

# Gastrointestinal involvement in primary Sjögren´s syndrome

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## Introduction

Sjögren´s syndrome (SS) is an autoimmune inflammatory disease resulting in destruction of exocrine glands. Since the function of the gastrointestinal tract is dependent on numerous exocrine glands, it is not surprising that morbidity from this area is commonly seen in Sjögren´s syndrome (1).

SS is frequently seen as a complication to inflammatory joint diseases such as rheumatoid arthritis (RA), pelvispondylitis and systemic lupus erythematosus. However, SS does also occur without such association, and is then called primary SS (1°SS), while SS associated with RA etc. is consequently named secondary SS (2°SS). There are reasons to believe that 1°SS and 2°SS are two separate diseases with differences regarding clinical profile as well as autoantibody- and HLA-expression. The present review regards mainly gastrointestinal involvement in 1°SS.

Sometimes the oral cavity is included in the gastrointestinal tract, which otherwise is subdivided in the oesophagus, stomach, small and large bowel, pancreas and the liver with biliary tracts. In this presentation I will exclude symptoms from the oral cavity, since that subject will be dealt with somewhere else at the Symposium.

## Oesophagus

Patients with SS frequently complain about dysphagia. This symptom could be explained by lack of saliva, oesophageal dysmotility or oesophageal webs. Presently, there is some controversy regarding the role played by these factors. Manometric studies of oesophageal motility have in the hands of several investigators showed contradictory results, and a recent study (2) found – in addition to absent dysmotility – no difference between wet or dry swallows. Oesophageal webs are found in 10-20% of SS patients (3), as opposed by the finding of webs in 1% of normal controls. Oesophageal webs may - or may not - cause dysphagia.

## Stomach

Nausea, epigastric pain and dyspepsia are common complaints of patients with SS. Biopsy studies of the gastric mucosa have revealed chronic inflammation with mononuclear infiltrates and/or glandular atrophy, a finding similar to those in the salivary glands. Chronic atrophic gastritis is age-dependent and a common finding (41%) in subjects aged 41-65 years. However, the frequency in SS is 81% (4), suggesting that the age factor can only be contributory. Chronic atrophic gastritis is associated with achlorhydria and autoantibodies to parietal cells, but low levels of vitamin B12 and pernicious anaemia are rare findings.

Epidermal growth factor (EGF) is secreted in large quantities by the salivary glands and its biological effects on the stomach include inhibition of gastric acid secretion, mucosal protection and healing of ulcers. The production of EGF is considerably reduced in rheumatoid disease (5) and this may contribute to an increased susceptibility to gastric ulceration in patients with subnormal salivation. An increased frequency of duodenal ulcers in patients with primary biliary cirrhosis and SS has been reported (6), which may be related to deficient production of EGF in both saliva and bile.

## Small and large bowel

Involvement of the small and large bowel in SS is only rarely reported, and it is not known why this part is less affected than other parts of the gastrointestinal organs. However, nutritional deficiencies have been noted in SS patients, but this may be related to poor nutritional intake secondary to

xerostomia (7). There are several case reports describing celiac disease in SS patients and in a recent study (8) of patients with celiac disease, SS was the most common rheumatic disease association. Lately, the association of IgA anti-endomysium antibodies (EmA) and celiac disease has been shown (9), and EmA has been used as a screening test for celiac disease. In a recent study at our institution two of 30 patients with 1°SS were EmA positive. On small bowel biopsy a mild degree of villous atrophy was noted, indicating latent form of celiac disease. A year later manifest celiac disease was noted in one of the two EmA positive patients. Therefore, selected screening for celiac disease in SS patients is indicated.

There are only two reported cases of 1°SS associated with each Crohn's disease and carcinoma of the colon and a single case of chronic idiopathic pseudoobstruction. Ulcerative colitis and "secondary" SS has been described in two patients, where the colitis preceded the diagnosis of SS by several years.

### **Hepatobiliary**

Hepatomegaly and abnormal liver function tests have been found in up to 25% of SS patients (10). Furthermore, there are many associations between SS and various hepatobiliary diseases, mainly primary biliary cirrhosis (PBC) and chronic active hepatitis (CAH). Antimitochondrial and antismooth muscle antibodies, usually associated with PBC and CAH respectively, are found in 11% of patients with SS. Liver biopsy in such patients show lesions of stage I PBC, CAH and mild portal tract fibrosis. In 69 to 81% of patients with PBC, SS is noted as a major extrahepatic disease, suggesting that it is a variant of secondary SS resembling that seen in RA (11). A rare symptom complex of sclerosing cholangitis, chronic pancreatitis and SS seems to be a well-defined entity with an autoimmune cause (12).

The HLA haplotype B8-DR3 is closely associated with 1°SS and other autoimmune diseases such as insulin dependent diabetes mellitus (IDDM), celiac disease, CAH and myasthenia gravis. Recently two patients with this haplotype and IDDM, ulcerative colitis and sclerosing cholangitis were described (13). Ulcerative colitis is present in 29-72% of patients with sclerosing cholangitis. At our institution we have seen a patient with ulcerative colitis, sclerosing cholangitis, chronic pancreatitis, autoimmune thyroiditis and SS. In the literature, a combination of SS with sclerosing cholangitis, chronic pancreatitis and retroperitoneal fibrosis has also been described. It seems that especially homozygosity of the autoimmune type HLA DR3 may predispose for multi-organ autoimmune disease with the above characteristics.

Patients with 1°SS have an increased risk of developing lymphoma, which may manifest itself as hepatomegaly, in most instances along with lymphadenopathy. Immunohistochemical examination as well as studies to determine the extent of lymphoid involvement should be done in such patients in order to arrive at correct diagnosis and therapy.

Retrospective studies have reported the presence of antibodies against hepatitis C virus (HCV) in 10% of patients with sicca symptoms. A recent study (14) showed an increased prevalence of chronic HCV infection in patients presenting with sicca symptoms. However, these patients were clinically and immunologically different from HCV-negative patients with SS: they had an increased frequency of neurological symptoms and were seronegative for SS-A/SS-B antigen. Further studies are therefore needed to determine whether HCV is an etiological agent of primary Sjögren's syndrome.

### **Pancreas**

Similarities in anatomy and physiology between the pancreas and salivary glands should lead to expectation of autoimmune inflammatory involvement also of the pancreas in SS. Studies have also shown a decrease in the volume of pancreatic external secretions after secretin stimulation in SS. In one study (15) abnormal results were found in 37.5% of SS patients, indicating impaired pancreatic

function. Other studies (16,17) conclude that the pancreatic dysfunction in SS is only subclinical, and that pancreatic enzyme supplementation is indicated only when clinical symptoms of pancreatic insufficiency are present.

Acute pancreatitis in SS is a rare event while chronic pancreatitis, most often clinically silent, can be demonstrated with appropriate testing. As mentioned above, chronic pancreatitis may occur together with sclerosing cholangitis in patients with Sjögren's syndrome.

## Conclusion

Sjögren's syndrome is an autoimmune disease mainly affecting exocrine glands. Involvement of the gastrointestinal tract is expressed as dysphagia originating in the oesophagus, atrophic gastritis and impaired pancreatic function. Involvement of the small and large bowel is remarkably insignificant although there may be an association to celiac disease. There is a marked association of SS to autoimmune liver disease, such as primary biliary cirrhosis, chronic active hepatitis and sclerosing cholangitis. The aetiology of these manifestations is unknown, but autoimmune mechanisms are probably important. Clinical workup should be initiated by the patient's subjective complaints.

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