Section: Miscellaneous

Case Report

SJÖGREN'S SYNDROME UNVEILED: A CASE OF RAPID PROGRESSION TO RHEUMATOID ARTHRITIS WITH DIAGNOSTIC CHALLENGES

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ABSTRACT

A 50-year-old female presented with xerostomia, recurrent oral ulcers, bilateral ocular dryness, and right submandibular swelling persisting for three months. Ultrasonography revealed an enlarged, heterogenous submandibular gland with increased vascularity, consistent with sialadenitis. Ophthalmic evaluation demonstrated markedly reduced Schirmer's test results (4 mm bilaterally). Fine-needle aspiration cytology (FNAC) of the submandibular gland showed polymorphous lymphoid infiltrates (mature lymphocytes, centrocytes, centroblasts) and epithelial cells, excluding mycobacterial infection (AFB-negative, CBNAAT-negative). Serum antinuclear antibody (ANA) testing showed 3+ positivity at 1:80 dilution with a speckled pattern and an endpoint titre of 1:320. Lingual biopsy confirmed Sjögren's syndrome (SS) with a focus score >1. Subsequent rheumatological evaluation revealed elevated rheumatoid factor (RF) and polyarthralgia, prompting a dual diagnosis of SS and rheumatoid arthritis (RA). Hematological and metabolic parameters (CBC, LFT, KFT, electrolytes, vitamin D, thyroid function) remained normal. This case highlights the diagnostic complexity of overlapping autoimmune syndromes, emphasizing the role of histopathology (focus score) and serology (ANA, RF) in differentiating primary Sjögren's Syndrome (SS) from secondary RA-associated SS. The rapid progression from glandular to systemic manifestations underscores the need for vigilant monitoring in SS patients for evolving rheumatological conditions. Multidisciplinary management involving ENT, ophthalmology, pathology, and rheumatology was critical to achieving diagnostic clarity and initiating immunomodulatory therapy.

Keywords: Sjögren syndrome, xerostomia, keratoconjunctivitis sicca, autoimmune disease, rheumatoid arthritis, ANA, submandibular swelling.

INTRODUCTION

Sjögren's Syndrome (SS) is a chronic autoimmune disease characterised by lymphocytic infiltration that primarily affects the exocrine glands, leading to symptoms of dryness, most notably of the eyes (xerophthalmia) and mouth (xerostomia). This systemic condition can, however, affect a wide range of other organs, including the kidneys, stomach, lungs, and joints. SS is recognised as the most common connective tissue disease, significantly impacting patients' daily lives and work capacity.[1]

Estimating the global prevalence of Sjögren's Syndrome has been the subject of recent research. A systematic review and meta-analysis, combining findings from 24 observational studies involving over 21,000 participants, estimated the overall worldwide prevalence of SS to be approximately 13%. The syndrome affects both sexes, but shows a marked predilection for females, with a female-to-male ratio of approximately 9:1. The prevalence among females is slightly higher than the overall prevalence, estimated at 15%. SS can manifest at any age, but appears to be most prevalent in older age groups, with the 50-59 age bracket facing a

heightened susceptibility, demonstrating a prevalence of 24% in one analysis.[2]

Sjögren's Syndrome is broadly categorised into two types: primary SS, which occurs as a standalone condition, and secondary SS, which develops in association with other autoimmune diseases. Secondary SS is frequently observed alongside other rheumatologic conditions, most notably rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The presence of one autoimmune disorder is considered a significant risk factor for the development of another. Indeed, systematic reviews and meta-analyses have shown a substantial prevalence of secondary SS in populations with other autoimmune diseases, with the combined prevalence of secondary SS linked to rheumatoid arthritis reported to be as high as 19.5%.

The diagnosis of Sjögren's Syndrome can be challenging and is often subject to delay. This difficulty is partly attributable to the considerable overlap in clinical and serologic features with other autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus, which can lead to initial misdiagnosis or confusion. Symptoms such as sicca, fatigue, and musculoskeletal pain can be common across multiple rheumatic conditions. Over the years, diagnostic criteria for SS have undergone several modifications, with the 2016 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification criteria representing the current consensus and diagnostic foundation. These criteria were developed using a data-driven methodology and expert consensus. While laboratory tests for autoantibodies like anti-Ro 60 and anti-Ro 52 play an important role in diagnosis, particularly when present simultaneously, other indicators like antinuclear antibodies (ANA) and rheumatoid factor (RF) are not included in the latest guidelines due to their lower specificity and presence in other autoimmune diseases, including RA and SLE. The potential for overlapping antibody profiles further contributes to diagnostic complexity in differentiating SS from, or confirming its co-occurrence with, other conditions.

The complex interplay between Sjögren's Syndrome and other autoimmune disorders, particularly rheumatoid arthritis, presents significant clinical challenges, especially when symptoms suggesting a secondary condition emerge shortly after an initial SS diagnosis. While the literature highlights the common overlap and diagnostic difficulties, specific insights into the clinical presentation and diagnostic journey when features of rheumatoid arthritis appear to manifest rapidly following a diagnosis of Sjögren's Syndrome remain less explored.

This case report unveils the intricacies of such a presentation of Sjögren's Syndrome. By focusing on a specific instance where a patient diagnosed with Sjögren's Syndrome subsequently developed features strongly indicative of rheumatoid arthritis in a seemingly rapid manner, this research provides a tangible example of the diagnostic challenges inherent in these overlapping conditions. The novelty of this study lies in its detailed examination of a specific case demonstrating potential rapid progression to rheumatoid arthritis following an SS diagnosis, offering valuable insights into the diagnostic process and the complexities faced by clinicians in managing such dynamic and overlapping autoimmune presentations.

Clinical History: A 50-year-old female presented in May 2023 with xerostomia, recurrent oral ulcers, ocular dryness, and a right submandibular mass. Three months later, she developed polyarthralgia affecting the shoulders and other joints.

Initial Evaluation

Clinical Examination

- **Oral cavity:** Parched tongue, multiple aphthous ulcers.
- **Neck:** Firm, non-tender 1.5 x 1.5 cm submandibular mass.

Investigations

- **Imaging Studies**
  - Ultrasonography (USG) of the neck: Revealed an enlarged submandibular gland with heterogenous echotexture and increased vascularity on color Doppler. These findings were suggestive of sialadenitis.
- **Ophthalmic Examination:**

Schirmer's test: Moisture spread measured at 4 mm bilaterally, indicating reduced tear production.

- **Cytopathology:** FNAC revealed lymphoid proliferation (mature lymphocytes, centrocytes, centroblasts) and macrophages, excluding tuberculosis.
- **Serology:** ANA 3+ (speckled pattern, titer 1:320), elevated RF.

Histopathology: Lingual biopsy demonstrated lymphocytic foci (> 1 focus score /4 mm²), confirming SS.

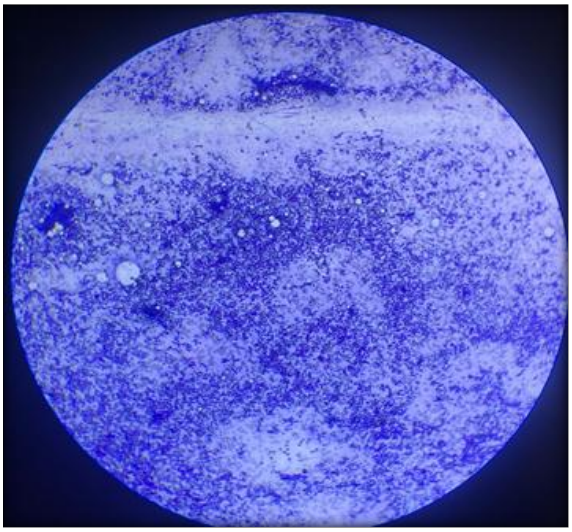

Figure 1: Microscopic appearance of Fine needle aspiration cytology of submandibular mass (10x magnification)

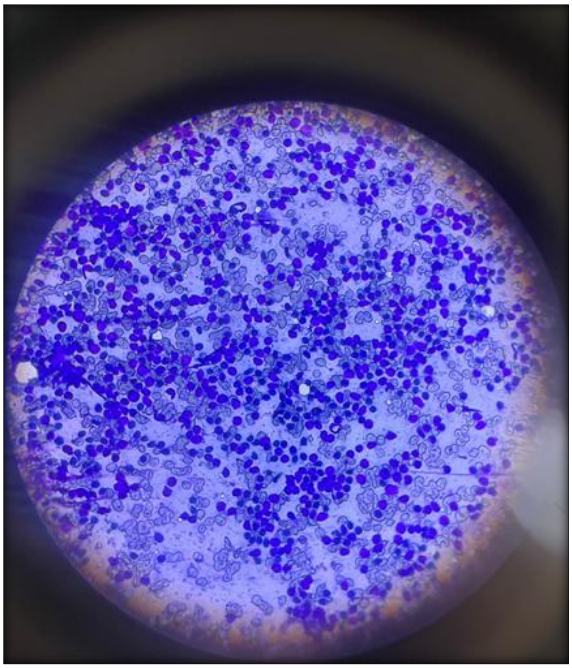

Figure 2: Microscopic appearance of Fine needle aspiration cytology of submandibular mass (40x magnification)

DISCUSSION

SS and RA coexistence exemplifies the "secondary SS" phenomenon, occurring in 20–30% of RA patients. The patient met both SS and RA criteria, with glandular inflammation preceding systemic joint involvement-a progression observed in 5% of SS cases. The speckled ANA pattern and RF elevation suggest shared autoantibody pathways (e.g., anti-SSA/Ro in SS and anti-CCP in RA). Histopathological focus score >1 remains the gold standard for SS diagnosis, as demonstrated here.

The present case report illustrates the complex and often overlapping nature of autoimmune rheumatic diseases, particularly Sjögren's syndrome (SS) and rheumatoid arthritis (RA). It is well-established that SS can occur as a standalone primary condition or as a secondary syndrome associated with other autoimmune diseases, most commonly RA, systemic lupus erythematosus (SLE), or systemic sclerosis (SSc). In fact, SS is frequently associated with RA, and patients diagnosed with SS should be evaluated for other associated autoimmune conditions like RA, given the shared clinical features, phenotype, and underlying mechanisms.[3-5]

The diagnosis of overlapping autoimmune syndromes can present significant challenges, as highlighted by the diagnostic complexities in this case. The criteria used for diagnosing SS itself show variability; for instance, studies demonstrate differing prevalence estimates of SS in RA patients depending on whether the 2002 American-European Consensus Group (AECG), 2012 American College of Rheumatology (ACR), or 2016 ACR/European League Against Rheumatism (EULAR) criteria are applied, ranging from 6.3% to 8.7% in one cohort based on different criteria and rheumatologist's diagnosis.[6] The final diagnosis often relies on a combination of clinical symptoms (sicca symptoms like dry eyes and dry mouth), ocular signs, histopathology (minor salivary gland biopsy), salivary gland involvement assessments (like sialography or scintigraphy), and serological markers.[3]

The presence of specific autoantibodies provides crucial diagnostic clues for SS in RA patients with dryness symptoms. Seropositivity for rheumatoid factor (RF), anti-nuclear antibodies (ANA), and particularly anti-Ro (SS-A) antibodies are more frequent in RA patients who also have secondary SS compared to those with RA alone. The anti-Ro antibody demonstrates high specificity for SS, and its detection in RA patients significantly increases the probability of concurrent SS. One study found that 67.6% of RA patients positive for the anti-Ro antibody also had SS. Similarly, ANA positivity (at titres $\geq$ 1:80) is more common in RA-SS overlap cases (17%).[6,7]

Beyond serological overlap, SS and RA share underlying pathogenic mechanisms. Both are characterized by lymphocytic infiltration in affected tissues; specifically, lymphocytic infiltration of exocrine glands is a hallmark of SS, and lymphoid infiltrates are seen in affected tissues in both diseases.[8] Studies indicate that patients with SS complicated by RA can exhibit impaired cellular immune responses, such as diminished delayed hypersensitivity responses, potentially linked to an increase in large lymphocytes or deficiency of uncommitted small lymphocytes.[4] Elevated levels of beta2-microglobulin have been observed in the salivary and synovial fluids of patients with both SS and RA, suggesting this could be a marker for local disease activity.[7]

Recent insights from transcriptional profiling offer further understanding into the shared pathology. A notable finding across RA, SLE, and primary SS is the shared megakaryocyte (MK) expansion in peripheral blood. This expansion is associated with common gene expression signatures related to platelet activation and haemostasis. Specifically, upregulated cell-lineage-specific transcription factors such as PBX1, GATA1, TAL1, and GFI1B demonstrate a strong signature of MK expansion. Flow cytometry has confirmed the expansion of specific MK populations (CD41b+CD42b+ and CD41b+CD61+ MKs) in these autoimmune diseases. Furthermore, single-cell RNA sequencing data revealed a distinct immune subpopulation within MKs functionally enriched for antigen presentation. This suggests that aberrant regulation of MK expansion and the immunological activity of certain MK subsets could contribute to the pathogenesis of these overlapping conditions.[2,4,7]

Shared genetic susceptibility and epigenetic mechanisms also contribute to the propensity for polyautoimmunity, including the co-occurrence of SS and RA. Studies have identified shared genetic

loci and explored the role of epigenetic modifications, such as DNA methylation, histone modifications, and microRNAs, in the development and function of immune cells involved in both diseases.[2,3,6]

CONCLUSION

In the context of this case, the rapid progression from SS symptoms to full-blown RA highlights the dynamic nature of autoimmunity and underscores the importance of considering shared pathogenic pathways. The observed progression could potentially be influenced by the interplay of shared genetic and epigenetic predispositions and the dysregulation of common cellular processes, such as the newly identified MK expansion and their potential role in immune initiation. This case serves as a reminder that despite differing primary manifestations, RA and SS share deep biological connections, necessitating vigilance for overlap and further research into shared pathogenic drivers like the immunological role of MKs to improve diagnosis and potentially target therapies in complex presentations. This case also underscores the importance of longitudinal serological and clinical surveillance in SS patients to detect evolving autoimmune comorbidities. Early diagnosis and immunomodulatory therapy may mitigate the systemic progression of the disease.

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