AUTOIMMUNE EPITHELITIS IN RHEUMATOLOGY: PATHOGENESIS, EPIDEMIOLOGY AND CLINICAL FINDINGS

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Autoimmune epithelitis, or Sjögren’s syndrome, is a chronic autoimmune connective tissue disorder that manifests as oral and ocular dryness due to lymphocytic infiltration of exocrine glands and extraglandular involvement that reveal the severity of this disorder.
Autoimmune epithelitis, or Sjögren’s syndrome (SS), can occur alone as primary SS or accompany other autoimmune disorder as secondary SS, or associate with other autoimmune diseases (poliautoimmunity).
PATHOGENESIS OF SJÖGREN’S SYNDROME
The pathogenesis of SS remains unclear. A genetic predisposition with epigenetic modification lies in the base of the disorder, which is further triggered by environmental factors. This has been termed the 'mosaic of autoimmunity'.
A prone individual with genetic tendency, and in some cases a subclinical immune dysregulation, will encounter at several points of his life immune stimuli such as hormone disbalance, infections, chemicals and physical agents and emotional stress that will eventually trigger autoimmunity.
RECENT ADVANCES IN THE PATHOGENESIS OF SS

Genetic variants associated with pSS

- A genetic influence on SS has been reported mainly based in aggregation on ADs in family members with SS.
- A great step forward understanding of genetic determinants of pSS was taken in 2013 with the completion of a large international genome-wide association study (GWAS).
- Genes involved in both innate and adaptive immunity in SS play a crucial role into the susceptibility towards the disease with HLA locus disclosing the strongest association.
- Whether the combination of such genetic risk factors could constitute a diagnostic tool, or even a predictive instrument, has yet to be evaluated.
Epigenetics aberrations in pSS

- Epigenetics became a major topic for discussion and research reports. Epigenetic reflects both genetic and environmental processes that affect T cells and B cells. Studies in twins lead to the concept of the partial „heritability“ of ADs.
- Epigenetics refers to heritable changes in gene expression that do not involve mutations in the DNA itself.
Two main mechanisms have been described:

- DNA methylation, which can repress or increase the expression of various genes, and
- microRNAs which are able to specifically inhibit various messenger RNA.
In pSS:

- Global DNA methylation is reduced in salivary gland epithelial cells
- This is associated with a dysregulation of key enzymes regulating DNA methylation.
- An epigenome wide DNA methylation study identified several genes which were hipo or hypermethylated in peripheral naive CD4+ T cells from pSS patients.
- Hypomethylated genes were mainly involved in lymphocyte activation and immune response.
- Hypermethylated genes were involved in antigen processing and presentation.
Micro RNAs are small RNAs which can decrease a specific gene expression through either mRNA degradation or disruption of translation.

A single microRNA may target several genes involved in a given function.

Microarrays have been developed to study the expression of all microRNAs in cell type or tissue, in order to an expression profile.

In pSS salivary glands, this microRNA expression profile is altered compared to healthy controls, and could constitute a signature of the disease.
REGULATORY LYMPHOCYTE SUBSETS

- Both T cells and B cells play a major role in the development of pSS.
- Growing evidence accumulates on the importance of regulatory lymphocytes in the pathogenesis of autoimmune diseases.
- The common feature of regulatory cells is their ability to decrease the proliferation of T cells in order to maintain a state of tolerance toward self-antigens.
The phenotypic characterization of regulatory T cells (Treg) is widely accepted (CD3+ CD4+ CD25+ FoxP3+).

No clear phenotype of regulatory B cells (Breg) has been described yet.

Several specifications of Breg have been claimed, such as production of IL-10 or TGF beta, high expression of CD24 and CD38 (transitional B cell-like phenotype), or expression of CD5.

In the blood of pSS patients, an increase of several potential Breg populations has been described, whereas Treg proportions were not different from healthy control.
Type I IFN is one of the major cytokines of innate immunity.
The major sources of type I IFN are plasmacytoid dendritic cells (pDC).
Type I IFN may act through inhibition of viral replication, activation of natural killer (NK) cells, generation and activation of DC and maturation of B cells toward antibody secreting cells.
Numerous isoforms of type I IFN exist, so the direct dosage of the protein is not appropriate. Instead, techniques have been developed to measure the consequences of high levels of type 1 IFN, i.e. the level of expression of various type I IFN-inducible genes, which has been referred to as the IFN signature. Around 50% of pSS patients display an IFN signature, either in the blood or in the salivary glands.
NK CELLS, MACROPHAGES, AND INTERFERON SIGNATURE (3)

- A recent study described a link between an NK-cell specific receptor (NCR3/NKp30) gene promoter polymorphism and pSS, and demonstrated a correlation between the levels of this receptor, the type of IFN production, and the severity of salivary gland inflammation.

- NK cells accumulate in the lymphocitic foci within the salivary glands when salivary gland epithelial express the specific ligand of NKp30.
NK CELLS, MACROPHAGES, AND INTERFERON SIGNATURE (4)

- Inflamed salivary glands of pSS patients contain activated lymphocytes, which are able to recruit macrophages on the site. Macrophages then exacerbate the inflammatory response, leading to tissue destruction, notably through the release of proteolytic enzymes such as matrix metalloproteinases and plasmin. Interestingly, one of the main determinants of plasmin secretion within the salivary glands is type I IFN.
Thus, targeting of type I IFN pathways could be a promising therapeutic possibility in the near future. In this context, therapeutic vaccination is a novel approach that offers several competitive advantages when compared to monoclonal antibodies. Therapeutic vaccination will indeed target all of the 13 type I IFN subtypes and will lead to a polyclonal antibody response.
The pathogenesis is multifactorial. Any model of Sjögren’s syndrome must include an explanation of why the syndrome is characterized by an organ specific infiltration of lymphocytes and the production of autoantibody to SS-A, an antigen found in nucleated cells. Also, models must include the female predominance and the association with HLA DR.
OVERVIEW OF PATHOGENESIS

Enviromental factors
Activation of glandular cells

Impaired secretion due to glandular dysfunction

HLA-DR-independent (innate) immune system

Activation of lymphocytes within the gland leading to: cell destruction, cytokines, autoantibodies, metalloproteinases

Alteration of glandular vascular endothelium (chemokines/receptors)

Infiltration of gland by lymphocytes of HLA-dependent (acquired) immune system
EPIDEMIOLOGY OF SJÖGREN’S SYNDROME
Sjögren’s syndrome epidemiology is poorly investigated. This disorder is among the most frequent systemic autoimmune diseases, with an estimated prevalence between 0.1 and 5% of the population.
Primary Sjogren’s syndrome is a systemic autoimmune disorder with a population prevalence of about 0-5 % and a female preponderance (female to male ratio nine to one).

Sjogren’s syndrome is therefore one of the three most common autoimmune disorders.

There are two age peaks of pSS, with the first after menarche during the 20s to 30s and the second after menopause in the mid-50s.
In a multicenter study, 40 cases of the syndrome with onset before age 16 years were identified on the basis of parotid-gland swelling and characteristic autoantibodies at presentation and a mild course during 7 years of follow-up.
SIGNIFICANCE AND INNOVATIONS IN A FRENCH MULTIRACIAL/MULTIETHNIC AREA

- A recent population-based census study in a French multiracial/multiethnic estimated the prevalence of pSS at 1-1.5 cases per 10,000 subjects.
- People of non-European racial/ethnic background were at increased risk of pSS and had a distinct clinical profile.
- To a large extent, the prominent between-study variations in published pSS frequency estimates seemed to account from methodologic differences.
<table>
<thead>
<tr>
<th>Author, year (ref)</th>
<th>Publication year</th>
<th>Country</th>
<th>Population size</th>
<th>Classification criteria</th>
<th>No. of pSS cases</th>
<th>Rate (per 100000)</th>
<th>Prevalence</th>
<th>No. of pSS cases</th>
<th>Rate (per 100000)</th>
<th>Annual incidence</th>
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<td>Miyasaka 1995</td>
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<td>Greece</td>
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<td>AECG NS</td>
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<td>422</td>
<td>0.53</td>
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### The Results of Population—Based Prevalence and Incidence Surveys for Primary SS Reported from Publications (2)

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<tr>
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<th>Rate (per 100000)</th>
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<tr>
<td>Goransson et al. 2011</td>
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<td>Norway</td>
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<td>Yu et al. 2013</td>
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<td>1.6</td>
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<td>Present study</td>
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<td>France</td>
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<th>Annual incidence</th>
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<td><strong>Sample surveys</strong></td>
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<td>Zhang et al. 1995</td>
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<td>Modified San Diego</td>
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<td>Copenhagen</td>
<td>16</td>
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<tr>
<td>Thomas et al. 1998</td>
<td>1998</td>
<td>UK</td>
<td>341</td>
<td>Study-specific</td>
<td>13</td>
<td>180/330</td>
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<tr>
<td>Tomsic et al. 1999</td>
<td>1999</td>
<td>Slovenia</td>
<td>332</td>
<td>European</td>
<td>2</td>
<td>60</td>
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In summary, the collective results from French study and previously published census surveys support that the prevalence of diagnosed pSS is between 1 and 9 cases per 10,000 people in the general population (0.01-0.09%).
CLASSIFICATION CRITERIA FOR SS
### AMERICAN EUROPEAN CONSENSUS GROUP (AECG) CRITERIA

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| **1. Ocular symptoms (at least one present)** | • Persistent, troublesome dry eyes every day for longer than 3 months  
• Recurrent sensation of sand or gravel in the eyes  
• Use of a tear substitute more than three times a day |
| **2. Oral symptoms (at least one present)** | • Feeling of dry mouth every day for at least 3 months  
• Recurrent feeling of swollen salivary glands as an adult  
• Need to drink liquids to aid in swallowing dry foods |
| **3. Objective evidence of dry eyes (at least one present)** | • Shirmer I test  
• Rose-Bengal |
| **4. Histopathology** | • Salivary-gland biopsy sample with focus score > 1 |
| **5. Objective evidence of salivary-gland involvement (at least one present)** | • Salivary-gland scintigraphy  
• Parotid sialography  
• Unstimulated whole sialometry (≤ 1.5 ml, per 15 min) |
| **6. Laboratory abnormality** | • Anti-SS-A or anti-SS-B |
CLASSIFICATION CRITERIA FOR SJÖGREN’S SYNDROME (1)

American European Consensus Group (AECG) criteria

- The AECG criteria require the presence of four out of six components (one of which is symptomatic dry eyes, and a second is symptomatic dry mouth), or three out of the four other objective components, although in either case one of the components has to be positive antibodies and/or a positive biopsy.
CLASSIFICATION CRITERIA FOR SJÖGREN’S SYNDROME (2)

American European Consensus Group (AECG) criteria

The four objective components are:

1. positive anti-Ro and/or anti-La antibodies;
2. a positive labial gland biopsy defined as at least one periductal focus of 50 or more lymphocytes per 4 mm² high powered field;
3. reduced whole salivary flow of 1 mL/min or less (or abnormal scintigraphy/sialography);
4. evidence of reduced tear production on van Bijsterweld staining, or 5 mm or less of flow in 5 min on Shirmer blotting paper strips.
CLASSIFICATION CRITERIA FOR SJÖGREN’S SYNDROME (3)

The SICCA-ACR criteria

- These alternative criteria require two out of three components – again requiring one to be either a positive biopsy or positive antibodies.
- As an alternative to anti-Ro/La antibodies, however, a positive antinuclear antibody (ANA) level of 1 in 320 or greater plus a positive rheumatoid factor is also allowed.
- The third component is a newly devised ocular staining score (OSS) of 3 or greater.
CLINICAL FINDINGS
The characteristic ophthalmological finding in Sjögren’s syndrome is keratoconjunctivitis sicca.

Methods to measure the integrity of the corneal surface and tear film include staining with Rose-Bengal, fluorescein, and lisamine green dye and the tear break-up time.
ORAL SYMPTOMS AND SIGNS

- Dryness of the mouth makes swallowing of food and even talking difficult, owing to dryness of the buccal mucosa. However, a dry mouth is not necessarily painful.

- The sudden development of pain in the mouth should stimulate a search for signs of angular cheilitis or erythematous petechial-type lesions on the palate (commonly under dentures); such findings suggest oral candidosis.
• The other important criterion of Sjögren’s syndrome has been the appearance of a biopsy sample of minor salivary gland.
• The key requirements are an adequate number of informative lobules (at least four) and the determination of an average focus score (a focus is a cluster of at least 50 lymphocytes) based on survey of at least four lobules.
EXTRAGLANDULAR SYSTEMIC MANIFESTATIONS

- Systemic manifestations are subdivided into non-visceral (skin, arthralgia, myalgia) and visceral (lung, heart, kidney, gastrointestinal, endocrine, central and peripheral nervous system).
# PROPOSED CLASSIFICATION OF SYSTEMIC MANIFESTATIONS IN PRIMARY SS

<table>
<thead>
<tr>
<th>Non-specific</th>
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<tbody>
<tr>
<td>• Musculoskeletal</td>
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<tr>
<td>• Raynaud’s</td>
</tr>
<tr>
<td>• Fatigue - Psychopathology</td>
</tr>
</tbody>
</table>

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<tr>
<th>Periepithelial (lymphocytic infiltration around epithelial tissues in parenchymal organs)</th>
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<tr>
<td>• Bronchial</td>
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<tr>
<td>• Liver</td>
</tr>
<tr>
<td>• Kidney</td>
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<tr>
<td>• Endocrine glands (thyroid, adrenals, ovaries)</td>
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**Immunocomplexes mediated disease**

(Deposition of immunocomplexes in small vessels of the skin, nerves, kidney as a result of B-cell hyperactivity)

**Lymphoproliferation**
## HISTOPATHOLOGICAL AND GENETIC RISK FACTORS FOR LYMPHOMA DEVELOPMENT IN PRIMARY SS

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Persistent lacrymal or salivary gland enlargement, purpura, peripheral neuropathy, vasculitis</th>
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<tbody>
<tr>
<td>Laboratory</td>
<td>Leucopenia, neutropenia, low C4 levels</td>
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<tr>
<td><strong>Histopathological</strong></td>
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<tr>
<td>Cellular</td>
<td>Macrophages, germinal cell formation</td>
</tr>
<tr>
<td>Cytokines</td>
<td>High IL-18, low IL-12 levels</td>
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<tr>
<td>Genetic</td>
<td>p53, BAFF variants</td>
</tr>
</tbody>
</table>
SECONDARY SJÖGREN’S SYNDROME
SS, secondary to rheumatoid arthritis (RA), seems to be a complication of these disorders: the sicca syndrome is less serious, anti-Ro/SSA and anti-La/SSB antibodies are less frequently present and the evolution of SS is closely linked to that of RA.

SS accompanying systemic lupus erythematosus (SLE) or autoimmune thyroiditis shows clinical and serological patterns similar to pSS, with the same occurrence of anti-SSA/SSB antibodies and the same severity as pSS.
POLIAUTOIMMUNITY
Sjogren’s syndrome is associated with and not secondary to systemic sclerosis (SSc)

SSc seems to be less serious when it associated with SS

Lung fibrosis occurred in 29% of the patients with SSc alone and in only 11% of the patients with SS-SSc

Reduced prevalence of scleroderma renal crisis in the SS-SSc

This association of SS and SSc is an example of the spreading of autoimmunity
THANK YOU FOR YOUR ATTENTION