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GASTROINTESTINAL INVOLVEMENT IN SJÖGREN'S DISEASE

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Abstract

Sjögren's disease (SjD) is a chronic autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands, which can also affect the gastrointestinal (GI) tract, hepatobiliary system, and pancreatic exocrine tissues. Approximately one-third of patients experience GI-related symptoms, with xerostomia, dysphagia, dyspepsia, and atrophic gastritis being the most commonly reported manifestations. SjD is also associated with autoimmune liver diseases, including autoimmune hepatitis and primary biliary cholangitis. Pancreatic involvement is less frequent, but may present as autoimmune pancreatitis or exocrine pancreatic insufficiency. The complexity of SjD and the variety of its manifestations underscore the importance of a multidisciplinary management approach, where collaboration among healthcare professionals is crucial for optimising patient outcomes.

Keywords: Sjögren's disease, gastrointestinal tract, autoimmune hepatitis, primary biliary cholangitis, pancreatitis

INTRODUCTION

Sjögren's disease (SjD) is an autoimmune exocrinopathy that can affect the entire gastrointestinal (GI) system, including the intestinal lumen, hepatobiliary tract, and pancreas. Given that the GI tract encompasses numerous exocrine functions, its involvement in SjD is expected. Over the course of the disease, approximately one-third of patients develop GI symptoms. Among the most bothersome manifestations is xerostomia, which results from lymphocytic infiltration of, and subsequent damage to, the salivary glands (1,2).

In addition, several other GI and hepatopancreatic manifestations have been reported, including dysphagia, esophageal dysmotility, chronic atrophic gastritis, irritable bowel syndrome, celiac disease (CD), primary biliary cholangitis (PBC), pancreatitis, exocrine pancreatic insufficiency, autonomic nervous system dysfunction, and liver disease (Table 1) (3-6).

General management aligns with the 2020 European Alliance of Associations for Rheumatology (EULAR) recommendations for SjD: evaluate systemic activity (e.g., EULAR SjD disease activity index); treat sicca symptoms (topical therapies; secretagogues such as pilocarpine or cevimeline when appropriate); screen for extraglandular involvement (hepatobiliary or pancreatic involvement where indicated); manage comorbidities; and monitor lymphoma risk in highrisk phenotypes. Co-ordinate care with gastroenterology or hepatology for abnormal liver tests or suspected biliary disease (7).

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Table 1. Anatomical distribution and clinical features of gastrointestinal involvement in Sjögren's disease (adapted from reference 6)

Organ	Type of involvement and clinical features
Oral cavity/salivary glands	Xerostomia, atypical dental caries, glossitis, taste disturbances, difficulty chewing, gingival problems, difficulty speaking, hoarseness, dysphagia, oral ulcers/aphthae, atypical angular cheilitis, lip dryness, oral candidiasis
Esophagus	Dysphagia, dysmotility, esophageal atrophy, Candida esophagitis
Stomach	Chronic atrophic gastritis, dyspepsia, delayed gastric emptying
Small intestine	Duodenal ulcers, celiac disease, pseudo-obstruction, pneumatosis cystoides intestinalis, protein-losing enteropathy, secondary vasculitic findings, increased risk of B-cell lymphoma, vitamin B12 deficiency/ pernicious anemia
Colon	Increased risk of colorectal cancer
Liver	Increased risk of complications from hepatitis C, primary biliary cholangitis, autoimmune hepatitis, and other autoimmune liver diseases
Pancreas	Autoimmune pancreatitis, chronic pancreatitis (weight loss, diarrhea, steatorrhea), exocrine pancreatic insufficiency
Gallbladder	Primary biliary cholangitis

MATERIAL AND METHODS

We conducted a narrative review to synthesize clinically relevant evidence on GI, hepatobiliary, and pancreatic involvement in primary SjD. Databases: Medline/PubMed and Scopus. Timeframe: inception to September 2025. Keywords (Boolean examples): ["Sjögren*" and (gastrointestinal or hepatobiliary or liver or biliary or pancreas or pancreatitis or dysphagia or gastritis or PBC or autoimmune hepatitis (AIH) or "exocrine pancreatic insufficiency" or microbiome)]. Study selection: English-language human studies prioritizing systematic reviews/ meta-analyses, large cohorts, guidelines/consensus statements, and clinically illustrative case series; single-case reports were used only to highlight rare entities. Statements reflect the level of available evidence. Abbreviations are defined at first mention in the text.

Gastrointestinal Tract Involvement in Sjögren's Disease

Oral involvement in SjD is primarily characterized by xerostomia (dry mouth), which affects approximately 80% of patients. Xerostomia may lead to a broad spectrum of secondary oral manifestations, either as a consequence of reduced salivary secretion or as direct effects of the disease. These include atypical angular cheilitis, lip dryness, non-classical dental caries, gingival disease, glossitis, taste disturbances, difficulty speaking, hoarseness, dysphagia, and oral ulcers (aphthae). On physical examination, the oral mucosa often appears dull and parchment-like and tends to adhere to the examiner's finger on palpation. Additionally, there may be reduced salivary pooling in the sublingual region and recurrent swelling of one or both of the parotid and submandibular glands. Furthermore, patients with SjD exhibit an increased susceptibility to oral candidiasis (1,5). Abnormalities in parasympathetic neurotransmission contribute to glandular dysfunction in SjD. Consequently, the management of xerostomia may involve the use of topical agents and secretagogues that stimulate muscarinic receptors, such as pilocarpine and cevimeline (1,4,7).

Autonomic neuropathy, a condition in which the nerves that control involuntary bodily functions are damaged, is associated with SjD and may contribute to GI dysmotility. This condition, along with impairment of muscarinic receptors by SjD-related autoantibodies, can lead to reduced salivary gland function and potentially altered intestinal motility, including peristalsis (4,8). Understanding these mechanisms is important for the comprehensive management of SjD patients. Studies evaluating dysphagia in patients with SjD have reported a prevalence as high as 80%. Reduced salivary secretion and esophageal dysmotility have been identified as major contributing factors to dysphagia in these patients. Since saliva is essential for pharyngo-esophageal bolus transfer, its deficiency may significantly exacerbate swallowing difficulties. Several studies have demonstrated that patients with SjD exhibit an increased frequency of non-specific motility abnormalities, including aperistalsis, tertiary contractions, non-peristaltic contractions, and reduced contraction amplitude, all of which may play a role in dysphagia (1,9,10). These abnormalities most commonly involve the cervical esophagus, the pharynx, or the mid-thoracic region, and, in advanced cases, esophageal atrophy may develop.

Patients with SjD may present with delayed gastric emptying; dyspepsia has been reported in approximately 20% of individuals with primary SjD. Among those undergoing upper

endoscopy, chronic atrophic gastritis has been reported in up to approximately 60% of patients in hospital-based series (age and selection-dependent), with its prevalence increasing with age. Although gastric parietal cell antibodies are detected in approximately 30% of patients, low serum vitamin B12 levels and pernicious anemia are rarely observed (4,11). Patients with SjD also have an increased risk of duodenal ulcers, and the likelihood of CD in primary SjD is approximately tenfold higher, with an estimated prevalence of 4.5%. Furthermore, the risk of lymphoma is increased; evidence for solid tumors (e.g., colorectal cancer) is inconsistent and should be interpreted cautiously in this population. Additional GI complications reported in SjD include intestinal pseudo-obstruction, pneumatosis cystoides intestinalis, and protein-losing enteropathy (12,13). Predictors reported in SjD include persistent parotid enlargement, palpable purpura or vasculitis, lymphadenopathy, cryoglobulinemia, low C4 levels, and monoclonal gammopathy of undetermined significance; composite risk scores have been proposed in cohorts (14,15).

Isolated case reports have also described the coexistence of ulcerative colitis and Crohn's disease in patients with SjD. GI vasculitis is uncommon, but, when present, is often associated with hypocomplementemia and cryoglobulinemia. In severe cases, vasculitis may lead to intestinal ischemia, necrosis, or gangrene, potentially resulting in an acute abdomen (14,15). Reported GI symptoms in patients with SjD affecting the small and large intestines include abdominal discomfort (37%), nausea (5%), constipation (23%), diarrhea (9%), and iron-deficiency anemia secondary to malabsorption (5%). However, data from extensive cohort studies indicate that direct intestinal involvement in SjD is either rare or absent (1,3). The prevalence of CD in SjD, as assessed by small-bowel biopsies, has been reported to range from 4.5% to 14.7%. Evidence supporting the benefit of a gluten-free diet in improving sicca symptoms remains limited. When SjD coexists with CD, celiac-type enamel defects may be observed, potentially contributing to an increased risk of dental caries. The coexistence of SjD and inflammatory bowel disease has rarely been reported in the literature. Although uncommon, serious GI complications have been described in SjD, including pneumatosis cystoides intestinalis, colorectal cancer, and intestinal pseudo-obstruction (1,12).

Hepatic and Biliary Tract Involvement in Sjögren's Disease

Hepatic involvement is observed in approximately 30% of patients with SjD and is associated with the systemic clinical features of the disease, autoimmunity, and inflammatory markers. After excluding patients with chronic liver diseases and hepatotoxic drug use, the primary etiologies include chronic viral hepatitis [hepatitis C virus (HCV), hepatitis B virus] in approximately 50% of cases and autoimmune liver diseases, such as PBC and AIH, in approximately 20%. Among these, chronic viral liver disease—most commonly HCV-related—is the leading cause of hepatic involvement in SjD, with a prevalence of approximately 13%, roughly three times as frequent as autoimmune liver involvement. Immunologic abnormalities can be observed in viral infections—including elevated cryoglobulin levels and low complement levels—and in autoimmune liver diseases such as AIH, with an increased frequency of autoantibodies. Mild elevations in liver enzymes are reported in 5-49% of patients with SjD; however, the majority of patients remain asymptomatic, and clinically significant liver disease is uncommon (1,3). Abnormal liver function tests typically show a cholestatic pattern but may also present as hepatocellular or mixed patterns (1). Idiopathic granulomatous hepatitis has also been associated with SjD. Although the overall risk of lymphoma within the liver is not increased, cases of pseudolymphoma secondary to dense lymphocytic infiltration have been described (16,17). Additionally, hepatomegaly is observed in approximately 15% of patients with SjD (1).

SjD is among the systemic rheumatic diseases (SRDs) most frequently associated with autoimmune liver diseases. In heterogeneous cohorts of patients with primary SjD, the reported prevalence of AIH ranges from 0.4% to 4% (2). Although AIH occurs relatively frequently in patients with rheumatoid arthritis (RA) or systemic lupus erythematosus, PBC is more common in patients with SjD, RA, or systemic sclerosis (18-20).

In patients with primary SjD, the prevalence of PBC varies between 1% and 9% across different studies (21,22). Among anti-mitochondrial antibody-positive (AMA+) patients with primary SjD, histopathological examination of liver biopsies reveals features characteristic of PBC in up to 95% of cases. Importantly, AMA+, asymptomatic patients should be closely monitored for potential development of PBC. Early diagnosis of PBC and timely initiation of ursodeoxycholic acid therapy are critical for optimizing disease management and improving long-term outcomes (22,23).

Among SRDs, SjD is most frequently associated with PBC, with a reported prevalence ranging from 3.5% to 38%. In addition to their clinical coexistence and comparable epidemiologic characteristics, SjD and PBC share overlapping pathogenetic mechanisms and genetic susceptibility factors (22,24). One notable example is the E2 subunit of the pyruvate dehydrogenase complex, a major PBC-specific autoantigen, which has also been detected on the surface of salivary epithelial cells in SjD.

Furthermore, human leukocyte antigen (HLA)-DR2 and HLA-DR3 alleles have been identified as shared genetic susceptibility markers for both conditions (22,24). Although the prevalence of anti-smooth muscle antibodies in SjD is generally higher than that of AMA, the occurrence of co-existing AIH among SjD patients is less frequent than the occurrence of coexisting PBC. Small-scale studies and case series have described SjD-PBC overlap syndromes, suggesting that these associations may represent a causal relationship rather than sporadic coexistence. Importantly, clinicians should consider the coexistence of immunoglobulin G4-related disease (IgG4-RD) in patients who present with autoimmune pancreatitis in the context of SjD-PBC overlap disease (22,24).

Pancreatic Involvement in Sjögren's Disease

Pancreatitis has been reported infrequently (generally ≤7% across heterogeneous series; overlap and selection likely contribute) in patients with SjD (1). It may present as either autoimmune pancreatitis or chronic pancreatitis. Notably, in nearly all reported cases of overlap between SjD and primary sclerosing cholangitis, patients exhibit chronic pancreatitis, characterized by the triad of weight loss, diarrhea, and steatorrhea (2,25,26).

Several distinct pancreatic findings have been described in SjD, including isolated pancreatic calcifications, enlargement of the pancreatic head mimicking a neoplasm, and elevated serum cancer antigen 19-9 levels in benign pancreatic conditions (1). Furthermore, abnormal exocrine pancreatic function has been detected in approximately 18-37.5% of asymptomatic SjD patients, but steatorrhea remains an uncommon clinical finding in this population (2,27,28).

Chronic pancreatitis has also been reported in association with other autoimmune diseases, including SjD, PBC, and primary sclerosing cholangitis (28-30).

When autoimmune pancreatitis is suspected, apply the international consensus diagnostic criteria and histology, imaging, serology, other organ involvement, response to therapy diagnostic frameworks and distinguish type 1 (IgG4-RD) from type 2 (idiopathic ductcentric). Include malignancy in the differential diagnosis when focal enlargement mimics a neoplasm (31).

CONCLUSION

GI, hepatobiliary, and pancreatic involvement represents a clinically relevant yet often under-recognized component of SjD. Sicca-related oral and esophageal symptoms remain the most frequent manifestations, but a subset of patients experiences broader GI dysfunction, including dysmotility, chronic atrophic gastritis, CD, and rare but significant complications such as pseudo-obstruction or protein-losing enteropathy. Hepatobiliary disease—most notably PBC and, less commonly, AIH—constitutes an important extra-glandular domain with implications for long-term monitoring. Pancreatic involvement, although uncommon, encompasses autoimmune pancreatitis and exocrine dysfunction and should be considered in patients with unexplained abdominal symptoms or malabsorption. These findings emphasize the importance of systematic evaluation of GI and hepatopancreatic systems in SjD. Multidisciplinary collaboration is essential to ensure timely diagnosis, tailored management, and improved patient outcomes.

Footnotes

Authorship Contributions

Concept: F.A., Design: F.A., E.İ., S.Y., Data Collection or Processing: E.İ., S.Y., Y.A., Analysis or Interpretation: F.A., E.İ., S.Y., Literature Search: E.İ., S.Y., Y.A., Writing: F.A., Y.A.

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