REVIEW

Systemic Manifestations of Sjögren's Syndrome

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Abstract: Sjögren's syndrome is a common autoimmune rheumatic disease, identified by its two most common symptoms - dry eyes and a dry mouth. It can also damage other parts of your body, such as joints, thyroid, kidneys, liver, lungs, skin, nerves. Other clinical manifestations are vaginal dryness, non-productive cough, salivary gland swelling and systemic symptoms (arthralgia, fatigue and general discomfort). The unquestionable role of both the innate and adaptive immune system, participating actively in the induction and evolution of the disease, was recognized. This process can manifest either as the independent phenomenon of primary Sjögren's syndrome or as secondary Sjögren's syndrome when found in the context of another autoimmune process. The condition often accompanies other immune system disorders, such as rheumatoid arthritis and systemic lupus erythematosus. Sjögren's syndrome can develop at any age; most people are older than 40 at the time of diagnosis. The condition is much more common in women. The objective of this review paper is to summarize the recent literature on Sjögren's syndrome, starting from its pathogenesis to systemic manifestations.

Keywords*: Sjögren's syndrome, systemic manifestations*

DOI **10.56082/annalsarscimed.2026.1.9**

INTRODUCTION

In the early 1900s, Swedish physician Henrik Sjögren first described a group of women whose chronic arthritis was accompanied by dry eyes and dry mouth. Sjögren's disease is a chronic, systemic, immune-mediated disease that causes extensive dryness, fatigue and joint pain. Sjögren's Syndrome is one of the most frequent rheumatic diseases, with a prevalence of 0.1-0.6% in the adult population, a male-female ratio of approximately 1:9 and an average age at diagnosis of 50 years [1]. Sjögren's syndrome may occur alone (primary) or in association with another autoimmune disease (secondary) [2].

Extraglandular involvement may be present in about one third of patients with primary Sjögren's syndrome [3]. The most affected organs are thyroid, lungs, gastrointestinal tract, blood, kidneys, skin and central and peripheral nervous system. Besides, dryness may affect other mucosal surfaces such as airways, digestive tract and vagina, resulting in the clinical picture of "sicca syndrome" or "sicca complex". While the cause of Sjögren's disease is unknown, genetic and environmental factors may be involved [4,5].

The diagnosis of Sjögren's syndrome is based on characteristic clinical signs and symptoms, as well as on specific tests including salivary gland histopathology and autoantibodies [6].

Concerning the impact of Sjögren's syndrome on quality of life, the disease negatively affects patient daily activity due to the high prevalence of fatigue, depression, anxiety and decreased physical performances. Other non-specific general symptoms are sleep disorders, anxiety, depression and chronic widespread pain.

The pathophysiology underlying Sjögren's syndrome is not well deciphered, but several converging lines of evidence have supported the conjuncture of different factors interplaying together to foster the initiation and perpetuation of the disease [2].

Previously, a dominant role of the adaptive immune system in the pathogenesis of Sjögren's syndrome was suspected. Its pathogenesis begins with glandular dysfunction resulting from the infiltration of T lymphocytes [7]. This is followed by the activation of B lymphocytes and synthesis of autoantibodies capable of immune manifestations at a distance from the glandular structures. New evidence indicates that a third actor linking innate and adaptive immunity plays a leading role in the Sjögren's syndrome play the monocyte [7,8].

The pathogenesis of Sjögren's syndrome is characterized by the production of inflammatory cytokines and lymphocyte infiltration [2].

The etiology of Sjögren's syndrome is unknown.

In the pathogenesis of Sjögren's syndrome, the activation of salivary gland epithelial cells appears to be the initial event [9].

Healthcare providers classify Sjögren's syndrome into two types: primary Sjögren's syndrome develops on its own and isn't caused by another health condition; primary Sjögren's syndrome happens with no known trigger or cause [10].

When Sjögren's syndrome occurs by itself, it's called primary Sjogren's syndrome [11].

Secondary Sjögren's syndrome happens when another condition or issue causes (triggers) Sjögren's syndrome. Secondary Sjögren's syndrome refers to patients with an underlying autoimmune disease, such as systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, systemic sclerosis, or others and who concurrently develop Sjogren's syndrome [12].

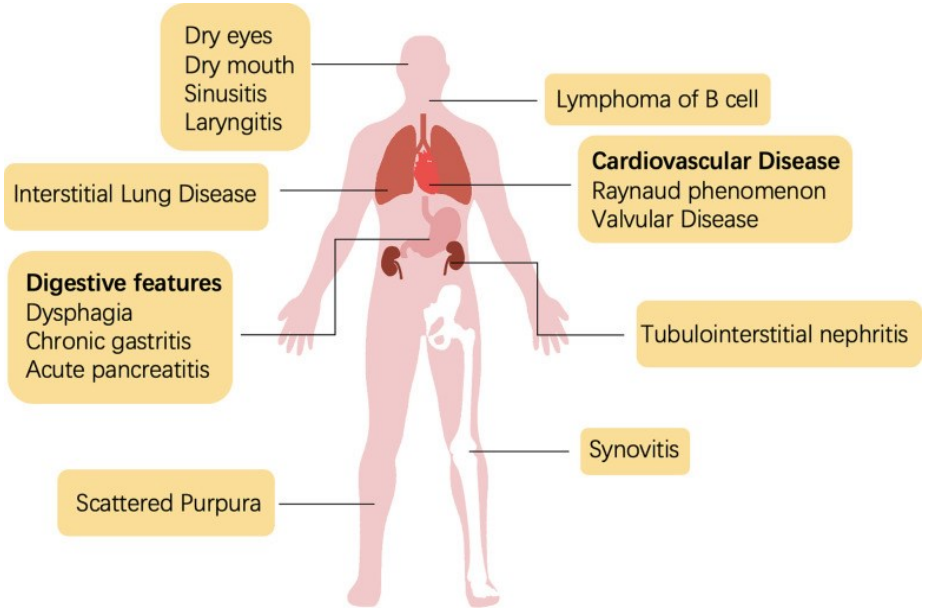

Fig. 1. Typical glandular and extraglandular manifestations of Sjögren's syndrome (2)

Primary and secondary forms of Sjögren's syndrome can have similar symptoms. Secondary Sjögren's syndrome can accompany the following conditions: rheumatoid arthritis, primary biliary cholangitis, lupus, systemic sclerosis. A recent study reported that the oral microbiome of patients with Sjögren's syndrome who have salivary hypofunction was under stress and dysregulated; Veillonella parvula is a potential biomarker of Sjögren's syndrome [13].

This review summarizes the actual status of knowledge concerning the systemic manifestations in Sjögren's syndrome.

Oral manifestations

The most common symptoms of Sjögren's syndrome are extreme tiredness, along with dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Xerostomia can eventually lead to difficulty in swallowing, severe and progressive tooth decay, or oral infections. Despite having excellent oral hygiene, individuals with Sjögren's syndrome have elevated levels of dental caries, along with the loss of many teeth, early in the disease. Glandular swelling usually involves parotid glands; however, submandibular or sublingual glands may be affected too. Glandular enlargement may start unilaterally, although it generally becomes bilateral [14].

Ear, nose, and throat manifestations

Sjögren's syndrome does not appear to be associated with increased otologic or audiologic disease, except perhaps in conjunction with systemic autoimmunity [15].

Nose and throat symptoms are common in Sjögren's syndrome, but the complications of mucosal dryness on examination are unusual. There is also a significant risk of lymphomas that often present as parotid masses, necessitating long-term follow-up. Nasal septal perforation and nasal mucosa dryness were also noted in patients with Sjögren's syndrome [16].

A diagnosis of Sjögren's syndrome should be considered and investigated in smell deprivation and/or nasal septal perforation patients [17].

Ophthalmologic manifestations

Ocular signs and symptoms are represented by surface disorders with different severity grades. Primary Sjögren's syndrome usually presents with different types of severity, e.g., dry eye and dry mouth symptoms, due to early involvement of the lacrimal and salivary glands, which may be associated with parotid enlargement and dry eye; keratoconjunctivitis sicca is its most common ocular manifestation [18].

Lachrymal gland dysfunction causes qualitative and quantitative abnormalities of the tear film, thus leading to ocular surface chronic inflammation. Moreover, eyes symptoms are worsened by windy, dusty, smoky or dry environments [19].

Dermatologic manifestations

Nearly half of the patients with Sjögren's syndrome develop cutaneous manifestations, which may include dry skin (xeroderma), palpable and nonpalpable purpura, and/or urticaria-like lesions [20].

Skin involvement in Sjögren's syndrome is relatively common, and various manifestations may be present, in particular xeroderma, eyelid dermatitis, annular erythema, and cutaneous vasculitis [21].

Additional skin non-vasculitic manifestations include livedo reticularis which may occur in the absence of vasculitis and localized nodular cutaneous amyloidosis possibly representing lymphoproliferative diseases related to Sjögren's syndrome [22].

Arthritic manifestations

The disease also affects the musculoskeletal system targeting bones, specific joints, muscles, and the peripheral nerve

system. Arthritis is predominantly symmetrical, generally mono- or oligoarticular with the involvement of proximal interphalangeal, metacarpophalangeal joints and wrists [23].
The large majority of Sjögren's syndrome-related arthritis is non-erosive, while synovitis and bone erosions are characteristic features of secondary Sjögren's syndrome associated with rheumatoid arthritis. It is estimated that about 20% of patients with severe rheumatoid arthritis have sicca symptoms (particularly eye involvement) [24].

Endocrine manifestations

Hypothyroidism appears commonly in Sjogren's syndrome patients. Hypoactivity of the hypothalamic-pituitary-adrenal axis has been previously demonstrated in patients with primary Sjögren's syndrome as a result either of a pituitary defect and/or of adrenal gland dysfunction [25].
Androgen deficiency in Sjögren's syndrome may be reflected in a low dehydroepiandrosterone and dehydroepiandrosterone-sulfate level patients. An additional finding of interest is the role that androgens play in both lacrimal and salivary glandular function [26].
The incidence of insulin-dependent diabetes (type I diabetes) is not significantly increased, although diabetic patients with hyperglycemia frequently have complaints of dryness [27].

Pulmonary manifestations

Respiratory tract involvement is often described among Sjögren's syndrome patients [28].
Sjögren's syndrome typically develops late in the course of disease and are rarely chronic bronchitis, nasal mucosal dryness, recurrent pneumonia [29].
The interstitial lung disease associated with Sjögren's syndrome was termed lymphocytic interstitial pneumonitis [30].
The most common presenting complaint is dyspnea for several months, and chest radiographs usually show bilateral interstitial infiltrates [31,32].
Other respiratory complications described in Sjögren's syndrome patients include amyloidosis, bronchus-associated lymphoid tissue lymphomas, thromboembolic disease, pulmonary arterial hypertension and pleural disease [33,34].

Cardiovascular manifestations

The involvement of the cardiovascular system is not a common feature of Sjögren's syndrome [35].
Sjögren's syndrome can be associated with vasculitis, which may cause an increased risk of hemorrhagic strokes due to the inflammatory infiltrate in the vascular wall [36].
Severe complications as acute pericarditis and myocarditis have been rarely reported, although the best-known cardiac complication is congenital heart block, which is one of the manifestations of neonatal lupus [37].
Although not conventionally considered a feature of the disease, cardiovascular events represent a major burden in Sjögren's syndrome patients. Pericarditis manifests as acute symptomatic disease with an exudative effusion and is a rare complication of primary Sjögren's syndrome [38].

Gastroenterology manifestations

Nausea, epigastric pain, and dyspepsia, acute pancreatitis, liver disease are other frequent complaints. Dysphagia is common in Sjögren's syndrome and is most often due to lack of saliva [39].
Besides, diminished secretion of the exocrine glands of the digestive tract may involve pancreas and stomach causing pancreatic dysfunction and hypochlorhydria, respectively. Subclinical pancreatic dysfunction, characterized by exocrine pancreatic impairment with reduced production of amylase and lipase, can be

observed in Sjogren's syndrome patients. Abnormal liver function tests can be detected in up to 50% of patients, but only a minority of them have a frank liver disease such as primary biliary cholangitis, autoimmune hepatitis or non-alcoholic fatty liver disease [40].

Renal manifestations

Chronic tubulointerstitial nephritis is the predominant form of Sjögren's syndrome-associated renal involvement, which clinically translates mostly into distal renal tubular acidosis [41].

Distal renal tubular acidosis is characterized by a cortical collecting duct dysfunction that involves the acid-secreting alpha-intercalated cells leading to an impaired H^+ elimination [42]. The defect may be complete, with systemic metabolic acidosis, or incomplete, characterized by the inability to acidify urine following an oral acid loading challenge [43]. In symptomatic patients, distal renal tubular acidosis presents with weakness/paralysis due to hypokalemia and less frequently with renal calculi and osteomalacia [44]. Mildly elevated serum creatinine and low-grade proteinuria may be present [45].

Other less common forms of Sjögren's syndrome-related tubulointerstitial nephritis are represented by dysfunctions involving cortical collecting duct (principal cells), proximal tubular, loop of Henle and distal convoluted tubule [46,47].

Urology manifestations

Interstitial cystitis - symptoms are more common in Sjögren's syndrome patients and may be severe. Sjögren's syndrome patients' bladder symptoms may be exacerbated by these patients' large fluid intake (due to dry mouth) and the antibodies to muscarinic cholinergic receptors found on bladder epithelial cells [48,49].

Women with Sjögren's syndrome may develop dysuria, urinary frequency, nocturia, and urgency-symptoms that are thought, in the absence of infection, to be due to interstitial cystitis [50,51].

Gynecologic manifestations

Women are affected 10 times more often than men, gynecologic manifestations of Sjögren's syndrome are: vaginal mucosal dryness, or dyspareunia can contribute to pain during penetration, soreness, and itching. The relationship of infertility to a long menstrual cycle may simply indicate the presence of ovulatory dysfunction or inadequate luteal phase unrelated to Sjögren's syndrome [52].

Reduced vaginal secretion leads to dyspareunia and local discomfort. Sjögren's syndrome does not directly impair fertility; however, pregnancy complications among Sjögren's syndrome patients are described. Indeed, Sjögren's syndrome affected women present an increased rate of miscarriage and preterm deliveries. Moreover, they give birth to babies with lower birth weight and have complications during deliveries more frequently than unaffected women [53].

Neurological manifestations

Sjögren's syndrome may affect both central and peripheral nervous systems [54].

The neurologic manifestations of primary Sjögren's syndrome are varied and can be divided anatomically into 2 categories: peripheral neuropathies and central nervous system conditions [55].

Distal sensory and sensorimotor neuropathies are the most common manifestations of peripheral nerve disease in primary Sjögren's syndrome [56,57]. Central nervous system manifestations associated with primary Sjögren's syndrome include focal central lesions, conditions that mimic multiple sclerosis, encephalitis, aseptic meningitis, cerebellar syndromes, movement disorders, and problems with memory, cognition, and depression [58].

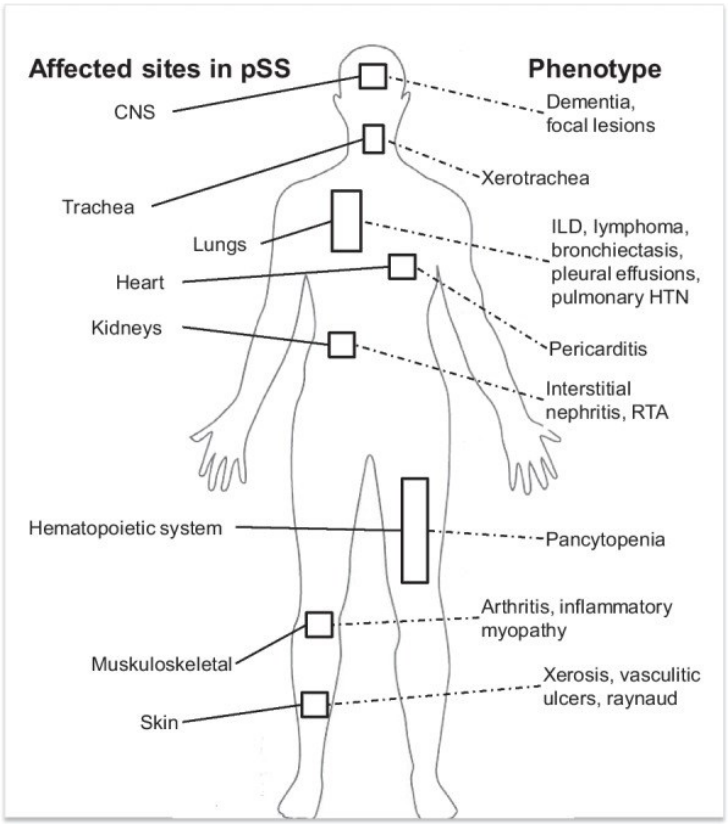

Fig. 2. Primary Sjögren's syndrome. CNS Central nervous system, HTN hypertension, ILD Interstitial lung disease, RTA renal tubular acidosis (29)

Hematologic manifestations

Patients also have a higher chance of developing lymphoma. Waldenström's hypergammaglobulinemia is a relatively common vasculitic manifestation in Sjögren's syndrome, characterized by palpable purpura, marked polyclonal hypergammaglobulinemia, and high levels of rheumatoid factor and anti-Ro/anti-La antibodies [59-61]. Cryoglobulinemia is associated with leukocytoclastic vasculitis in Sjögren's syndrome [62-64].

Patients with primary Sjögren syndrome may present hematologic abnormalities, such as anemia, hemocytopenias, monoclonal gammopathies and lymphoprolipherative disorders, predominantly non-Hodgkin's lymphoma of B-cell origin. It should be noted that an isolated finding of anti-SSA/Ro and/or SSB/La is not sufficient to make a diagnosis of Sjögren's syndrome, as these autoantibodies can be found in other connective tissue diseases and even in healthy subjects [65-67).

CONCLUSIONS

Sjögren's syndrome is a chronic autoimmune disease associated with functional disorders of the exocrine glands (e.g., parotid and lacrimal glands) and extraglandular manifestations. Sjögren's syndrome typically presents as dry eyes (xerophthalmia) and dry mouth (xerostomia). The recognition of these extraglandular manifestations is important since they have prognostic and therapeutic implications. This condition is frequently associated with other autoimmune disorders including rheumatoid arthritis and systemic lupus erythematosus.

Compliance with Ethics Requirements
"The author declares no conflict of interest regarding this article. No funding for this study."

Acknowledgements
None.

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