

Sjögren's Syndrome–Vasculitis: Azathioprine Induced Myelosuppression–A Case Report

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ABSTRACT

Sjögren's syndrome is a chronic autoimmune disease causing destruction of exocrine glands, due to lymphocytic infiltration predominately affects middle age women. Sjogren's syndrome classified may be either primary or secondary Sjogren's syndrome. The prevalence of primary Sjögren's syndrome is approximately 0.5–1.0%, while 30% of patients with autoimmune rheumatic diseases suffer from secondary Sjögren's syndrome. Treatment focuses on relief of the symptoms affecting particular areas of the body. Glucocorticoids (Prednisolone) and/or immunosuppressive agents (azathioprine) are indicated for the treatment of systemic vasculitis. In this case, the patient is suffering from Sjogren's syndrome and patient was prescribed with a glucocorticoid and an immunosuppressive agent (azathioprine). Use of Azathioprine has lead to myelosuppression. So, the dosing schedule of these drugs are important and dosing of drug should be done according to the patient response and at the same time check for adverse effects during course of treatment and any altered lab parameters.

Key words: Sjögren's syndrome, Vasculitis, Azathioprine, Prevalence, Myelosuppression

INTRODUCTION

Sjögren's syndrome is an autoimmune disease in which the body's immune system mistakenly attacks glands that produce moisture in the eyes (lacrimal gland), the mouth (salivary glands), and elsewhere in the body. The most common symptoms of Sjögren's syndrome are dry eyes and dry mouth.¹ Sjogren's syndrome classified may be either primary or secondary Sjogren's syndrome. When gland inflammation resulting in both dry eyes and mouth that is not associated with another connective tissue disease occurs, it is referred to as, 'Primary Sjogren's Syndrome.' When these symptoms are associated with a connective tissue disease such as systemic lupus erythematosus, scleroderma, or rheumatoid arthritis, it is referred to as, 'Secondary Sjogren's Syndrome.'²

Sjögren's predominately affects woman (90% of people with Sjögrens are women: 10%

men).³ Middle-aged women (female-to-male ratio, 9:1) are primarily affected, although it may occur in all ages, including childhood. The prevalence of primary Sjögren's syndrome is approximately 0.5–1.0%, while 30% of patients with autoimmune rheumatic diseases suffer from secondary Sjögren's syndrome. Approximately one-third of patients present with systemic manifestations.⁴ Vasculitis refer to inflammation of blood vessels. Vasculitis is complication of sjogren's syndrome.¹³

CAUSES

Sjogren's syndrome is thought to be associated with genetic factors, which may be triggered by some viruses and stress. The exact cause is not yet known. There is much research being done into the cause and the treatment of Sjogren's. Some research has

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suggested there is an association with exposure to some environmental toxins/chemicals and autoimmune diseases.³

PATHOLOGY

Sjogren's syndrome is a chronic autoimmune disease causing destruction of exocrine glands, due to lymphocytic infiltration,⁵ causing progressive damage and loss of function of these glands.³ The aetiology is unknown, but there is an association with an HLA-DR3 and other HLA genotypes. There is also hyperactivity of B cells, shown by autoantibodies.⁵

CLINICAL FEATURES

Sjogren's syndrome (SS) is a chronic, multisystem inflammatory disorder characterized by diminished lacrimal and salivary gland function due to lymphocytic infiltration of the secretory glands. This results in the "sicca complex," a combination of dry eyes (keratoconjunctivitis sicca [KCS]) and dry mouth (xerostomia).⁶

The general drying up of exocrine secretions may cause effects on many organ systems, though in most patients the disease remains a minor mouth and eye problem. These effects include:

- Eyes: grittiness, irritation, morning lid stickiness and conjunctivitis.
- Mouth: there is difficulty in chewing and swallowing food; inability to speak continuously; a smooth, erythematous, sensitive tongue; greatly increased dental caries and parotid gland enlargement. Candidal infection is common.
- Respiratory tract: the failure of secretion predisposes to infection.
- Genital tract: atrophic vaginitis and dyspareunia (difficult or painful coitus) in premenopausal women.
- Kidneys: some patients develop nephritis, but major renal pathology is rare.
- Raynaud's syndrome (in 25% of patients).
- Non-erosive arthritis (33%).
- **Vasculitis**, causing purpura and sometimes glomerulonephritis.⁵

Systemic extraglandular features include arthritis, renal, hematopoietic, and pulmonary involvement, and vasculitis. Neurologic manifestations include peripheral neuropathy, myelopathy, and cognitive disturbances. These extraglandular manifestations may result from vasculitis, autoantibody-mediated mechanisms, or lymphocytic infiltration of the target organs.^{6,7}

Vasculitis is considered to be a significant extraglandular manifestation of Sjogren's syndrome (SS).^{8,9} Incidence of vasculitis is about 11%.⁴

EVALUATION AND TESTS

For Sjogren's syndrome:

- Blood tests:
 - ANA (anti-nuclear antibody)
 - Anti-SSA and SSB antibodies (tests for antibodies that are often present in people with Sjogren's)
 - RF antibody (rheumatoid factor)
 - Erythrocyte sedimentation rate
 - Immunoglobulin electrophoresis
- Lip biopsy or biopsy of minor salivary glands (tests for evidence of inflammation)
- Urine test (to test for kidney damage)
- Additional tests relating to the mouth and eyes (e.g., Schirmer's test to determine whether eyes are excessively dry).¹⁰

TREATING SJOGREN'S SYNDROME

There is currently no cure for Sjogren's syndrome. Treatment focuses on relief of the symptoms affecting particular areas of the body.²

To replace deficient tears, there are several readily available ophthalmic preparations (Tearisol; Liquifilm; 0.5% methylcellulose; Hypo Tears). If corneal ulcerations are present, eye patching and boric acid ointments are recommended. Certain drugs that may decrease lacrimal and salivary secretion such as diuretics, antihypertensive drugs, anticholinergics, and antidepressants should be avoided.

For xerostomia the best replacement is water. Propionic acid gels may be used to treat vaginal dryness. To stimulate secretions, pilocarpine (5 mg thrice daily) or cevimeline (30 mg thrice daily) administered orally appears to improve sicca manifestations, and both are well tolerated. Hydroxychloroquine (200 mg) is helpful for arthralgias.

Patients with renal tubular acidosis should receive sodium bicarbonate orally (0.5–2.0 mmol/kg in four divided doses).

Glucocorticoids (1 mg/kg per day) and/or immunosuppressive agents (e.g., azathioprine,¹¹ cyclophosphamide) are indicated only for the treatment of systemic vasculitis.⁴

Sjogren's syndrome

Prednisone 5 to 60 mg/day ORALLY initially, vary dose depending on patient response.¹²

CASE STUDY

A 61yr old female patient known case of Sjogren's syndrome (ANA with IF: positive ; lip mucosal biopsy: lobules shows 2-3foci of inflammatory foci comprising predominantly of plasma cells (<30 plasma cells/HPF); Nerve biopsy: inflammatory neuropathy favouring probable vasculitis- left sural nerve) who is on Tab. Prednisolone and Tab. Azathioprine 50 mg once daily for vasculitis. The dosing schedule of Tab. Prednisolone in this patient included 20 mg BD for 7 days followed by 20 mg in morning and 10 mg in evening for next 10 days.

In the (1st) next review (30/10/15) the patient had no complaints and advised for same treatment with altered dosing of Tab. Prednisolone as 10 mg in the morning and 5 mg in the evening for first 10 days followed by 10 mg OD in the morning for next 10 days and 10 mg OD in the alternate mornings for last 10 days.

In the (2nd) next review (30/11/15) patient had no complaints and advised to continue same treatment as Tab. Prednisolone 10 mg OD on alternate mornings for 2 months. Routine CBP was performed which showed in decreased Hb (10.6 gm%) and T.RBC (3.5 m/cmm).

In the (3rd) next review patient is doing well with no complaints but routine CBP showed decreased Hb(7.5 gm%), T.RBC (2.7 m/cmm), T.WBC (3500/cmm) with raised platelet count (5.45L/cmm) and advised to discontinue Tab. Azathioprine and the dose of Tab. Prednisolone was made as 5 mg OD on alternate mornings for 20 days and then advised to stop it.

After a day the patient started experiencing severe shortness of breath and mild chest pain. Patient was taken to a tertiary care hospital and got admitted for treatment. The cardiac and chest evaluation was found to be normal. Complete haemogram was performed which showed abnormalities as Hb: 6 (12-15 gm%), total RBC count: 1.77 (3.8-4.8 m/cmm), PCV: 18.50 (36-46%), MCV : 104.40 (83-101fL), MCH: 34 (27-32 pg), R D W-CV : 28.80 (11.6-14%), platelet count: 4.20 (1.5- 4.1L/cmm), RBC morphology: Anisopoikilocytosis, macrocytes, macro ovalocyte, tear drop cells, occasional nucleated red blood cells (NRBCS).

Treatment advised was to perform whole blood transfusion 1 pint (350 ml) daily for 3 days and dechallenge Tab. Prednisolone. Along with whole blood transfusion, oral ferrous sulfate was also given.

After whole blood transfusion of 3 pints, haemogram report showed improvement– Hb: 9.5 gm%, total RBC

count: 3.6 (3.8-4.8 m/cmm). Finally patient was discharged with no complaints of shortness of breath and chest pain.

DISCUSSION

The patient was suffering from Sjogren's syndrome with vasculitis and patient was prescribed with a glucocorticoid and an immunosuppressive agent. The hematologic alterations in this patient are due to Tab. Azathioprine (immunosuppressive agent) which leads to myelosuppression. The treatment given in this patient is de-challenging of both glucocorticoid and immunosuppressive agents and whole blood transfusion is done along with oral ferrous sulfate.

The dosing of drugs is important and at the same time monitor for adverse effects during course of treatment and any altered lab parameters.

CONCLUSION

Sjögren's syndrome is an autoimmune disease. Vasculitis is an extraglandular manifestation of Sjögren's syndrome. Glucocorticoids (Prednisolone) and/or immunosuppressive agents (azathioprine) are indicated only for the treatment of systemic vasculitis. In this case use of Azathioprine has lead to myelosuppression. The drug was stopped and supportive treatment was given to patient. The dosing of drug should be done according to the patient response and check for onset of any adverse effects. Early detection of adverse effects should be done and treatment should be given accordingly either by reducing the dose or by dechallenging the drug and by providing supportive therapy.

ABBREVIATIONS

HLA-DR3: Human leukocyte antigen D related 3; **KCS:** Keratoconjunctivitis sicca; **ANA:** Anti nuclear antibody; **Anti-SSA:** Anti-Sjogren's syndrome related antigen-A; **Anti-SSB:** Anti-Sjogren's syndrome related antigen-B; **RF:** Rheumatoid Factor; **HPF:** High power field; **PCV:** Packed cell volume; **MCV:** Mean cell volume; **MCH:** Mean corpuscular hemoglobin; **RDW:** Red blood cell distribution width.

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