PRIMARY SJOGREN'S SYNDROME INITIALLY PRESENTING AS BICYTOPENIA IN ELDERLY FEMALE: A RARE CASE REPORT

Somee Rauniyar[1], Deepak Subedi[2], Bishwodip Baral [3], Pramod Kafle[4], Neha Bista [1], and Prajwal Sapkota[1]

[1]Madan Bhandari Academy of Health Sciences
[2]Nepalese Army Institute of Health Sciences
[3]Sukraraj Tropical and Infectious Disease Hospital
[4]Chitwan Medical College

August 25, 2024

Authors details:

1. Somee Rauniyar (Corresponding Author)

Affiliation: Madan Bhandari Institute of Health Sciences (Hetauda Hospital), Makawanpur, Nepal

Contribution: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing-original draft, Writing-review & editing

Supervision, Writing- Original draft, Writing-review, and editing

Orcid No: 0009-0007-5466-3183

Email: rauniyarsomee4@gmail.com

2. Deepak Subedi

Affiliation: Nepalese Army Institute of Health Sciences College of Medicine,

Kathmandu, Nepal

Contribution: Data curation, Formal Analysis, Investigation, Methodology, Supervision, Writing-original draft, Writing-review, and editing

Orcid No: 0000-0001-8512-1482

Email: subedideepak28@gmail.com

3. Bishwodip Baral

Affiliation: Sukraraj Tropical and Infectious and Disease Hospital, Kathmandu

Contribution: Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing-review, and editing

Orcid No: 0000-0002-2066-7940

Email: bishwodipbaral@gmail.com

4. Pramod kumar Kafle

Affiliation: Chitwan Medical College and Teaching Hospital, Chitwan, Nepal

Contribution: Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing-review, and editing

Orcid No: 0000-0003-3945-7190

Email: pramodkafle18@gmail.com

5. Neha Bista

Affiliation: Madan Bhandari Institute of Health Sciences (Hetauda Hospital), Makawanpur, Nepal

Contribution: Investigation, Methodology, Supervision, Validation, Writing-review, and editing

Writing- Writing-review and editing

Orcid No: 0009-0009-1934-6347

Email: nehabista992@gmail.com

6. Prajwal Sapkota

Affiliation: Madan Bhandari Institute of Health Sciences (Hetauda Hospital), Makawanpur, Nepal

Contribution: Formal analysis, Methodology, Resources, Writing-review, and editing

Orcid No: - 0009-0009-5933-5837

Email: dr.prajwalsapkota@gmail.com

PRIMARY SJOGREN'S SYNDROME INITIALLY PRESENTING AS BICYTOPENIA IN ELDERLY FEMALE: A RARE CASE REPORT

ABSTRACT

Introduction

Primary Sjogren's syndrome (SS) is a systemic autoimmune disorder commonly characterized by dryness of the eyes and mouth due to inflammation and subsequent pathology of the lacrimal and salivary glands. The hallmark feature of SS is exocrinopathy, which frequently results in xerostomia and keratoconjunctivitis sicca, accompanied by fatigue and joint pain. Although extra-glandular manifestations are rare, they can affect musculoskeletal, renal, pulmonary, and hematological systems. SS should be considered in the differential diagnosis of idiopathic cytopenia and actively investigated through patient history, Schirmer's test, and autoantibody screening. Cytopenia in primary SS is uncommon, with few cases reported in the literature. Here, we present the case of a 60-year-old woman with persistent unexplained bicytopenia (anemia and thrombocytopenia). After a comprehensive evaluation, she was diagnosed with SS.

Case Presentation

A 60-year-old female presented to our outpatient department with a complaint of generalized weakness for the last 6 months. She did not complain of fever, rash, abdominal pain, headache, weight loss, and diaphoresis.

Case Discussion

Sjogren's syndrome is an autoimmune disease that primarily affects women (female to male ratio 9:1.3) with a prevalence ranging from 0.1% to 4.8%. It is characterized by inflammation of exocrine glands such as the salivary and lacrimal glands. Diagnosis of Sjogren's syndrome can be complex due to similarities with other conditions like rheumatoid arthritis, systemic lupus erythematosus (SLE), and cryoglobulinemia. Biomarkers such as rheumatoid factor and autoantibodies (e.g., Ro/SSA) play a crucial role in distinguishing Sjogren's from other conditions like SLE. The disease also has systemic manifestations, including liver involvement

due to autoimmune liver disease and elevated LDH (Lactate Dehydrogenase) levels. Additionally, hematological abnormalities, such as anemia (34.1%), leukopenia (14-42%), and thrombocytopenia (5-15%), are common. These abnormalities are often overlooked but can precede typical symptoms, leading to delayed diagnosis. The mechanisms involved in Sjogren's syndrome include cytokine-mediated inflammation and an immune response involving innate and adaptive immunity, leading to autoimmunity. Elevated LDH levels are also noted, underscoring the systemic nature of the disease. Hematological abnormalities, including anemia (34.1%), leukopenia (14-42%), and thrombocytopenia (5-15%), are common but often overlooked as clinically insignificant laboratory findings. However, they can precede typical symptoms, delaying diagnosis. Mechanisms involve cytokine-mediated inflammation and autoimmune mechanisms targeting red blood cells and platelets.

Conclusion

This case report highlights the initial presentation of Primary Sjogren's syndrome as bicytopenia (anemia and thrombocytopenia), emphasizing its significance in evaluating cytopenia. While uncommon, it is often overlooked in the assessment of unexplained cytopenia. Therefore, Primary Sjogren's syndrome should be considered an important differential diagnosis in evaluating cytopenia. Additionally, our patient responded well to corticosteroid treatment, but long-term follow-up is essential to understand the hematological manifestations in such cases.

KEYWORDS Sjogren's syndrome, ccytopenia, case report, autoimmune diseases, rare case report

Key Clinical Message

Cytopenia is rarely reported in Sjogren's syndrome (SS), but it is an important consideration when evaluating cytopenia. SS might not always initially present with sicca symptoms but rather with cytopenia, which, while uncommon, should be considered in the differential diagnosis during cytopenia evaluation. The typical presentation is asymptomatic normocytic anemia.

INTRODUCTION

Primary Sjogren's syndrome (SS) is a chronic autoimmune disease, characterized by lymphocytic infiltration and destruction of exocrine glands, especially the salivary and lacrimal glands along with occasional extra glandular involvement. [2] The hallmark of the disease is exocrinopathy, which often results in dryness of the mouth and eyes, fatigue, and joint pain. Although extra glandular manifestations are uncommon, they can occur with musculoskeletal, renal, pulmonary, and hematological diseases. The prevalence of primary SS is found to be 6.92 per 100,000 person-years.[11] It is more predominant in females than males (female-to-male ratio = 9:1.3). Primary SS should be considered in the differential diagnosis of apparently 'idiopathic' cytopenia and actively sought by directed history, Schirmer's test, and autoantibody screening.[1]Cytopenia is considered rare in primary SS, with only a limited number of cases documented in the existing literature.[4] We report the case of a 60-year-old woman who presented with persistent unexplained bicytopenia (anemia and thrombocytopenia) and was later diagnosed as SS after comprehensive investigations.

CASE HISTORY/EXAMINATION

A 60-year-old female presented to the outpatient department with a complaint of generalized weakness for the last 6 months. She did not report experiencing fever, rash, abdominal pain, headache, weight loss, or sweating. Additionally, she had no significant history of cardiovascular illness, thyroid disorders, chronic kidney disease, or neurological disorders.

On general examination, the lower palpebral conjunctiva was pale. The vital parameters were in the normal range and the remainder of systemic examinations were unremarkable. On further query, the patient acknowledged that she had been experiencing dry eyes for the past month, but it was not serious enough to bother her. To find out the cause of dry eyes, an ophthalmological examination was performed and it revealed a positive Schirmer's test (3mm in the right and 2mm in the left eye).

METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT)

Considering the patient's symptoms, differential diagnoses include Systemic lupus erythematosus (SLE), Rheumatoid Arthritis (RA), iron deficiency anemia, hemolytic anemia, and blood malignancies. Further investigations were conducted to determine the exact cause of the generalized fatigue and dry eyes. At the initial presentation, the laboratory reports are shown in Table -1.

Table 1: Laboratory reports of the patient at the initial presentation

Laboratory Parameters	**Range**
Hemoglobin(Hb)	8.3 g/dl (Normal range in Women**:** 12.1 to 15.1)
White blood cell count(WBC)	8,400/mm^3 (Normal range: 4,000 to 11,000/mm^3)
Platelets count	62,000/mm^3 (Normal range:150,000 to 450,000/mm^3)
Lactate dehydrogenase (LDH	690 IU/L(Normal range: 140 to 280/mm^3)
Erythrocyte sedimentation rate (ESR)	48 mm/hr (Normal range in women: 0-30mm/hr)

A complete blood count revealed a hemoglobin level of 8.3 g/dl, white blood cell count (WBC) of 8,400/mm3, and platelet count of 62,000/mm3. Biochemical analysis showed elevated lactate dehydrogenase (LDH) levels of 690 IU/L. The erythrocyte sedimentation rate (ESR) also significantly increased to 48 mm/hr. Coombs tests both direct and indirect were negative along with normal bilirubin levels and thyroid function. Peripheral blood smear showed normocytic, normochromic red blood cells (RBC). We then started a bicytopenia workup after obtaining these results.

Serum protein electrophoresis was normal. Human immunodeficiency virus (HIV), Hepatitis B, and Hepatitis C tests were negative. Ultrasound and Pap smear were unremarkable. Antinuclear antibody (ANA) showed a homogenous pattern with a high titer (1:145); rheumatoid factor (RF) was positive (30 IU/ml).

A bone marrow biopsy was performed, yielding normal results and thereby excluding blood malignancies.

Further comprehensive investigations were conducted to rule out autoimmune conditions like SLE and RA, which revealed Sjögren's syndrome antigen A (SSA-A/Ro52) positivity, narrowing our diagnostic possibilities. SSA/RO is a marker for systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS). However, in our patient's case, the absence of a photosensitive rash and serositis ruled out SLE.

Consequently, we diagnosed the patient with SS based on the 2016 ACR-EULAR Classification Criteria for primary Sjogren's syndrome.[11] Our patient meets the score of more than or equal to 4 required to diagnose Sjogren's syndrome.

An oral dose of prednisolone (1mg/kg) was started along with supportive therapy (oral pilocarpine, artificial tear, and saliva). After a month of follow-up, her symptoms subsided along with an increase in hematological markers which is tabulated below in Table No-2.

Table No 2: Laboratory reports of the patient after a month of follow-up

Laboratory Parameters	**Range**
Hemoglobin(Hb)	10 g/dl (Normal range in Women**:** 12.1 to 15.1)
White blood cell count(WBC)	9,200/mm^3 (Normal range: 4,000 to 11,000/mm^3)
Platelets count	100,000/mm^3 (Normal range:150,000 to 450,000/mm^3)
Lactate dehydrogenase (LDH	690 IU/L(Normal range: 140 to 280/mm^3)
Erythrocyte sedimentation rate (ESR)	15mm/hr (Normal range in women: 0-30mm/hr)

CONCLUSION AND RESULTS

Cytopenia may present before sicca symptoms in Sjogren's syndrome as presented in our case so it should be considered an important differential while evaluating unexplained cytopenia. Asymptomatic normocytic

anemia is the usual presentation. Our patient improved with corticosteroids but long-term follow-up is still needed to know more about the hematological presentation in these patients. Thus, SS should be kept an important consideration while evaluating unexplained cytopenia that might be missed due to its rare incidence and few studies on it.

DISCUSSION

Sjögren's is a chronic autoimmune disease associated with lymphocyte hyper-reactivity and involvement of various body parts. It is characterized by the infiltration of lymphocytes into glands that produce saliva and tears. The occurrence of Sjögren's varies from 0.1% to 4.8% and is more common in women than men (female-to-male ratio of 9:1.3) .[1] While gland involvement is typical, symptoms can vary widely from no symptoms to frequent experiences of dry eyes and mouth. Less common symptoms include non-Hodgkin's lymphoma and kidney inflammation. Therefore, even patients exhibiting typical Sjögren's symptoms may face diagnostic challenges [2,3].

The dilemma in diagnosing primary Sjögren's often overlaps with conditions like rheumatoid arthritis, systemic lupus erythematosus, and cryoglobulinemia. Factors such as the presence of rheumatoid factor, elevated circulating immunoglobulins, and autoantibodies to RO/SSA and LA/SSB indicate activated lymphocytes.[4] In our case, the fact that RO/SSA was positive, along with a high ESR and a positive Schirmer test, all point towards primary Sjögren's. While ANA is an important marker for autoimmune disorders, it is not very specific. To confirm or rule out autoimmune conditions, we conducted an ENA (Extractable Nuclear Antigens) panel which showed a positive result for RO/SSA. RO/SSA is linked to both SLE and Sjögren's, but in this instance, since there were no typical photosensitive rashes or signs of serositis and other consistent features, SLE was ruled out.[5]

An ESR above 50 mm/hr and anti-RO/SSA positivity strongly suggest extra glandular involvement.[6] Liver issues in patients with primary Sjögren's syndrome can be due to chronic viral infections or autoimmune liver disease[7]. With high ALP levels in our patient, we conducted serology for viruses and AMA, which came back negative. LDH levels are often seen as a fatigue biomarker in primary Sjögren's syndrome[8], and our patient had elevated LDH levels as well. One of the factors associated with a higher incidence of anemia is the presence of ANA, anti-RO, and anti-LA antibodies. A study revealed that patients with primary Sjögren's syndrome and anti-RO antibodies have more systemic characteristics such as hematological issues like anemia and thrombocytopenia. [9]

Patients with primary Sjögren's often experience hematological manifestations, which are not uncommon. Unfortunately, these manifestations receive less attention and are usually considered mere laboratory abnormalities without clinical significance. Anemia is the most common cytopenia affecting the majority of the patients with Sjogren's syndrome. Our patient showed similar lab results with a hemoglobin count of 10.3 and a platelet count of 62,000, despite not exhibiting the typical dryness symptoms of Sjögren's.

Cytopenia can precede the typical dryness symptoms, making early diagnosis challenging. Mild anemia in Sjögren's is believed to result from cytokine-mediated chronic inflammation, although the exact mechanisms behind hemolysis and bone marrow suppression are still unclear.

Reports suggest that anti-neutrophil and anti-RBC antibodies are found in a significant percentage of patients. Iron metabolism disturbances lead to anemia, while functional impairment of megakaryocytes results in thrombocytopenia. While hematological manifestations are frequent in various autoimmune diseases, they lack specificity for diagnostic purposes on their own. Therefore, even in the absence of typical dryness symptoms, hematological changes should not be overlooked in primary Sjögren's syndrome.

In conclusion, significant cytopenia could be the initial sign of underlying primary Sjogren's disease even without obvious symptoms. Thus, primary Sjogren's should be considered when investigating unexplained cytopenia. Factors like being female, having a positive ENA (Extractable Nuclear Antigens) panel result, and high ESR levels may suggest primary Sjogren's. Given the diverse presentations of primary Sjogren's, healthcare providers should remain attentive to less common manifestations like hematological abnormalities.

ACKNOWLEDGEMENT

None.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data were used.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report by the journal's patient consent policy.

REFERENCES

1. Schattner A, Friedman J, Klepfish A, Berrebi A. Immune cytopenias as the presenting finding in primary Sjögren's syndrome. *QJM* . 2000;93(12):825-829. doi:10.1093/qjmed/93.12.825

2. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med* . 2004;164(12):1275-1284. doi:10.1001/archinte.164.12.1275

3. P. Oxholm, Asmussen K. Primary Sjogren's syndrome: the challenge for classification of disease manifestations. *Journal of internal medicine* . 1996;239(6):467-474. doi:https://doi.org/10.1046/j.1365-2796.1996.482818000.x

4. Ramakrishna R, Chaudhuri K, Sturgess A, Manoharan A. Haematological manifestations of primary Sjögren's syndrome: a clinicopathological study. *Q J Med* . 1992;83(303):547-554.

5. Alsubki R, Tabassum H, Alfawaz H, et al. Association between antinuclear antibodies (ANA) patterns and extractable nuclear antigens (ENA) in HEp-2 cells in patients with autoimmune diseases in Riyadh, Saudi Arabia. *Intractable Rare Dis Res* . 2020;9(2):89-94. doi:10.5582/irdr.2020.03012

6. Pathak DR, Kumar Chaurasiya A, Subedi R, Khatri P, Shah P. Primary Sjogren's Syndrome with Bicytopenia: A Case Report. *JNMA J Nepal Med Assoc* . 2024;62(269):49-51. Published 2024 Jan 2. doi:10.31729/jnma.8406

7. Zeron PB, Retamozo S, Bové A, Kostov BA, Sisó A, Ramos-Casals M. Diagnosis of Liver Involvement in Primary Sjögren Syndrome. *J Clin Transl Hepatol* . 2013;1(2):94-102. doi:10.14218/JCTH.2013.00011

8. .Rajagopala L, Tan SJ, Ng WF, Tarn J. Ab0532 Lactate Dehydrogenase as a Predictor of Fatigue in Primary Sjogren's Syndrome: A Pooled Analysis.*Annals of the Rheumatic Diseases* . 2022;81(Suppl 1):1394-1394. doi:https://doi.org/10.1136/annrheumdis-2022-eular.3864

9. Rudolph SE, Kouba M, Hrdlicka P. [Severe corticoid-refractory autoimmune thrombocytopenia associated with mixed connective tissue disease (Sharp's syndrome). Treatment with rituximab]. *PubMed* . 2009;134(36):1734-1738. doi:https://doi.org/10.1055/s-0029-1234008

10. .Meena DS, Bohra GK. Primary Sjogren's Syndrome Presenting as Autoimmune Cytopenia. *Clinics and Practice* . 2019;9(4):109-110. doi:https://doi.org/10.4081/cp.2019.1190

11. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* . 2017;69(1):35-45. doi:10.1002/art.39859

Hosted file

`Table 1.docx` available at https://authorea.com/users/638490/articles/1218299-primary-sjogrens-syndrome-initially-presenting-as-bicytopenia-in-elderly-female-a-rare-case-report

Hosted file

`Table 2.docx` available at https://authorea.com/users/638490/articles/1218299-primary-sjogrens-syndrome-initially-presenting-as-bicytopenia-in-elderly-female-a-rare-case-report