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Occlusive Retinal Vasculitis Secondary to Sjogren's Syndrome: A Case Report and Review

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Occlusive Retinal Vasculitis Secondary to Sjogren's Syndrome: A Case Report and Review

Abstract

Background: To bring attention to the potential and serious ophthalmic sequalae of Sjogren's syndrome, specifically occlusive retinal vasculitis.

Case: A 70-year-old male patient without previous ocular pathology presented with acute onset, bilateral, painless vision loss. Fundus evaluation revealed extensive retinal occlusive disease with bilateral disc edema, cystoid macular edema, and diffuse phlebitis. The patient was admitted, received a full systemic work-up and was carefully co-managed by ophthalmology, neurology, infectious disease, vascular surgery, dermatology, rheumatology and medicine. Evaluation supported a leading diagnosis of Sjogren's syndrome associated vasculitis.

Conclusion: The patient underwent treatment with oral steroids and intravitreal injections of anti-vascular endothelial growth factor; treatment successfully restored usable vision in one eye. This case will highlight the importance of prompt and thorough evaluation of patients diagnosed with or with suspected diagnosis of Sjogren's syndrome since severe ocular manifestations can mirror severe, potentially life-threatening, levels of systemic complications.

Keywords

retinal vasculitis, Sjogren's syndrome, disc edema, macular edema

INTRODUCTION

Sjogren's syndrome (SS) is a progressive, systemic, autoimmune disease. It primarily impacts the salivary and lacrimal glands thus resulting in xerostomia and xerophthalmia. While this condition largely targets the aforenoted exocrine glands, it has the potential to affect all organ systems through mechanisms of inflammation and infiltration.[1]

The most commonly known ophthalmic manifestation of SS is keratoconjunctivitis sicca. This is secondary to impaired tear secretion after inflammatory infiltration of the lacrimal gland. Since ocular surface disease associated with SS is extensively known and widely researched, this report will not cover it in full detail. Additional SS anterior segment manifestations can include filamentary keratitis, corneal infiltrates, conjunctivitis, corneal vascularization, and opacification and scleritis.[1] The lesser known ophthalmic manifestations, those involving the posterior segment, can include retinitis, neuromyelitis optica, ischemic optic neuropathy, phlebitis, and retinal detachment.[2,3]

This case report demonstrates how a severe and lesser-known ophthalmic manifestation, occlusive retinal vasculitis, may be the first observable and symptom-causing indication of SS. The diagnosis, co-management approach, and treatment modalities will also be discussed. Lastly, the rapid timeline during which drastic changes can occur will be presented to emphasize the importance of prompt diagnosis and treatment for patients with SS complications.

CASE

A 70-year-old African American male presented with a chief complaint of bilateral, sudden, painless, reduction of vision, right eye greater than left. Over the course of the next several hours, vision in both eyes continued to deteriorate. Ocular history was unremarkable as was family history of eye disease.

He denied jaw claudication, temporal scalp tenderness or malaise. Two-months prior, the patient experienced acute left-sided facial swelling and was diagnosed with a sinus infection. He completed a course of oral antibiotic prescribed by his primary care physician. This resolved most symptoms, though he reported chronic gingival tenderness since then and was referred to a dentist. Additionally, the patient had noticed a pustular rash on his palms and soles of feet that evolved into flat, dark rashes. He also developed arthritis-type swelling of his bilateral phalangeal joints with symptoms that lasted for a few days and self-resolved. He denied any genital lesions or tick exposure.

Medical history included hypertension, hyperlipidemia, hypothyroid, osteoarthritis, benign prostate hyperplasia, chronic kidney disease (stage 3),

thrombocytopenia, and colon cancer status post partial colectomy. His current medications were baby aspirin, citalopram, tamsulosin, finasteride, levothyroxine, amlodipine, and metoprolol. The patient had recent cardiac echocardiogram and cardiac stress tests which were normal. Social history was negative for smoking, alcohol, and drugs.

Entering visual acuity was 5/120 in the right eye (Feinbloom) and 20/400 in the left (Snellen) with no improvement on pinhole or refraction. Ocular motilities were full, pupil reaction appeared normal without presence of APD, slit lamp anterior segment exam was unremarkable and intraocular pressures were normal. Confrontation visual fields were markedly constricted in all quadrants in both eyes.

Dilated retinal examination and OCT of the disc and macula showed hyperemic, edematous optic nerves with peripapillary retinal edema and pronounced macula edema in both eyes. (See Figure 1).

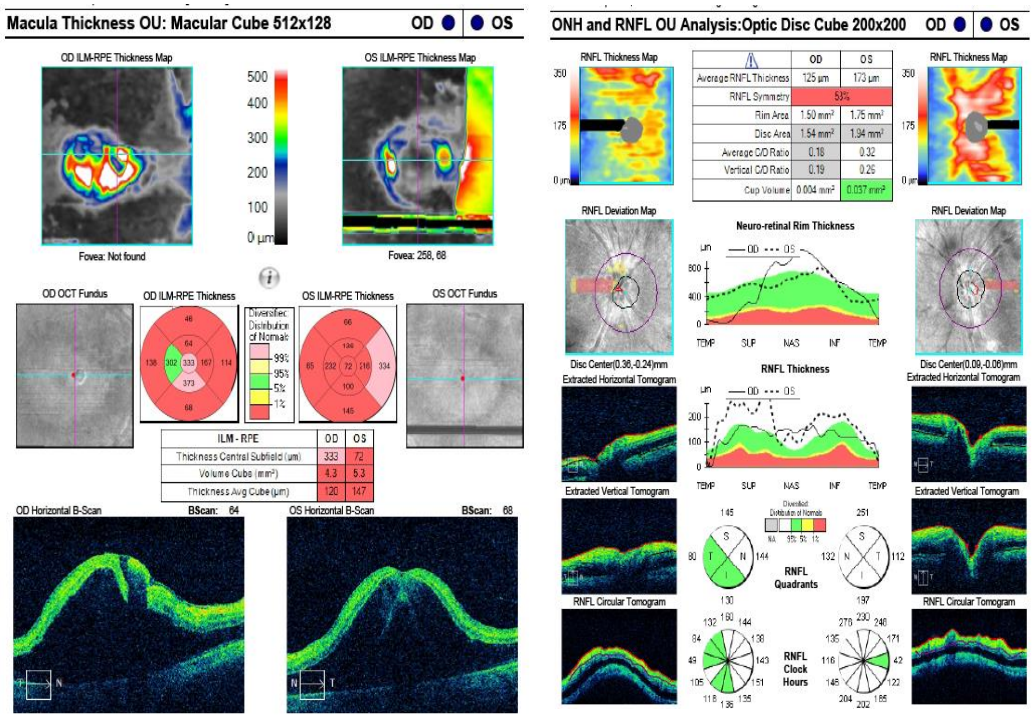
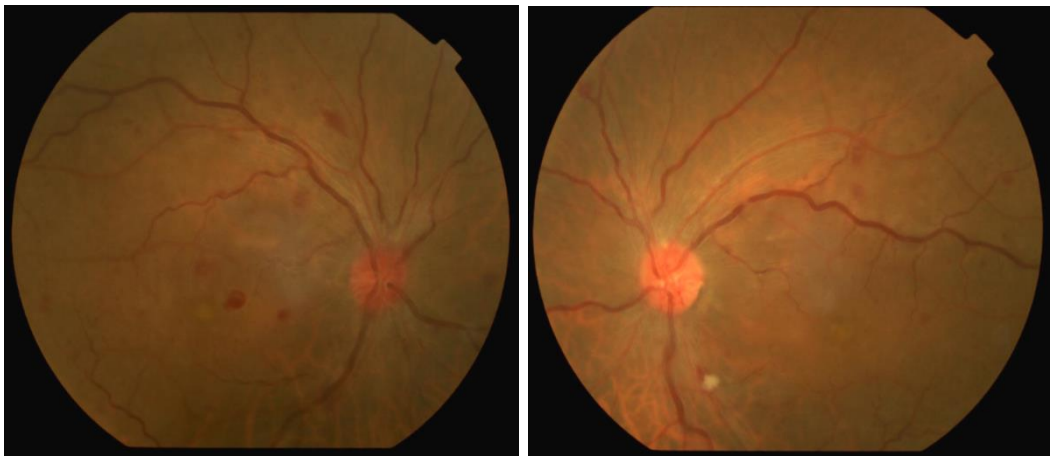


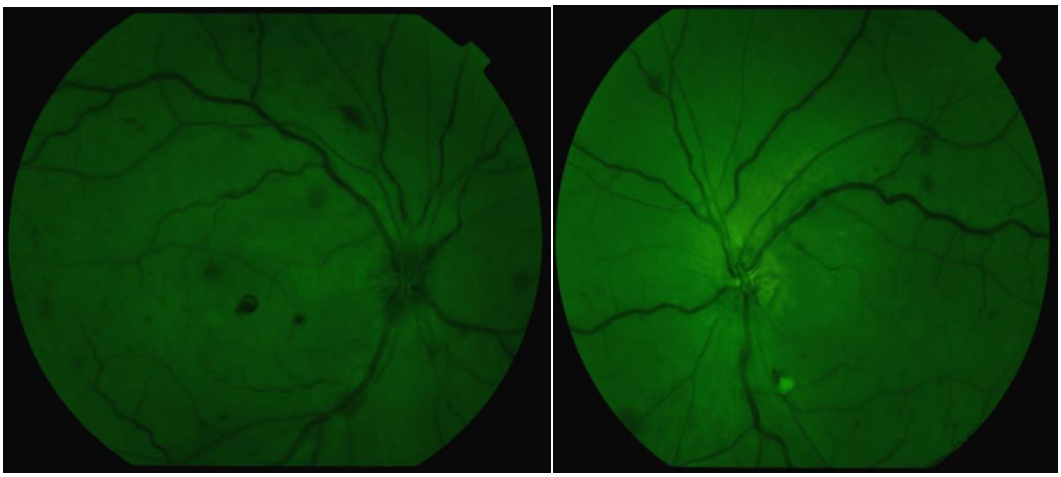
Figure 1: OCT Macula & OCT Optic Disc Cube

Bilateral intraretinal hemorrhages were evident throughout the posterior pole and mid-periphery with markedly attenuated retinal arteries and venous tortuosity, a presentation consistent with bilateral central retinal vein occlusion. A cotton wool

spot was noted at the left eye's inferior arcade. Fundus appearance can be seen in Figures 2 & 3. The patient's blood pressure was taken and was 136/78 mm Hg.



Figures 2: Fundus Photos OD/OS



Figures 3: Red-Free Fundus Photos OD/OS

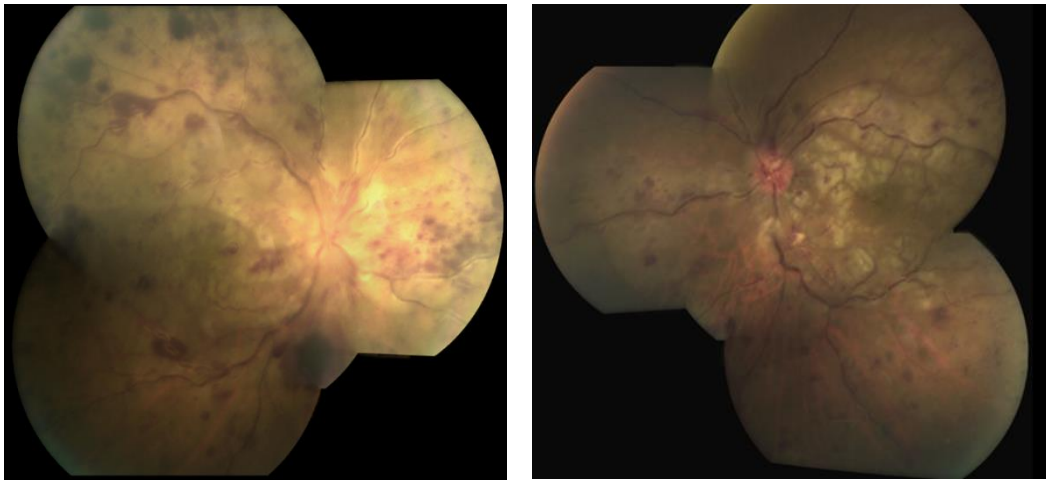
He was referred for an urgent retina specialist consultation. Given the unclear etiology and severity of the patient's bilateral vision loss it was recommended that he be admitted to the hospital for further testing and observation. Table 1 lists the tests ordered along with the respective results; initial lab work results were significant only for elevated ESR and CRP.

TEST	RESULT
Complete Blood Count	Mild anemia
Sed Rate **Week 1, Day 1** **Week 2** **Week 3** **Week 4**	 **High (125 mm/hr)** **High (55 mm/hr)** Normal (3 mm/hr) Normal (5 mm/hr)
Cholesterol panel	Normal
COAG Panel	Normal
C Reactive Protein **Week 1, Day 1** **Week 2** **Week 3** **Week 4**	 **Positive** Negative Negative Negative
ANA Titer	**Positive**
Rheumatoid Factor	Negative
Lyme C6	Negative
RPR, qualitative	Negative
Treponema Pallidum ABS	Negative
HIV	Negative
C-ANCA/P-ANCA	Negative
Toxoplasma Gondii	Negative
Bartonella Henselae/ Quintana	Negative
Mycoplasma Pneumoniae	Negative
Varicella Zoster	Ab present - Immune
Herpes Simplex	Negative
NMO-IgG Auto Ab	Negative
Epstein-Barr Virus	Negative
Hepatitis B&C	Negative
QuantiFERON TB	Negative
Lupus (Russell Viper)	Negative
DS DNA Crithidia (SLE)	Normal
HLA B27	Negative
Angiotensin Converting enzyme	Negative
CPK	Normal
Homocysteine	Normal
Strongyloides	Negative
Schistosoma	Negative
Anti -scleroderma	Negative
Anti SS-A (Connective tissue disease: SLE, SS, RhA)	**High**
Anti SS-B	Normal
HLA B51 (Behcet's disease)	**Positive**
G6PD	Normal
Factor V Leiden	Negative
Protein S & C	Normal
Factor II Prothrombin, DNA	Negative
CSF	Negative: HSV, EBV, CMV, VZV, Fungus, Lyme, ACE, VDRL Non-reactive, Gram stain (-), zero oligoclonal bands

Table 1: Lab tests ordered and results

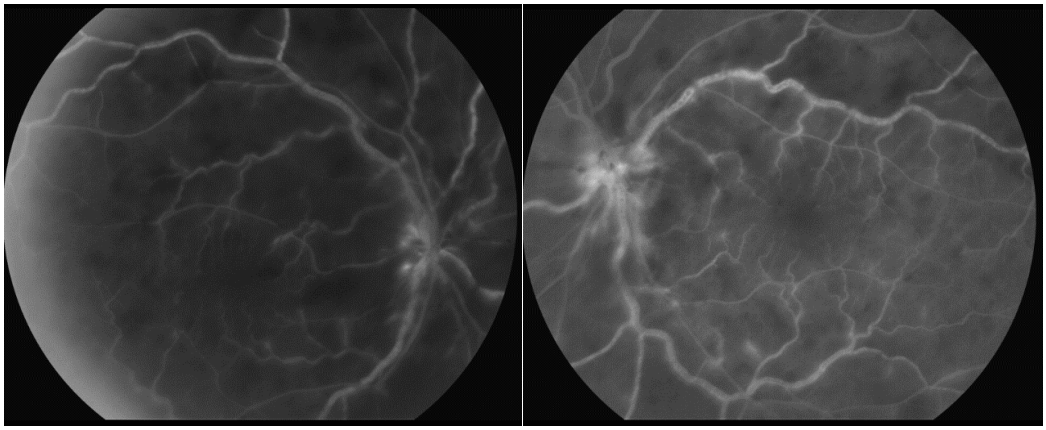
A dermatology exam was normal except for the non-blanchable, maculopapular rash on both hands and feet with multiple spots, radius ranging from 1-3 mm. Because of the rash, infectious disease was consulted for a syphilis evaluation. An infectious disease work-up showed syphilis, TB, HIV, Lyme, hepatitis, and toxoplasmosis tests were all negative. A neurological exam was normal. Dentistry was consulted; a biopsy of labial mucosa and minor salivary gland showed non-specific, mild sialadenitis with lymphocytic aggregates. This corresponded to the patient's complaint of a general dry mouth (treatment was not initiated immediately due to the urgency of systemic management). A rheumatology workup revealed positive ANA and SS-A, raising the concern for SS, Systemic Lupus Erythematosus (SLE) and Behchet's disease. Additional SLE testing was negative. Behcet's was thought to be less likely because HLA-B51 was positive but no oral or genital lesions were present (though it is possible the patient had both SS and Behcet's). IV steroids were initiated under the management of rheumatology with the intention of initiating immunomodulatory therapy subsequently.

One week later, the patient returned for a retinal exam and fluorescein angiography. A dilated retinal exam continued to show disc edema and hyperemia, dilated tortuous veins, attenuated arteries with silver-wire appearance, scattered dot/blot and flame hemorrhages and microaneurysms in both eyes; the cotton wool spot on the inferior arcade OS persisted. The right eye's retina had a new overall whitening of the fundus grounds. There was no vitritis in either eye. Fundus appearance can be seen in Figure 4.



Figures 4: Fundus Photography Collage OD/OS

Fluorescein angiography demonstrated diffuse occlusive vasculitis with large areas of capillary nonperfusion and vascular sheathing (right eye greater than left) with bilateral central retinal vein occlusion. (See Figure 5).



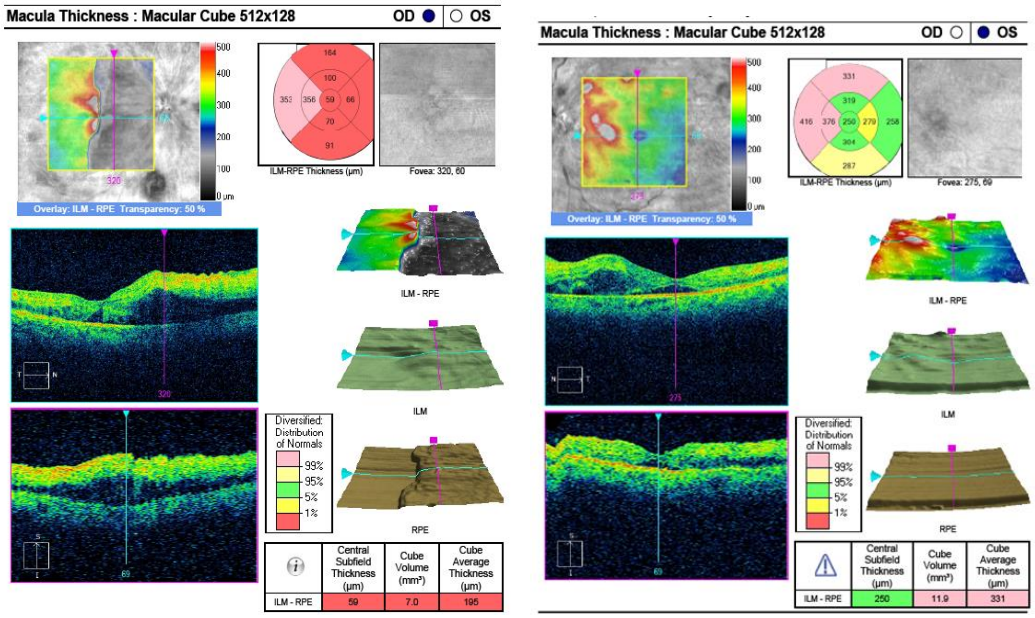
Figures 5: Fluorescein Angiography OD/OS (Mid-phase)

Based on the marked change in fundus appearance and macular status, significant progression had occurred over the past days. At this point, the patient had completed his course of IV Solumedrol and was being treated with 80 mg prednisone PO daily.

A few days later an RAPD of the right eye was noted along with mild anterior vitritis (1+ cells), phlebitis and an increase in retinal hemorrhaging of the right eye only. Retinal findings of the left eye were unchanged from the previous exam. A treatment plan was made to initiate bilateral, intravitreal Avastin injections. The patient was discharged from the hospital several days later and continued his course of 80 mg prednisone PO.

After the first course of Avastin injections, vision was 2/200 (Snellen "E") in the right eye and improved to 20/70+2 in the left. At this time, no vitritis or cells were noted. Optic disc edema was improving. OCT showed persistent bilateral macular edema but with signs of improvement. Schirmer I test (without anesthetic) was performed and was positive in the right eye according to the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification (4 mm in the right eye, 8 mm in the left) after five minutes. The patient also had irregular ocular surface staining with sodium fluorescein and reduced TBUT in both eyes. Rose Bengal staining was not performed.

At the follow up, visual acuity was 2/200 (Snellen "E") in the right eye and 20/40 in the left; vision had improved significantly in the left eye. OCT showed improving bilateral macula edema. (See Figure 6). Fundus exam revealed improving optic nerve edema and hemorrhages in both eyes. The patient received a second round of intravitreal Avastin injections. He was also examined by a neuro-ophthalmologist. At this time, he continued treatment with 60 mg PO daily of prednisone as per his taper by rheumatology.



Figures 6: OCT Macula OD/OS

Visual acuity two weeks later improved to 6/200 (Snellen "E") in the right eye and 20/30-2 in the left. Optic nerve pallor was noted in the right eye more than the left and some resolution of retinal hemorrhaging was noted in both eyes. The patient received his third course of Avastin injections. OCT revealed near resolution of macular edema with both maculae appearing relatively flat with minimal intraretinal fluid. (See Figure 7). Unfortunately, two months later the patient passed away and the exact cause was not identified. For a timeline of major points of the case see Figure 8.

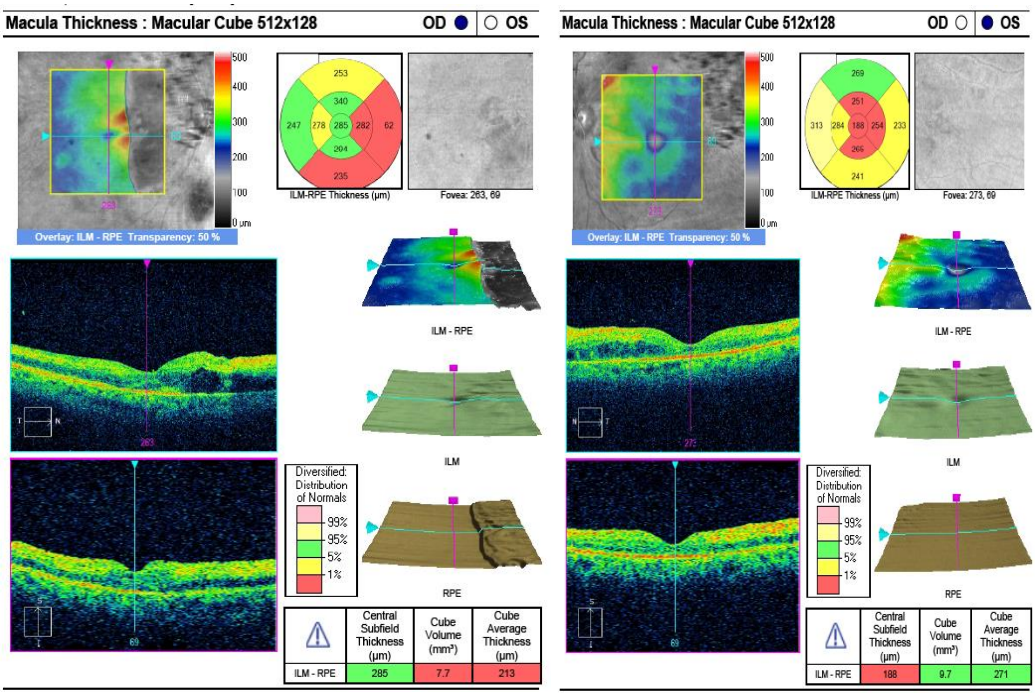


Figure 7: OCT Macula OD/OS

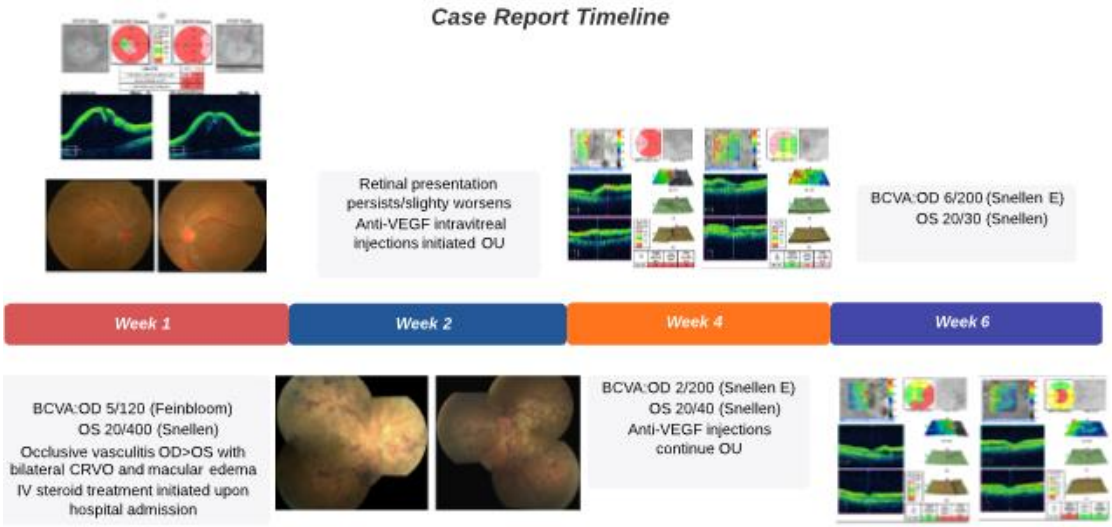


Figure 8: Case Report Timeline

After an exhaustive systemic work-up, infectious, and neurologic causes for the patient's retinal presentation were ruled out. Initially CRP was positive and ESR was elevated, both trended downward after initiation of steroid therapies. The only labs to return positive results were the ANA, SSA, and HLA-B51 which could indicate SS or Behcet's syndrome (or both) as possible autoimmune etiologies. Rheumatology ultimately diagnosed SS given the absence of oral or genital lesions typically associated with Behcet's. Additionally, the patient's symptomatic dry mouth and evidence of dry eye lent themselves to a diagnosis of SS. Lip biopsy showed lymphocytic sialadenitis. There was no salivary analysis performed. According to the ACR/EULAR classification, there was enough evidence to warrant the SS diagnosis. Despite the history of palmar/ plantar rash which may have been a dermatologic representation of vasculitis from SS, no biopsy was performed due to significant resolution post-steroid therapy. Therefore, a diagnosis of cutaneous vasculitis versus hypersensitivity to ASA treatment or other causative agents was not definitively made.

DISCUSSION

Sjogren's Syndrome currently affects roughly 1 to 2 million people in the United States. It is more common in females, accounting for approximately 93% of cases, and the mean age of onset is 53 years old. SS is multifactored in causation; a combination of genetic predisposition, environmental influence and hormonal effects.[4] Primary Sjogren's syndrome (pSS) is diagnosed when the condition is present without an underlying autoimmune disease. Secondary Sjogren's syndrome (sSS) is diagnosed when the condition is associated with a known, underlying autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, etc.).[1] SS is also associated with a higher incidence of lymphoproliferative disease and malignancy; the risk of lymphoma is 40 times greater in SS patients than the general population.[4-5]

The histochemical basis for tissue damage secondary to SS lies in defective immune responses and inappropriate activation of the inflammatory cascade. Autoreactive T-cells along with autoreactive and hyper-reactive B-cells are present. Epithelial cells seem to be the hub of irregular cytokine and chemokine production playing a major role in the faulty immune activation process. The resulting autoimmune epithelitis can occur in any organ system.[6] Systemic manifestations of SS include cardiomyopathy, arthralgia, gastrointestinal disease, pulmonary disease, cutaneous vasculitis and purpura, peripheral neuropathy, lymphadenopathy, and renal disease.[2,4]

The diagnosis of SS is established based upon a combination of laboratory testing and evaluation of xerophthalmia and xerostomia. Laboratory testing includes antinuclear antibody (ANA), anti-SSA autoantigen, anti- SSB autoantigen and

rheumatoid factor (RF). ANA positivity in SS ranges from 55 to 97%, anti-SSA positivity in SS ranges from 16 to 70%, anti-SSB positivity ranges from 7 to 50%, and RF positively ranges from 32 to 90%. Anti-SSA and anti-SSB antigens are not specific to SS since they can be present in patients with other autoimmune conditions and, occasionally, in healthy people. Xerophthalmia is diagnosed utilizing Shirmer tear testing and rose bengal staining. Xerostomia is detected by saliva collection, sialography, scintigraphy and sometimes lip biopsy.[4] Skin biopsy is often performed for vasculitis diagnosis if rash or purpura is present and often identifies leukocytoclastic or lymphocytic vasculitis. Cutaneous vasculitis of this type has been identified in up to 60% of SS patients.[2]

A consensus on formal criteria for SS diagnosis was made in 2016 by the ACR/EULAR.[7] The diagnosis is based on a weighted score of the following 5 items: positive anti-SSA(Ro) antibody, positive lymphocytic sialadenitis, abnormal ocular surface staining score, a Schirmer test less than or equal to 5 mm in 5 minutes, and an unstimulated salivary flow rate less than or equal to 0.1mL/min. The first two factors are assigned scores of 3 points each, while the following three factors are assigned 1 point each. A total score of greater than or equal to 4 meets the criteria for SS. The sensitivity and specificity in the detection of SS using this system were 96% and 95% respectively.[8,9]

Vasculitis in Sjogren's Syndrome

Vasculitis secondary to SS is due to irregular deposition of immune complexes; this is a rather uncommon extraglandular complication that can be severe. The reported prevalence of Sjogren's-associated vasculitis is 5-32%.[3] There are two classes of systemic vasculitis that can occur secondary to SS: small-vessel and medium-large vessel. Small-vessel vasculitis is immune-complex mediated and can be subcategorized as either cryoglobulinemic vasculitis or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The former is the most commonly presenting vasculitis associated with SS and involves cryoglobulins (monoclonal immunoglobulins) that are over stimulated by autoantigens. Medium-large vessel vasculitis can be acute and necrotizing, often presenting with a purpura like that of polyarteritis nodosa.[6] Small vessel vasculitis accounts for approximately 5% of Sjogren's vasculitis and most commonly presents as skin rash or purpura. Eighty eight percent of cutaneous lesions present as purpura (palpable or non-palpable) of the lower limbs or urticariform macules in the upper extremities, face or trunk.[9]

Cutaneous vasculitis associated with SS is a notable finding because it is a predictor of more severe disease and comorbidities (including arthritis, peripheral neuropathy, glomerulonephritis, and increased hospitalizations). Sjogren's vasculitis can also cause secondary peripheral neuropathy and neuromyelitis optica,

also known as Devic's disease. The latter is a complication involving an autoimmune inflammatory attack of the optic nerve and can often be mistaken for multiple sclerosis.[3]

Cases of retinal vasculitis associated with SS have been noted, albeit they are rare. Wanatabe et al. reported a case of SS-associated retinal vasculitis similar to ours: a 49-year-old man who presented with dry mouth, rash on the skin of the hands and legs and bilateral visual disturbances. Retinal exam revealed bilateral intra and pre-retinal hemorrhages, exudates, and vascular sheathing and extensive areas of vascular non-perfusion on fluorescein angiography. Skin biopsy was performed along with the systemic work-up. Anti-SSA and anti-SSB antibodies were positive, while ANA, anti-dsDNA antibodies and ANCA were negative. Parotid scintigraphy demonstrated hypofunction. The patient was eventually diagnosed with small-vessel retinal and cutaneous vasculitis secondary to SS. Treatment included oral prednisone and pan retinal photocoagulation (PRP) which gradually improved the patient's presentation and symptoms.[10]

Farmer et al. reported two cases of females with severe bilateral retinal vasculitis associated with SS. Both had autoantibodies against SSA antigen and mild systemic signs of the disease. Like Wanatabe's case report, treatment included a course of systemic steroid therapy and PRP. Unlike the previous case, however, the therapy course did little to remedy the severe ophthalmic impact of the disease; both patients suffered progressive, irreversible vison loss from extensive retinal ischemia, neovascularization of the optic disc, retina and anterior segment and ultimately tractional retinal detachment.[11]

When we consider the aforenoted cases established in the literature along with the case at hand, similarities can be identified. Firstly, the initial complaint and presentation of sudden, bilateral, severe vision loss and secondarily, the initial fundus presentation that was already at a severe stage of retinal disease. The presence of cutaneous lesions and systemic work-up results varied among cases, however, incongruous systemic features are rather typical of SS patients and autoimmune conditions in general. All cases were treated with systemic steroids and retinal intervention (either PRP or anti-VEGF) to reduce vascular proliferation.

Treatment Options

SS treatment options are determined based on the disease manifestation and extent. In treating xerophthalmia, topical anti-inflammatory agents (cyclosporine A) are a mainstay along with tear replacement therapy. Xerostomia treatment includes salivary stimulation and replacement therapy and treatment of complications such as increased frequency of dental carries. Muscarinic agonist agents administered orally (pilocarpine and cevimeline) have been shown to

improve ocular signs and symptoms of keratoconjunctivis sicca and reduce symptomatic oral dryness. Systemic complications of SS are managed with anti-inflammatories (steroids and NSAIDS) and research has supported use of immune modulator, antimalarial (hydroxychloroquine) and monoclonal antibody (Rituximab) therapy.[4]

Because of the wide range and variety of SS manifestations, a multi-specialty team is often required for proper diagnosis and treatment. As seen in this case report, the team can include ophthalmology, neurology, infectious disease, rheumatology, vascular surgery, dermatology, and internal medicine.

CONCLUSION

Eyecare practitioners are aware of Sjogren's syndrome's proclivity for producing inflammation in the salivary and lacrimal glands. However, the autoimmune response from this disease can also cause extraglandular inflammation leading to potentially sight-threatening complications as well as serious systemic implications. This case reminds clinicians to remain vigilant for ocular manifestations, since they can range from ocular surface disease to disorders of the optic nerve and retina, in this case a rare instance of occlusive retinal vasculitis. The presence of these ocular signs warrants prompt evaluation of patients with suspected Sjogren's syndrome in order to effectively initiate systemic treatment and mitigate potentially life-threatening sequalae.

Author Statements:
The authors have no financial disclosures or conflicts of interest to report. Identifying features and patient names have been masked/removed from all images. No clinical trials were involved in this manuscript.

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