PEER REVIEWED

Complex Case of Dry Eye Management Associated with Sjogren's Syndrome

Franklin Bui, OD, MS, FAAO, and Harriette Canellos, OD, FAAO

Abstract

Sjogren's syndrome (SS) is a chronic, systemic, autoimmune disease that causes exocrine gland dysfunction, which can lead to many conditions including dry eye disease. Any patient with SS is at greater risk of developing sicca symptoms, including keratoconjunctivitis sicca. Filamentary keratitis can develop in patients with severe keratoconjunctivitis sicca as a result of dysfunction in the mucus and corneal epithelial adherent complexes. This report discusses the diagnosis and management of a patient with several ocular and systemic complications.

Key Words: *Sjogren's syndrome, filamentary keratitis, keratoconjunctivitis sicca, ocular surface disease*

Background

The following case report is a guide for teaching optometry students and residents. It is relevant in all levels of training, especially for students during clinical training. Students may see few of these cases in their optometry training but are likely to see more during their careers. Sjogren's syndrome (SS) is a chronic, systemic, autoimmune disease that causes exocrine gland dysfunction. Damage of the lacrimal glands results in keratoconjunctivitis sicca. In chronic and severe cases, keratoconjunctivitis sicca can lead to filamentary keratitis (FK). While there are genetic associations with the pathogenesis of SS, environmental factors play a role as triggers in the development of the disease. This case illustrates the importance of accurate examination of FK and treatment of the condition along with underlying causes.

Case Description

Case history

• Patient demographics: 53-year-old African American female
• Chief complaint: Patient presented with dry eyes with symptoms of grittiness, soreness, irritation, occasional redness and white-yellowish discharge twice per week that she removes digitally.
• Ocular, medical history: In 2007, patient was diagnosed with keratoconjunctivitis sicca and SS, which she has been managing with preservative-free artificial tears (PFATs), ointment and silicone punctal plugs OU. She also has ocular hypertension secondary to long-term use of oral and ophthalmic steroids, and is currently using eye drops to lower intraocular pressure (IOP). The patient was diagnosed with stage 3 multiple myeloma in 2014, received bone marrow transplant in 2015, and is undergoing chemotherapy.
• Medications: Travoprost ophthalmic solution 0.004% (Travatan Z) every bedtime OU, prednisone 5 mg/day, dexamethasone 40 mg, pomalidomide 2 mg, daratumumab
• Other salient information: Patient worked near the World Trade Center for many years including before and after Sept. 11, 2001 (9/11). Patient reported that prior to 9/11 her medical history had been unremarkable. Patient developed dry eye disease in 2007 and initially managed with PFATs and

ointment. However, given the patient's low aqueous tear production, punctal plugs were inserted in both eyes. Patient was using prednisolone acetate ophthalmic suspension 0.12% (Pred Mild) twice a day OU for bilateral FK that subsequently developed. She was on a higher dose of oral prednisone (20 mg/day) to minimize her inflammatory response to the graft bone marrow transplant. Patient developed a steroid response to oral and topical steroids that resulted in elevated IOP in both eyes, for which she was prescribed IOP-lowering drops, and subsequently discontinued Pred Mild and reduced prednisone dosage to 5 mg/day after consulting with her oncologist.

Pertinent findings

Clinical:

• Best-corrected visual acuity: 20/20 OD and OS
• Dry eye assessment: Schirmer I test without anesthetic yielded OD 1 mm and OS 5 mm, low tear meniscus (< 0.25 mm) OU, instant tear break-up time (TBUT) OU, tear osmolarity of 325/332 mOsm/L
• IOP 12/12 mmHg with Travatan Z every bedtime OU
• Initial IOP prior to initiating Pred Mild: 20/20 mmHg
• Tmax (highest measured IOP) 32/32 mmHg subsequent to use of Pred Mild twice a day OU
• Thin central corneal thickness: 504 µm OD, 497 µm OS

Physical:

• Ocular surface: OU: (-)lagophthalmos, (+)silicone punctal plugs right lower lid and left lower lid, 1+ papillae upper lid and lower lid, conjunctival injection, temporal and nasal bulbar staining with sodium fluorescein and Lissamine green staining; OD: loose mucus strand across cornea; OS: 3 filaments along inferior cornea
• Lens: trace nuclear sclerosis OU
• Funduscopy: OU: C/D ratio 0.30/0.30, (-)hemes; vitreous, macula, vasculatures, and periphery all unremarkable

Imaging studies:

• Retinal nerve fiber layer and macular optical coherence tomography: within normal limits OD and OS

Others:

• In-office filament removal with jewelers forceps OS (1 gtt proparacaine OU), and mucus strand removal from bulbar conjunctiva with forceps OD. Patient tolerated procedure well.

Differential diagnosis

• Primary/leading: FK with mucus fishing syndrome and SS with underlying aqueous-deficient and inflammatory dry eye disease

Treatment, management

• Patient's treatment for FK and keratoconjunctivitis sicca includes PFATs four times a day OU, preservative-free ophthalmic ointment, cold compresses 5 minutes prn, avoid fishing mucus out, and cyclosporine 0.05% ophthalmic emulsion (Restasis) twice a day OU. Patient was advised to lubricate with PFATs every hour for 1 day OS after in-office filament removal with forceps.

Education Guidelines

Key concepts

- Recognize the clinical findings of FK and SS
- Differential diagnosis of FK
- Treatment and management options of FK

Learning objectives

At the conclusion of the case, participants should be able to:

- Identify and describe the signs of FK
- Know the ocular manifestations of SS
- Understand the relationship of SS, keratoconjunctivitis sicca and FK
- Understand the association between exposure to environmental pollutants and autoimmune diseases
- Provide proper patient education on management of FK and keratoconjunctivitis sicca

Discussion questions/points

- Describe the signs and symptoms of FK
- What are the most effective treatment options for FK?
- How would you educate patients with SS about their ocular condition and prognosis?
- Which other healthcare providers would you communicate with and engage in interprofessional care?

Learning assessment

- Use slit lamp photos to identify and describe the abnormal findings in keratoconjunctivitis sicca and FK
- Literature review on environmental exposure, including World Trade Center exposure, and health consequences
- Engage students in report writing to different healthcare providers, including primary care physicians and rheumatologists

Discussion

There is a genetic risk factor for susceptibility to developing SS. The strongest associations are with the human leucocyte antigen (HLA) locus.[1] Genetic variants in the IRF5 and STAT4 loci of the interferon (IFN) signaling pathways are also associated with SS and its pathogenesis. However, these identified genetic risk variants only contribute to a modest increased risk of SS, indicating that environmental factors play a role in developing SS.[2] While infectious agents, such as Epstein Barr virus, can play a role in SS pathogenesis,[3] several environmental factors including stress, environmental pollution and silicone may contribute as triggers for predisposed genetic backgrounds.[4] Several studies suggest a correlation between development of autoimmune diseases and aerosolized World Trade Center dust – a mixture of cement, glass fibers, silica, asbestos, lead, polycyclic aromatic hydrocarbons, polychlorinated biphenyls and polychlorinated furans and dioxins.[5-7] Residents, workers and rescuers in the area were exposed to aerosolized World Trade Center dust, and the effect of chronic exposure increased by 13% for each month worked at the site. Those who worked at the site for 10 months compared with those who worked for 1 month had a 3.09-fold risk of developing systemic autoimmune disease.[8]

SS is an autoimmune disease associated with keratoconjunctivitis sicca.[9-12] SS is associated with dysfunction of exocrine glands, including the lacrimal glands and salivary glands. Common symptoms are dry eyes (keratoconjunctivitis sicca) or dry mouth (xerostomia), but symptoms can also extend to the nose, throat and skin. Most individuals with SS are women.[1] Ophthalmic procedures for confirming signs of keratoconjunctivitis sicca include Schirmer test, TBUT, phenol red thread test and dye staining.

Serology is also recommended to confirm the diagnosis of SS. Positive results in antinuclear antibody (ANA), rheumatoid factor (RF) or SS-specific antibodies (anti-Rho [SS-A] or anti-La [SS-B]) can help confirm the diagnosis.[13]

FK is characterized by strands of degenerated epithelial cells and mucus that adhere to the corneal surface. It is a chronic and recurrent corneal disorder that is associated with various ocular surface diseases including dry eye.[14] Other causes include ocular surgery, corneal exposure (e.g., seventh nerve palsy), blepharoptosis, graft vs. host disease (GVHD) and extended use of anticholinergic medications. Alterations and abnormalities in the tear film and corneal surface can lead to the development of FK. Often, a decrease in aqueous tear production or an increase in tear-film mucus production is responsible. The decrease in aqueous- to tear-film mucus ratio leads to the formation of mucoid strands, or filaments.

Patients with FK complain of foreign body sensation and ocular surface irritation, which worsen with blinking. They may also experience redness, epiphora, blepharospasm and photophobia. Filaments adhered to the corneal surface are best viewed under slit lamp examination, as are additional signs including decreased aqueous tears and tear production, increased mucin in the tear film, subepithelial opacities at the base of the filaments, or epithelial defects at the sites where filaments have been detached.

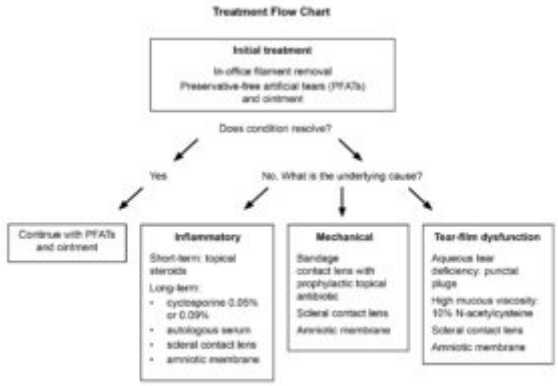


Figure 1. Treatment for filamentary keratitis includes providing symptomatic relief via in-office filament removal and managing the underlying condition.
Click to enlarge

Treating FK includes providing symptomatic relief via in-office filament removal and managing the underlying condition, which in this case is keratoconjunctivitis sicca **(Figure 1)**. Constant topical lubrication with PFATs and ophthalmic ointment should be the first line of treatment.[14] Over-the-counter PFATs contain cellulose derivatives, which are ophthalmic demulcent agents that help protect and lubricate mucous membranes on the ocular surface.[23] Lubricating ointments that contain ophthalmic emollient agents can protect and soften tissue to prevent drying and cracking of the ocular surface and increase tear stability and TBUT.[23] Restasis or cyclosporine ophthalmic solution 0.09% (Cequa) addresses the underlying cause by reducing inflammation when corticosteroid is not an option.[10-12] Topical autologous serum is another option.[10-12] Patient education is important in minimizing issues such as mucus fishing syndrome. In these cases, cold compresses and lubricants are recommended.[15] For cases where lubrication alone is not sufficient, low water-content bandage contact lenses may be used in combination with prophylactic topical antibiotic. A topical mucolytic agent, 10% N-acetylcysteine, can be used to decrease the viscosity of the mucinous layer of the tear film. Punctal plugs are also helpful in cases where aqueous tear deficiency is present. In moderate to severe dry eye disease, scleral contact lenses and amniotic membrane can be considered to manage patients whose chronic dry eye affects vision and comfort.[16,17] Prognosis is generally good, but patience is required given the chronic state of

this condition as well as long-term management of the underlying systemic condition contributing to the chronicity of the disease.

Patients with a history of steroid response need to be monitored carefully even after discontinuation of topical steroids to ensure no rebound effect, especially when these patients remain on oral steroids.[18,19] While topical steroids can be used to manage FK, patients should be monitored carefully for elevated IOP and potential long-term side effects. When topical steroids need to be prescribed, it is important to consider less potent steroids that have safer side effect profiles, such as loteprednol etabonate and fluorometholone.[24]

Studies have demonstrated that multiple myeloma and prostate and thyroid cancer are associated with post-9/11 environmental exposure.[20] A case series study found that firefighters had a 1.8-fold higher risk of developing multiple myeloma.[21] Likewise, workers in manufacturing occupations and industries, particularly textile, apparel and furnishing machine operators and tenders, were significantly at greater risk of developing multiple myeloma.[22] 9/11 particulate exposure has been linked to development of autoimmune diseases.

Individuals with history of bone marrow transplant are susceptible to developing GVHD.[25] Chronic GVHD can involve multiple systems, including the musculoskeletal and hematologic systems, as well as organs including the skin, gut and eyes.[25] GVHD is thought to involve type 1 T-helper cells, interleukin (IL)-2, IFN-? and IL-1.[26] In ocular GVHD, this T-cell-mediated process occurs along the conjunctival and lacrimal gland tissues.[25]

As demonstrated in this case, it is important to manage patients with systemic autoimmune diseases with other healthcare providers, including the primary care physician and rheumatologist. Likewise, the case highlights the importance of interprofessional communication when managing systemic medications for autoimmune diseases, especially when ocular side effects develop. Careful monitoring is indicated for patients on oral steroids, who may develop ophthalmic side effects including elevated IOP. For patients with increased IOP or development of steroid-induced glaucoma, it is important to manage the ophthalmic condition and communicate the findings with patients' physicians. In this case, the patient's oncologist was also informed of the findings, which prompted the oncologist to reduce the dosage to a level that reduced the patient's IOP while maintaining good control of her systemic symptoms.

Differential diagnosis

Corneal filaments are pathognomonic for FK. However, the condition may have several underlying causes. Other causes include tear-film abnormalities and dysfunction and mechanical causes including lid ptosis, previous ocular surgery and toxic keratopathies. Keratoconjunctivitis sicca is often the underlying cause of FK.

The location of the filaments can be helpful in differentiating between the potential underlying causes. Filaments caused by keratoconjunctivitis sicca and tear-film abnormalities typically are observed along the interpalpebral space. Filaments that form superiorly are due to lid ptosis, and those due to surgery will be seen at the site of the wound.

In this case, tear-film dysfunction, specifically aqueous-deficient dry eye disease secondary to SS, was the leading contributor for the condition given that Schirmer testing, tear meniscus and TBUT were all reduced. Ocular surface hyperemia and elevated tear osmolarity indicate an inflammatory component is also associated with the development of FK. The patient's normal lid anatomy and location of the filaments made mechanical causes unlikely underlying factors in the development of her FK. The patient's medical history suggests that she developed GVHD, and consequently SS, following her bone marrow transplant in 2015.

The patient presented with an initial treatment regimen that included PFATs, lubricating ointment, cold compresses 5 minutes prn and punctal plugs OU, all of which she was advised to continue. She was also advised to avoid fishing mucus out and educated on how this action delays resolution of the condition. Restasis was additionally prescribed to address the underlying inflammatory component. During acute episodes of severe dry eyes and presence of filaments, a less potent loteprednol etabonate 0.5% ophthalmic suspension was prescribed for twice a day OU, and the patient was monitored closely given her history of steroid response and ocular hypertension. The patient continued to use Travatan Z at bedtime OU for her ocular hypertension, and her IOP remained stable. Scleral lenses and amniotic membrane were discussed as potential future treatments if the condition fails to resolve. Long-term management includes monitoring for recurrence of filaments and measuring IOP. If IOP remains normotensive, Travatan Z may be removed and the patient will continue to be followed carefully to ensure IOP remains normotensive. The removal of topical medications when possible can potentially provide a beneficial treatment in patients with dry eye disease.

Teaching instructions and assessment methodology

This teaching case report is most appropriate for third- and fourth-year optometry students and optometry residents who have learned about FK and ophthalmic manifestations of SS in a didactic setting and can apply their knowledge clinically. Review of this case should provide these students and residents a better understanding of the pathogenesis of SS and how it can lead to conditions such as FK. Also, students should gain insight on causes of SS and FK, as well as the optometrist's role in the management of these conditions in an eye exam and in an interdisciplinary healthcare setting.

This teaching case report can be delivered to optometry students and residents in a grand rounds format or a journal club reading assignment for discussion in primary care, ocular disease or anterior segment clinic or residency. Students and residents should share their thought process, develop differential diagnoses and discuss the case regarding how to treat and manage patients with SS and/or FK. Discussion can also include glaucoma management, the use of oral steroids and interdisciplinary communication with other healthcare providers.

Assessment of students' and residents' understanding of the case can include a group discussion of similar cases they have encountered in the past and their approach to managing the care of those patients, with a focus on how or if this case report changed their decision-making in the prior cases. Another option is to present anterior segment photos of patients with various dry eye conditions of varying severity, including FK, and have students ask and discuss symptoms, pertinent history, underlying causes and ultimately determine a treatment plan for each case.

Conclusion

This case highlights the need for increased clinician awareness of the possibility of autoimmune disorders in areas of chronic environmental exposures, including the World Trade Center. Keratoconjunctivitis sicca and FK are conditions that can be associated with autoimmune conditions, such as SS. A detailed medical history and careful ocular examination can assist in arriving at the correct diagnosis, appropriate treatment and management and co-management of associated systemic diseases with interprofessional providers. This case covers multiple treatment options and strategies to consider for this condition that are dependent on symptomatology, chronicity and responsiveness to prior treatment. Furthermore, this case emphasizes the importance of understanding the impact of systemic conditions on the eyes.

References

1. Lessard CJ, Li H, Adrianto I, et al. Variants at multiple loci implicated in both innate and

adaptive immune responses are associated with Sjogren's syndrome. Nat Genet 2013;45:1284-92.
2. Björk A, Mofors J, Wahren-Herlenius M. Environmental factors in the pathogenesis of primary Sjögren's syndrome. J Intern Med. 2020 May;287(5):475-492.
3. Igoe A, Scofield RH. Autoimmunity and infection in Sjögren's syndrome. Curr Opin Rheumatol. 2013;25(4):480-487.
4. Colafrancesco S, Perricone C, Shoenfeld Y. Chapter 10 – Sjogren's syndrome and environmental factors, p157-170. In: Sjogren's Syndrome. Academic Press; 2016.
5. Powell JJ, Van de Water J, Gershwin ME. Evidence for the role of environmental agents in the initiation or progression of autoimmune conditions. Environ Health Perspect. 1999 Oct;107 Suppl 5(Suppl 5):667-72.
6. Landrigan PJ, Lioy PJ, Thurston G, et al.; NIEHS World Trade Center Working Group. Health and environmental consequences of the world trade center disaster. Environ Health Perspect. 2004 May;112(6):731-9.
7. Parks CG, Conrad K, Cooper GS. Occupational exposure to crystalline silica and autoimmune disease. Environ Health Perspect. 1999 Oct;107 Suppl 5(Suppl 5):793-802.
8. Webber MP, Moir W, Zeig-Owens R, et al. Nested case-control study of selected systemic autoimmune diseases in World Trade Center rescue/recovery workers. Arthritis Rheumatol. 2015 May;67(5):1369-76.
9. Goto E, Matsumoto Y, Kamoi M, et al. Tear evaporation rates in Sjögren syndrome and non-Sjögren dry eye patients. Am J Ophthalmol. 2007 Jul;144(1):81-85.
10. Hyon JY, Lee YJ, Yun PY. Management of ocular surface inflammation in Sjögren syndrome. Cornea. 2007 Oct. 26(9 Suppl 1):S13-5.
11. Akpek EK, Lindsley KB, Adyanthaya RS, Swamy R, Baer AN, McDonnell PJ. Treatment of Sjögren's syndrome-associated dry eye an evidence-based review. Ophthalmology. 2011 Jul;118(7):1242-52.
12. Akpek EK, Klimava A, Thorne JE, Martin D, Lekhanont K, Ostrovsky A. Evaluation of patients with dry eye for presence of underlying Sjögren syndrome. Cornea. 2009 Jun;28(5):493-7.
13. Akpek EK, Klimava A, Thorne JE, Martin D, Lekhanont K, Ostrovsky A. Evaluation of patients with dry eye for presence of underlying Sjögren syndrome. *Cornea*. 2009 Jun. 28(5):493-7.
14. Chen S, Ruan Y, Jin X. Investigation of the clinical features in filamentary keratitis in Hangzhou, east of China. Medicine (Baltimore). 2016 Aug;95(35):e4623.
15. Milner MS, Beckman KA, Luchs JI, et al. Dysfunctional tear syndrome: dry eye disease and associated tear film disorders – new strategies for diagnosis and treatment. Curr Opin Ophthalmol. 2017 Jan;27 Suppl 1(Suppl 1):3-47.
16. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007 Apr;5(2):163-78.
17. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018 Apr 9;12:677-681.
18. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. Arch Ophthalmol. 1963 Oct;70:482-91.
19. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. II. The effect of dexamethasone in the glaucomatous eye. Arch Ophthalmol. 1963 Oct;70:492-9.
20. Li J, Cone JE, Kahn AR, et al. Association between World Trade Center exposure and excess cancer risk. JAMA. 2012;308(23):2479-88.
21. Landgren O, Zeig-Owens R, Giricz O, et al. Multiple myeloma and its precursor disease among firefighters exposed to the World Trade Center disaster. *JAMA*

*Oncol.*2018;4(6):821-827.
22. Gold LS, Milliken K, Stewart P, et al. Occupation and multiple myeloma: an occupation and industry analysis. Am J Ind Med. 2010;53(8):768-779.
23. Larson T. Artificial tears: a primer. EyeRounds.org. Nov 23, 2016.
24. Bielory L, Bielory BP, Wagner RS. Allergic and immunologic eye disease. In: Leung DY, Szefler SJ, Bonilla FA, et al. editors. Pediatric allergy: principles and practice. 3rd rev. ed. New York: Elsevier; 2016. p.482-97.
25. Nassiri N, Eslani M, Panahi N, Mehravaran S, Ziaei A, Djalilian AR. Ocular graft versus host disease following allogeneic stem cell transplantation: a review of current knowledge and recommendations. J Ophthalmic Vis Res. 2013;8(4):351-358.
26. Ferrara JL, Reddy P. Pathophysiology of graft-versus-host disease. Semin Hematol. 2006;43:3-10.

Dr. Bui [fbui@sunyopt.edu] is an Assistant Clinical Professor at SUNY College of Optometry. He is a graduate of University of California – Berkeley School of Optometry and completed his Combined Graduate Residency Program at SUNY College of Optometry. He is a Fellow of the American Academy of Optometry and a Diplomate of the American Board of Optometry.

Dr. Canellos is an Associate Clinical Professor at SUNY College of Optometry, instructor of record for the fourth-year program and Director of the University Eye Center Referral Service. She supervises interns and residents in the anterior segment clinics of the Advanced Care Service. Dr. Canellos is a Fellow of the American Academy of Optometry, a member of the American Optometric Association and New York State Optometric Association, a Diplomate of the American Board of Optometry and a former member of the New York State Board of Optometry.