SYSTEMIC COMORBIDITIES AND OCULAR SURFACE DRYNESS

Taking a thorough systemic case history can prompt eye care providers to screen patients for ocular surface issues.

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Underlying systemic comorbidities can be the root cause for both chronic ocular surface dryness (OSD) and episodic OSD flares. OSD has been well documented to be a multifactorial inflammatory disease state.[1]

It can be helpful for both doctors and patients to recognize systemic conditions that could worsen signs and symptoms and trigger flare-ups of OSD. Early intervention can help to lessen the severity and duration of OSD flare-ups. This article reviews systemic conditions that can be associated with OSD, relevant diagnostic clues, and management options.

AUTOIMMUNE CONDITIONS

Autoimmune disease states are characterized by inflammatory outbursts throughout the body. Inflammation can often manifest on the ocular surface as part of the sequelae, seen as conjunctival injection and superficial punctate keratitis or erosions (Figure 1).

Sjögren disease is the most easily recognizable autoimmune disease that affects the ocular surface, as it attacks the lacrimal glands directly, reducing tear secretion.[1] Sjögren also targets the salivary and parotid glands.[1-5] Non–eye related red flags for detecting Sjögren include difficulty swallowing and constantly clearing the throat

AT A GLANCE

- The thread that connects most common systemic comorbidities to ocular surface dryness (OSD) is inflammation.
- Autoimmune diseases, characterized by inflammatory outbursts throughout the body, can often manifest on the ocular surface.
- For many systemic diseases, patients cannot stop taking the medications that are causing their concomitant OSD; these patients may require chronic local antiinflammatory therapy.

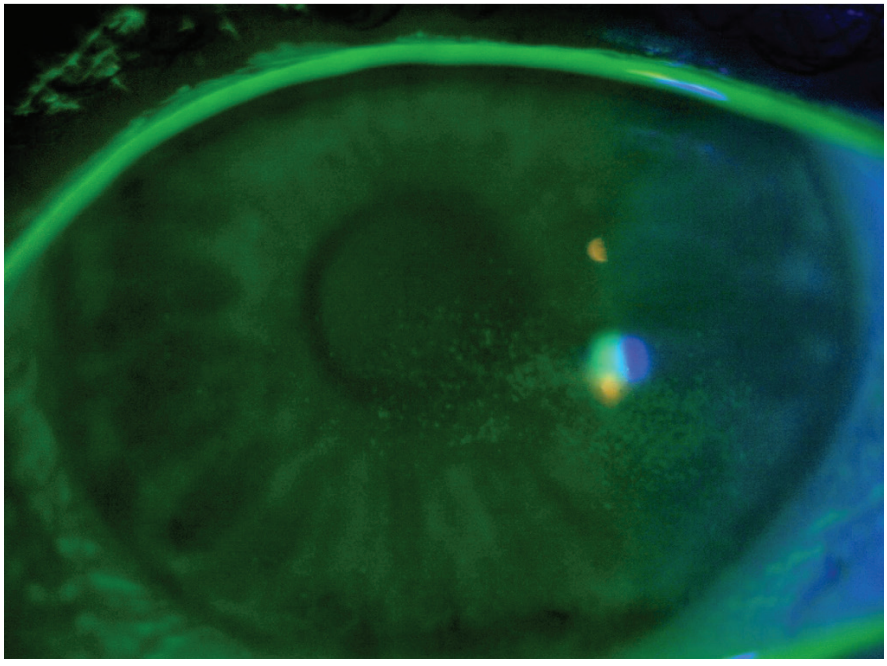

Figure 1. Punctate keratitis in inflammatory dry eye.

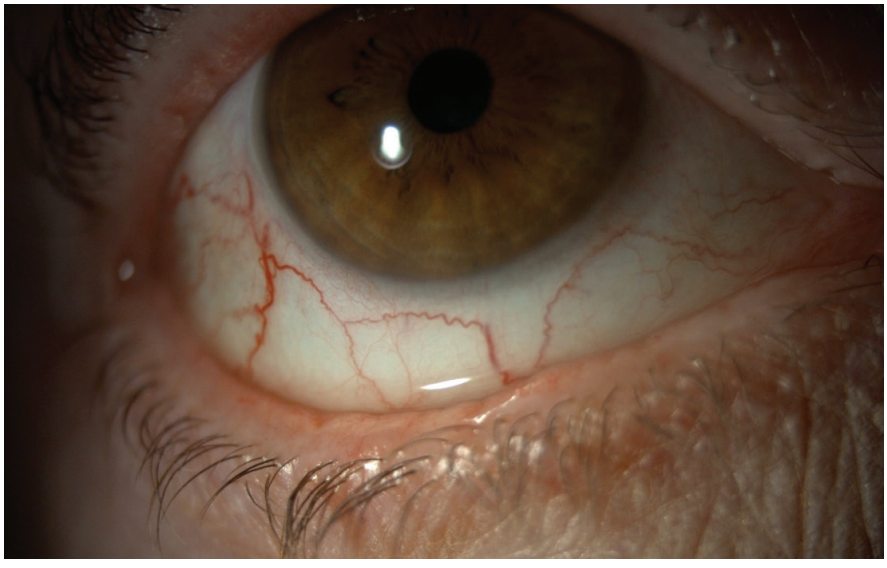

Figure 2. Thyroid ophthalmopathy resulting in exposure with scleral show.

to speak. People with Sjögren often carry large water bottles with them.

Refer patients with suspected Sjögren to rheumatology for classic SS-Ro and SS-La antibodies and a salivary gland biopsy, currently the best methods of detection.[2-5] Other early biomarkers such as antibodies to parotid secretory protein, salivary protein-1, and carbonic anhydrase-6 have been found to be less sensitive and specific to be helpful for diagnosis.[6] The differential of sarcoidosis should be ruled out when Sjögren syndrome is suspected, as sarcoid granulomatous infiltration of the lacrimal glands can mimic the T-cell–mediated destruction seen in Sjögren disease.[7]

Thyroid disease can also directly affect the ocular surface through inflammation or exposure (Figure 2).[8-12] The proptosis associated with infiltration of the extraocular space in Hashimoto disease can lead to incomplete lid closure at all hours of the day.[11]

Teprotumumab-trbw (Tepezza, Horizon Therapeutics) is an intravenously administered insulin-like growth factor-1 receptor inhibitor approved by the FDA last year for the treatment of thyroid eye disease. Administered by an endocrinologist, this medication can reduce proptosis.[13] For patients who are not candidates for teprotumumab, protective interventions such as sleep shields, scleral lenses, lubrication, and moisture eyewear can be helpful.

Hypothyroidism has also been positively associated with OSD due to decrease in the local creation of hormones necessary for tear production.[11,12] It crucial that patients with any type of thyroid disease be questioned and examined for signs and symptoms OSD.

Other autoimmune diseases associated with OSD include rheumatoid arthritis,[9] systemic lupus erythematosus,[10] and irritable bowel syndrome.[14]

All autoimmune disease–linked OSD can be well managed with a combination of topical antiinflammatory treatments such as short-duration topical steroids; long-term treatment with cyclosporine, autologous serum, or platelet rich plasma eyedrops; application of amniotic membranes; and intense pulsed light (IPL) treatment, in conjunction with systemic therapy provided by rheumatologists and internists. Punctal occlusion and scleral contact lenses can also be helpful for those whose tear production is severely reduced.

HEART CONDITIONS

The systemic medications used to help manage cardiovascular disease can be the cause of OSD.[1,8-10] Patients cannot stop taking the diuretics, beta-blockers, anti-arrhythmics, and statins

TABLE. Cardiovascular Medications Associated With OSD

MEDICATION CLASS	COMMON MEDICATIONS
Beta blocker	atenolol, bisoprolol, carvedilol, esmolol, metoprolol, nebivolol, propranolol
Diuretic	chlorthalidone, chlorothiazide, hydrochlorothiazide, furosamide, indapamide, metolazone
Statin	atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin

Sources: www.medicinenet.com/ and www.webmd.com/

Figure 3. The Eyeseals Hydrating Sleep Mask (Eye Eco) is a CPAP-compatible sleep mask.

necessary to keep them healthy and alive, and these medications can reduce overall hydration.[1,8-10]

Hypertension, dyslipidemia, hyperlipidemia, ischemic heart disease, stroke, peripheral vascular disorders, and even cardiac arrythmias have been associated with OSD.[1,8-10] In these situations, chronic use of anti-inflammatory interventions may be necessary to combat medication side-effects that cause OSD. See the Table for a list of common cardiovascular medications associated with OSD.

Cardiovascular disease often keeps company with another ocular surface–offending systemic disease: diabetes. The connections here to OSD are thought to be potential reduction in the blood supply to lacrimal glands and loss of innervation to the tear glands and the corneal surface.[8,10] Reduction in corneal sensitivity can lead to exposure from reduced blinking and to asymptomatic damage.[8,10] All patients with diabetes should be examined for OSD, including meibomian gland dysfunction (MGD), which has also been correlated with diabetes.[15]

MENTAL HEALTH CONDITIONS

It may surprise many practitioners to hear that one study found patients with OSD to have a higher prevalence of mental health conditions, including depression and anxiety disorders, than patients with glaucoma or macular degeneration.[16] Mental health conditions can raise the level of inflammatory cytokine activity in the body, including on the ocular surface.

The stress of OSD symptomatology, with its irritation, pain, loss of cosmesis, and vision fluctuations, can worsen depression and anxiety, leaving a patient feeling helpless. This sad cycle can perpetuate itself as dryness leads to worsening of mental health, which in turn worsens dryness.

Mental health is an important part of the OSD picture.[1,10,17] Patients may benefit from mental health services, such as counseling, support groups, or psychiatry. Eye care providers can take a great first step in assisting patients by acknowledging the role of mental health in OSD and engaging in an open discussion about it.

Antidepressant and antipsychotic mediations can worsen OSD,[1,17] but, as with treatments for other systemic conditions, these medications cannot be discontinued. OSD treatment in patients with mental health conditions should focus on antiinflammatory approaches to lessen the levels of inflammatory cytokines released locally on the ocular surface.

SLEEP DISORDERS

Lack of good quality sleep is associated with worsening of mental health and OSD,[18,19] and worsening of sleep is directly correlated with worsening of the severity of OSD.[19] Signs and symptoms of OSD have been found to be greater in patients with concurrent sleep disorders, including insomnia and obstructive sleep apnea (OSA).[18-21] OSA not only disrupts normal sleep, but also is associated with decreasing blood supply to the eye. This is not unlike diabetes, in that lack of normal blood supply leads to hypoxia and inflammation with subsequent ocular surface damage.[21]

To compound the issue, ill-fitting continuous positive airway pressure (CPAP) treatment masks for OSA can funnel air directly toward the ocular surface.[22] A leaking CPAP mask should be addressed by the patient's

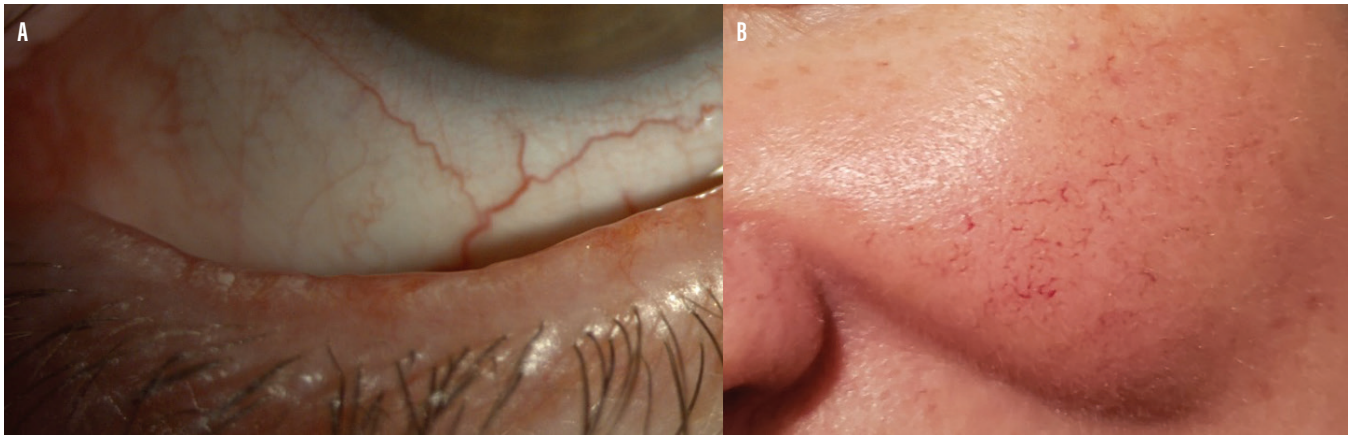

Figure 4. Telangiectasia in ocular (A) and facial (B) rosacea.

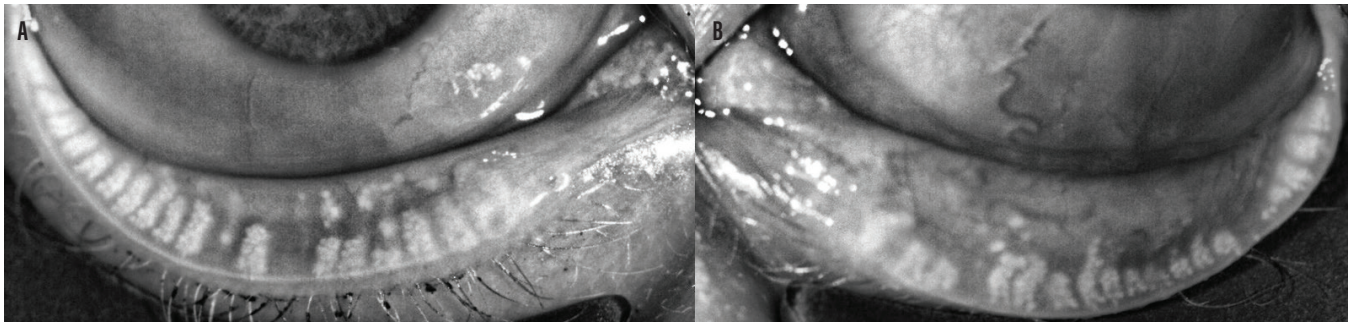

Figure 5. Meibography images of right (A) and left (B) eyes of a 23-year-old patient after 2 years of isotrentinoin treatment.

comanaging internist to ensure maximal oxygen delivery and avoidance of ocular irritation.

Commercially available sleep shields and patches, such as the Eyeseals Hydrating Sleep Mask (Eye Eco; Figure 3) can be used with a CPAP machine while the patient is working on finding a better fit.

SKIN CONDITIONS

The skin of the eyelid is not immune to skin conditions that affect the face. When the periocular skin is affected by conditions such as acne rosacea, it warrants a close look at the eyelids and meibomian glands. Both meibomian glands and skin oil glands are exocrine glands that can be similarly affected.

Acne rosacea is one of the most common skin conditions associated with OSD. Some studies have found that 90% of rosacea patients have OSD, and at least half are likely to have concurrent blepharitis.[23,24] Thickened meibum oil secretions result from the inflammatory T-cells delivered by multiple irregular telangiectatic blood vessels.[23,24] The red flush seen near the surface of the skin of the nose and cheeks is a true red flag to look for concurrent telangiectasia of the lid margin (Figure 4).

Secondary demodicosis is common, as thickened secretions and sloughed glandular and follicular epithelial cells create the perfect food source for *Demodex* mites, resulting in overpopulation.[25] IPL is a treatment modality that can help to both regress telangiectatic blood vessels and reduce *Demodex* populations.[26-28] IPL treatment of the periocular region and eyelids has resulted in improvement in measurable indices of OSD, including reductions in ocular inflammation (as measured by the inflammatory marker matrix metalloproteinase 9),[29] corneal staining,[30,31] meibomian gland turbidity,[31] and reported symptoms.[31-33] Increases in tear breakup time and lipid layer thickness have also been reported.[31-33]

Although other common ocular rosacea therapies do not directly treat the underlying telangiectasia, they can target concurrent MGD, blepharitis, and inflammation. These other therapies include okra seed oil– and tea tree oil–based lid treatments,[34-35] oral tetracycline derivatives,[36] topical cyclosporine,[36] topical azithromycin,[37] and gland expression techniques.[38]

Patients with a history of acne vulgaris should also be examined for MGD, particularly when associated with the use of oral isotrentinoin.[1,39-42] This oral therapy has been documented to reduce meibomian gland density, thicken meibomian gland ductules, and cause irreversible damage.[39-42] Young patients may find themselves in need of meibomian

gland therapy and chronic antiinflammatory treatment to regain meibomian gland function. Figure 5 illustrates meibomian gland loss in a 23-year-old patient who had taken isotretinoin for 2 years in her teens.

BE MINDFUL OF OSD

Clues from systemic case history can prompt eye care providers to screen patients for common ocular manifestations associated with systemic comorbidities. It is just as important to assess a patient's ocular surface as it is to examine his or her retina.

The thread that connects most common systemic comorbidities to OSD is inflammation. Antiinflammatory treatment should be considered as first-line therapy for patients with OSD. Bringing the focus to the ocular surface can help lessen the severity and duration of OSD flare-ups. ■

> **CLUES FROM SYSTEMIC CASE HISTORY CAN PROMPT EYE CARE PROVIDERS TO SCREEN PATIENTS FOR COMMON OCULAR MANIFESTATIONS ASSOCIATED WITH SYSTEMIC COMORBIDITIES.**

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