to glandular structures and progression into a chronic autoimmune process in SS patients with genetic predisposition[22]

- **Migration of the lymphocytes occurs to the gland** in response to chemokines, adhesion to specific vascular adhesion molecules and entry into the glandular cells where they interact with dendritic cells and epithelial cells [25]. The acquisition of lymphoid features by inflammatory foci in SS is critically associated with the enlargement of the inflammatory foci and with the expression of certain chemokines (e.g., CXCL and CCL21) by T-cells within the infiltrate, but is not associated with their expression by epithelial cells [24,26]. Overexpression of CXC chemokine receptor 4 (CXCR4) by circulating blood B-cells does not translate into enhanced migratory response to the cognate ligand, CXC ligand 12 (CXCL12). Retention of CXCR4+, CXCR5+, CD27+ memory B-cells in the inflamed glands seems to contribute to diminished peripheral CD27+ memory B cells in primary SS [27].

- **The role of epithelial cells has been emphasized by the term "autoimmune epitheliitis"**[23, 24]. The epithelial cells express CD86, which interacts with CD28 on T-cells[25]. After type I IFN stimulation or viral infection, SG epithelial cells can release cytoines such as BAFF[26, 27] and IL21 (which promotes follicular structures). Epithelial cells also promote lymphocytic infiltration by upregulation of CXCL12[28]. Finally, epithelial cells are the most likely source of antigens SS-A/SS-B which migrate to the surface of apoptotic cells in a surface bleb[29]. In contrast to other autoantigens, this unusual fate of SS-A/SS-B on surface blebs could augment its recognition in immune complexes delivered to Toll receptors[30].

- **The innate and acquired immune systems can be mutually co-stimulatory** [28]. Studies on cytokine production in the salivary gland biopsies using gene profiling suggest an important role for type I and type II interferons in this perpetuation of the immune response [25,29]. The process of continued stimulation of T- and B-cells may lead to gene mutations in B-cells that eventuate in pseudolymphoma and frank lymphoma. B-cell activation is associated with increased BAFF activation [30]. Of particular interest, a rationale for the association of anti-SS-A antibody and SS has been proposed [12-14]. It is known that SS-A binds to hYRNA (a double-stranded RNA) and that SS-A may migrate to the surface of apoptotic glandular cells. The complex of SS-A/hYRNA and antibody would form an immune complex that could bind to the Toll receptor and Fc receptor of dendritic cells. The resulting activation of dendritic cells would provide the type I interferon gene signature reported in SS [31]. Further, the

association of antibody SS-A production with HLA-DR3 would provide a further bridge between genetics, antibody formation and the gene expression profile.

LYMPHOMA-complicating SS--

Lymphomas-complicating SS have certain features that suggest a specific underlying pathophysiology. They often develop in mucosal locations where SS is active, such as salivary glands or gastrointestinal tract (MALT)[31] or lung (BALT)[32, 33]. Germinal center (GC) structures are associated with increased risk of lymphoma[34].

Theander et al found that GC-like structures were present in 86% of biopsies from SS patients who later presented with a non-Hodkins lymphoma compared to only 22% of patients without NHL[34]. GC-like structures undergo smati hypermutation and are subected to antien-driven selection of Bells. Polymoropphisms of CXCR5, involved in organization of GC structures are associated with SS and HNL[35]. Elevation of BAFF may be associated with lymphoma. A20 (encoded by gene TNFAIP3) is a regulator of NFkB activation and is downregulated in SS[1]. Further, a polymorphism of this gene has been found in a high percentage of SS patients. Mutations and downregulation of A20 have been associated with increased germinal center formation and MALT lymphomas[36].

Innate and Acquired Immune Cytokines Identified in the Glandular Epithelium

Within the glands (and in other lymphoid tissues), activation of T-lymphocytes and B-lymphocytes occurs as a result of HLA-DR restricted antigen-presenting cells in the presence of co-stimulatory molecules. This is called the "acquired immune system" that perpetuates immune response with memory lymphocytes and autoantibodies [38]. Extraglandular manifestations occur as a result of lymphocytic infiltration into other tissues or generation of pathogenetic autoantibodies.

Pathogenesis is currently assumed to represent a continuing cycle of inflammation between acquired and innate immune system.

A type I IFN signature in labial salivary gland biopsy of SS patients could be induced with immune complexes produced with anti-SS A/B antibody and extracts of salivary gland containing this antigen[30, 37, 38]. This immune complex was able to bind to Toll 3 receptors (TLR) that

have been detected in SS glands in the epithelial, dendritic and B-cells. Stimulation of the TLR 3 trigger release of type I IFN and further production of antibodies including SS-A/B. Also, stimulation of TLR receptors activates high endothelial venules to further promote lymphocyte homing to the gland[2].

Viral nucleic acids are potent stimulators of TLR3 (dsRNA viruses), TLR7/8 (ssRNA viruses) and TLR9 (dsDNA viruses) (5). Engagement of these TLRs results in the activation of multiple signaling pathways that culminates in the production of proinflammatory cytokines such as IL-6, tumor necrosis factor (TNF)-α, and type I interferons (IFNs) (IFN-α and IFN-β). The localized and rapid induction of proinflammatory cytokines forms the first line of defense to limit the dissemination of invading virus.

Thus, **it is proposed that SS results from an innate immune response to an environmental inflammatory insult in genetically predisposed individuals.** The innate immune system (particularly TLR3) perpetuates the activation of the acquired immune system leading to T-cell and B-cell stimulation.

In addition to T-helper cells, complex roles have also been attributed to **NK-like cells and T-17 cells** that produce IFN-gamma.

A complex family of cytokines has been identified in the salivary gland tissue, and represents potential targets for therapy:

- **IL-7** is a hematopoietic growth factor which promotes survival, proliferation and differentiation of mature naïve and memory cells and has increased expression in salivary glands of SS patients[39] IL-7 also drives Th1 and Th17 cytokine production in SS glands[40, 41]

- An additional area of renewed research interest involves **IL-12**[42] and resultant Stat 4 activation of T-cells[43]— mainly type 1 Thelper (Th1) cells[43] secreting type II iFN-g and also type 17 T-helper (Th17) cells and NK cells. Further, IL-17 is released in the eye as a result of desiccating stress [44].

- **IL-18** production has been noted on SS acinar cells, and may work synergistically with IL-17 to facilitate glandular destruction. It is secreted as a precursor and upon its activation may lead to caspace induction and apoptosis[45].

- **IL-21** has been implicated in B-cell activating factor (BAFF). This cytokine may act as a bridge between innate immunity and autoimmune B-cell activation in SS[46] and may be stimulated by viral infection of salivary glands[26].

- **T-reg cells** identified by their FoxP3 marker have an immune homeostatic role and have been identified in salivary glands of SS cells[47]. These cells are felt to represent an attempt at feedback[48, 49].

- An NK cell activating receptor **(NKp30)** was recently demonstrated in SS glands and markedly upregulated in the presence of IL-7, IL-17 and IFN-g[1]. This study suggests a role for a newly identified subset of unconventional NK cells expressing CD4+ and a novel triggering receptor (NCR2)

Effector mechanisms —

Several major **pathways for killing by cytotoxic T lymphocytes (CTL)** have been identified [121]. All have been suggested to be important in SS.

- The first mechanism is the **Fas-FasL cytotoxic pathway**. Fas (CD95, APO-1) is a member of the tumor necrosis factor (TNF) receptor family of cell surface proteins which with its ligand, FasL, is thought to have an important role in regulating immune responses and maintaining self tolerance. Ligation of Fas and FasL is capable of delivering either an apoptotic death signal to a cell or a costimulatory signal. FasL expression in induced by MHC class II and antigen interaction on activated T-cells (predominantly of the Th1 subset) [122] and on CD8+ cytotoxic T-cells.

- **Fas expression** has been demonstrated on ductal epithelial cells from patients with SS, particularly in areas of heavy inflammatory cell infiltrate [123,124]. Although this is a potential mechanism for cell death in SS, apoptosis is the result of a fine balance between pro-apoptotic proteins such as Fas and anti-apoptotic proteins such as bcl-2 and bcl-x-1. The relative contribution of each in SS remains to be evaluated.

- A second mechanism of cytotoxicity involves the **translation and secretion of cytolytic granules containing perforin,**

granzymes, and other cytotoxins. Granzyme A mRNA is present in salivary gland lymphocytes in SS and levels of mRNA have been found to correlate with the size of the infiltrate and clinical activity of the disease [125].

- More recently, there has been increased interest in **traditional and Nontraditional NK-cells.** The recognition of **Th-17 cells** has shown a potential role for traditional CD4+ NK cells. They produce proinflammatory cytokines such as IL-6, IL-17, IL-022 and IL-23—all of which have been shown increased in SS salivary glands[50]. In addition, a novel subset of unconventional NK cells (expressing a natural-cytotoxicity receptor 2, NC2, also known as NK-p44) were identified in SS salivary glands[50].

[WRITER: PLEASE INSERT OTHER PAGE FOR NEURO-ENDOCRINE]

NEW DIRECTIONS IN STUDY OF PATHOGENESIS —

Protein components of the tears of patients may help distinguish those with SS from others with complaints related to ocular dryness. One promising approach to identifying disease biomarkers in tear fluid uses a proteomic technique. A description of proteomics is beyond the scope of this discussion. The technology utilized is discussed elsewhere. (See "Overview of gene expression profiling, proteomics, and microRNA profiling in clinical oncology".)

The potential of a proteomic approach using surface enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) is illustrative [126]. Thirty-one SS patients and 57 control subjects were enrolled to this study. There were 23 patients with primary SS, eight with secondary SS, 14 with dry eyes, 22 with miscellaneous ocular diseases, and 21 of healthy volunteers. Multiple protein changes were reproducibly detected in the primary SS group, including 10 potential novel biomarkers. Seven of the biomarkers, referred to by their mass/charge (m/z) ratio were down-regulated (2094, 2743, 14191, 14702, 16429, 17453, 17792 m/z) and three biomarkers (3483, 4972, 10860 m/z) were up-regulated in primary SS group when compared to the protein profiles of control subjects. When cutoff value of SS down-score was set less than 0.5, this result yielded 87 percent sensitivity and 100 percent specificity. There was a significant inverse correlation between SS down-scores and epithelial damages of

the ocular surface in primary SS patients. These findings support the potential of proteomic pattern technology in tear fluids as the noninvasive diagnostic test for primary SS [126].

INFORMATION FOR PATIENTS —

UpToDate offers two types of patient education materials,

- "The Basics" and
- "Beyond the Basics"

The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials.

Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient information: Sjögren's syndrome (Beyond the Basics)")

SUMMARY

- *SS is a systemic autoimmune disease characterized by infiltration of glandular tissue by predominantly CD4 T lymphocytes*. The glandular epithelial cells express high levels of HLA-DR: it is possible that these cells are presenting antigen (viral or autoantigen) to the invading T-cells.
- *Cytokine production follows*, with IFNg and IL-2 being especially important.
- *There is also evidence of B-cell activation with autoantibody production* and an increase in B-cell malignancy.

It remains unclear, however, how these changes result in the clinical manifestations of SS. The traditional view that chronic inflammation results in tissue destruction of the exocrine glands is almost certainly not the whole story.

There is, for example, a poor correlation between the amount of damage upon biopsy and the measured decrease in fluid production, as the reduction in saliva is often greater than expected from the histologic appearance. Furthermore, some patients with low basal levels of salivary secretion are capable of producing normal amounts after stimulation by pilocarpine.

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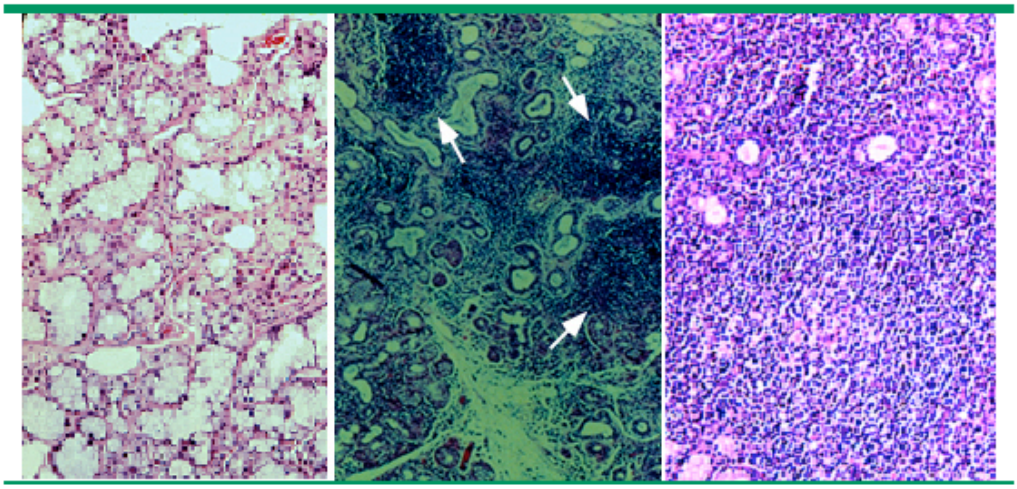
New or Modified Reference

Please fill out the area below for any new references to include in this document.

Graphics
picture 1

Lip gland histopathogy in Sjögren's syndrome



Lip gland biopsies in Sjögren's syndrome. Left panel: High power view showing lack of inflammatory infiltrates. Middle panel: Low power view showing focal areas of lymphocytic infiltration (arrows). Right panel: High power view showing extensive infiltration by lymphocytes with glandular and ductal atrophy.

Courtesy of Samuel L Moschella, MD and Cynthia Magro, MD.

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