Case Report
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Early-onset primary Sjögren's syndrome associated to Crohn's disease: An exceptional overlap syndrome

Abstract

Primary Sjögren's syndrome (PSS) is a connective tissue disease frequently associated with other autoimmune or autoinflammatory diseases but its association with chronic inflammatory bowel diseases (Crohn's disease (CD) and ulcerative colitis) remains exceptional and overlooked by clinicians. Early-onset forms of PSS, defined as age ≤35 years at diagnosis, remain rare and unusual. We report an original case of primary early-onset PSS associated to CD in a 35-year-old Tunisian woman diagnosed five months apart, and responding well to systemic corticosteroid therapy and 5-aminosalicylic acid (5-ASA) with complete remission.

As rare as it is, this association deserves to be recognized by all healthcare professionals and screening for Sjögren's syndrome appears useful in patients with Crohn's disease, particularly if dry syndrome and/or joint involvement.

Keywords: crohn's disease, primary sjögren's syndrome, inflammatory bowel, diseases, sicca syndrome, autoimmunity, overlap syndrome

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Introduction

Primary Sjögren's syndrome is a non-organ-specific autoimmune disease characterized by lymphocytic infiltration initially affecting the exocrine glands, causing the classic "dry syndrome", and the production of autoantibodies against soluble antigens, particularly anti-Ro/SSA and anti-La/SSB.[1,2] It is the most common connective tissue disease and the second most prevalent rheumatic disease after rheumatoid arthritis, and preferentially affects adults over 50 years of age.[1,2]. Early-onset forms, defined as age ≤35 years at diagnosis, remain rare and unusual.[3] This disease is frequently associated with other autoimmune or autoinflammatory diseases (organ-specific or systemic autoimmune diseases), the most common of which are systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, primary biliary cirrhosis, and autoimmune thyroiditis.[1,2] Its association with chronic inflammatory bowel diseases (Crohn's disease and ulcerative colitis) remains exceptional and overlooked by clinicians.[4,5] We report an original case of primary Sjögren's syndrome associated to Crohn's disease in a young woman.

Case presentation

A 35-year-old Tunisian woman with no significant past medical history was recently diagnosed with primary Sjögren's syndrome according to the 2016 ACR/EULAR criteria: xerostomia, xerophthalmia, polyarthritis with synovitis of hands and wrists (swelling, pain, and functional impairment of both wrists and both hands with clinical examination showing synovitis and arthritis of the wrists, metacarpophalangeal and proximal and distal interphalangeal joints with local inflammatory signs, without joint deformities or joint destruction on standard radiographs), dry eye syndrome on specialized ophthalmological examination, positive antinuclear autoantibodies at 1/380 with positive anti-SSA autoantibodies, and Chisholm stage 2 chronic lymphocytic sialadenitis on the biopsy of the accessory salivary glands). She was treated with systemic steroids (10mg/d), hydroxychloroquine (400mg/d), and symptomatic ocular drops with good evolution.

Five months later, she presented with rectal bleeding and anal pruritus, followed by the onset of diarrhea. Gastrointestinal investigations revealed positive *Helicobacter Pylori* chronic gastritis, for which she received eradication therapy, inflammatory ileitis, colitis, and a histological appearance consistent with Crohn's disease. Further investigations for infections, cancers, malignant homeopathies, systemic vasculitis, and other connective tissue diseases were negative. Bone densitometry did not show osteoporosis or osteopenia.

She was treated with 5-aminosalicylic acid (5-ASA) inducing complete remission. The final diagnosis was that of early-onset primary Sjögren's syndrome associated with mild Crohn's disease.

Discussion

The first description of the association between primary Sjögren's syndrome and Crohn's disease was reported by Gainey R et al. in 1985.[6] Since then, only about ten cases have been found in the medical literature as sporadic cases,[7–11] making this overlap syndrome one of the rarest in routine medical practice.[7] The timing of this association is highly variable. The diagnosis of both diseases may be concurrent or separated by time; significant intervals of up to 20 years between the onset of the two conditions have been reported.[8]

The association of Crohn's disease and primary Sjögren's syndrome may remain isolated or mask other autoimmune or autoinflammatory diseases (Sweet's syndrome, Hashimoto's thyroiditis, connective tissue diseases, and systemic vasculitis), resulting in more complex cases of dysimmune associations.[4,7,12] Similarly, Sjögren's syndrome associated with Crohn's disease may remain completely asymptomatic and be diagnosed during systemic screening or in the context of specific complications.[13]

This association raises the possibility (as differential diagnoses) of secondary Sjögren's syndrome occurring during Crohn's disease (ocular and/or oral sicca syndrome as an extra-digestive manifestation of Crohn's disease).[14] or of specific digestive involvement in primary

Sjögren's syndrome mimicking Crohn's disease.[15,16] This association usually has a good prognosis, but more severe cases with ocular, cerebral, and vascular complications have been reported.[11]

The association of Crohn's disease and primary Sjögren's syndrome responds very well to systemic corticosteroid therapy and, in the most severe cases, to biologic therapy.[7,10] The pathogenesis of this association is not yet well understood. Several mechanisms have been suggested: infection, autoimmunity, dysbiosis of oral and gut microbiota, inflammation, and genetic susceptibility.[4,7–11] Immune dysregulation, particularly of cellular immunity (recruitment and clonal expansion of T lymphocytes with overproduction of pro-inflammatory cytokines, including tumor necrosis alpha (TNF-α)), is central to the pathophysiology of both diseases.[10] This hypothesis is reinforced by the findings of Bar Yehuda S et al., who, in their large study of 12,625 patients with IBD, noted that treatment with anti-tumor necrosis factor medications is associated with a lower prevalence of primary Sjören's syndrome: 0.1% vs. 0.9%, OR=0.13, and $p<0.05$.[4]

Recently, polygenic susceptibility involving diverse and varied domains, such as innate and adaptive immunities, human leukocyte antigen (HLA) loci, cell adhesion, epithelial integrity, and drug transporters, has been demonstrated for both diseases.[17–19] These two diseases can thus be considered complex polygenic diseases whose pathogenesis involves polygenic susceptibility and inducing environmental factors.[17,19] Genome-wide association studies (GWAS) confirmed this polygenic susceptibility with multiple loci for Crohn's disease[20] and primary Sjögren syndrome.[21] Some of these susceptibility loci are common to both conditions.[18,22,23] However, these findings require further population studies in different ethnicities and races for greater accuracy.

This association should be considered by healthcare professionals during the follow-up of patients with Crohn's disease, particularly if dry eye and/or oral or joint symptoms appear.[8] In this context, joint manifestations pose the main differential diagnosis between a true association (Crohn's disease and primary Sjögren's syndrome) and a simply Crohn's-related arthritis.[4–11] Sjögren's-related arthritis affect up to 60% of patients, and typically manifesting as non-erosive polyarthritis involving the small joints of the hands, wrists, and ankles with no joint destruction nor deformities.[1,2] With an estimated frequency of 20-30%, arthritis is the most common extra-intestinal complication of Crohn's disease. Typically, this enteropathic arthritis presents as oligoarthritis of large joints (knees, ankles, hips, and wrists), often associated with spinal involvement, and generally correlated with the severity of IBD.[4–11] Our observation is distinguished by the early onset of Sjögren's syndrome, a finding not observed in other case reports of this association.[7–11]

Conclusion

As rare as it is, the association of Crohn's disease with primary Sjögren's syndrome deserves to be recognized by all healthcare professionals due to its specific clinical and evolutionary characteristics. This association further highlights the systemic nature of both conditions, as well as their shared pathophysiological mechanisms (autoimmunity, inflammation, microbiota, and infections). Screening for Sjögren's syndrome appears useful in patients with Crohn's disease, particularly if dry syndrome and/or joint involvement.

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None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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