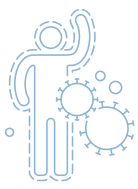
OCULAR RHEUMATOLOGY


Understand how systemic autoimmune disease can affect the eye and how to manage these complications.

BY SELINA R. MCGEE, OD, FAAO, AND JACOB LANG, OD, FAAO

A significant portion of the day-to-day work we do as optometrists falls under the category of rheumatology, which is the study of rheumatic diseases that are chronic in nature and cause inflammation. While traditionally, rheumatology focuses on the skeletal, muscular, and connective tissues, *ocular* rheumatology addresses the intersection of autoimmune diseases and ocular health. The eye, as a delicate and immune-privileged organ, can be significantly affected by systemic autoimmune disorders, which often directly target the ocular structures and can result in complications that impair vision and reduce quality of life. Dry eye disease (DED) is one of the most common conditions we treat and can be considered a localized autoimmune disease.[1]

In this article we explore how understanding DED as an autoimmune disease and examining the disease process through the lens of rheumatology can help decipher the manifestations that occur in patients with this condition.



AUTOIMMUNE DISEASE: THE BASIC PROCESS

What exactly happens in an autoimmune disease? First, let's review the concept of ocular immune tone. This term describes the baseline activity or balance of the immune system on the ocular surface. A healthy immune tone involves protection against infections and inflammation, while maintaining tolerance to avoid damage to tissues. The eyelids blinking, eyelashes sweeping, and tear film flushing collectively protect the front of the eye and maintain visual clarity. This is an intricate and dynamic system that works to maintain homeostasis.

This innate immunity of physical barriers, alongside inflammation and nonspecific immune cells, is the body's first line of defense. The body also deploys adaptive immune responses to protect itself from foreign invaders. When an antigen is presented to the body, B cells can recognize it and develop antibodies, so that in the future, when the body is presented with the same antigen, it can better attack and prevent infection. In this way, B cells are akin to factories that produce antibodies.

However, in autoimmune diseases, B cells misidentify normal

human tissue as a potentially harmful invader, churning out autoantibodies, which inflict harm to the body rather than protecting it. In turn, both antibodies (good) and autoantibodies (bad) activate T cells, which can be thought of as the soldiers of the immune system (they help to direct other immune cells [ie, B cells] to destroy infected or damaged cells, but confusion ensues when T cells accidentally cause B cells to make autoantibodies. In other words, T cells and B cells normally team up to protect the body from germs. However, the coordination between T cells and B cells is disrupted in autoimmune diseases, leading to friendly fire on the battlefield. If the immune system is an army that defends its country (ie, the body) from invaders (ie, germs), then autoantibodies are akin to soldiers who mistake their own side for the enemy and attack their fellow citizens. In this way, the defense system can go awry and harm the body.

AUTOIMMUNE DISEASE AND THE EYE

Following are some of the common systemic rheumatologic diseases we often encounter in the clinic that can affect the eyes, including ocular manifestations to watch out for.

Rheumatoid Arthritis

Commonly associated with DED and scleritis, rheumatoid arthritis can lead to corneal melt and peripheral ulcerative keratitis, which can potentially threaten vision.

Sjögren Syndrome

A hallmark condition in ocular rheumatology, Sjögren syndrome is characterized by DED due to autoimmune-mediated destruction. B cell and T cell infiltration of the lacrimal glands, accessory lacrimal glands, and other ocular tissues leads to progressive destruction of glandular tissue, resulting in decreased aqueous tear production and increased ocular inflammation.

Thyroid Eye Disease

Insulin-like growth factor 1 receptors (IGF-1R) become an unintended target of the immune system in patients with thyroid eye disease. Autoantibodies against the thyroid-stimulating hormone receptor form complexes with IGF-1R, which is then overexpressed on the surface of orbital fibroblasts, leading to cytokine release. The stimulation of fibroblasts leads to tissue remodeling, swelling, and orbital fibrosis, which contribute to the hallmark features of thyroid eye disease (ie, proptosis, periorbital edema, double vision, and DED), as IGF-1R are also found in the lacrimal glands.

Systemic Lupus Erythematosus

Patients with systemic lupus erythematosus often have involvement of the eye, leading to retinal vasculitis, choroiditis, and secondary DED.

Ankylosing Spondylitis

Uveitis is a common ocular manifestation of ankylosing spondylitis, potentially causing pain, redness, and photophobia.

Vasculitides

Vasculitides is a group of inflammatory conditions that affect the blood vessels, including granulomatosis with polyangiitis, can lead to scleritis, keratitis, and optic neuritis, and often require aggressive treatment.

Psoriatic Arthritis

Patients with psoriatic arthritis may experience uveitis or episcleritis, in addition to associated DED.

Sarcoidosis

This multisystem granulomatous disease frequently affects the eyes, leading to anterior or posterior uveitis, conjunctival granulomas, and secondary DED.

DIAGNOSTIC WORKUP AND LABORATORY TESTING

Proper diagnosis of ocular manifestations of autoimmune diseases requires a comprehensive evaluation, including laboratory testing, imaging, and clinical examination. Key components of the diagnostic workup may include serology testing, evaluating the tear film and ocular surface through

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AT A GLANCE

- The eye can be significantly affected by systemic autoimmune disorders, resulting in various ocular complications.
- In autoimmune diseases, B cells misidentify normal human tissue as a potentially harmful invader and produce autoantibodies, which inflict harm to the body instead of protecting it.
- Pipeline therapeutics such as Janus kinase inhibitors and reactive aldehyde species inhibitors may soon become exciting additions to the treatment arsenal for managing ocular manifestations of autoimmune diseases.

RHEUMATOLOGIC AND AUTOIMMUNE SCREENING PANELS

The following offers a list of usual testing to order in cases of suspected rheumatologic and autoimmune conditions.

GENERAL TESTING

- Antinuclear antibody (ANA): screens for connective tissue diseases (eg, systemic lupus erythematosus [SLE], Sjögren syndrome)
- Rheumatoid factor (RF): elevated in rheumatoid arthritis, among other autoimmune diseases
- Erythrocyte sedimentation rate (ESR): a nonspecific inflammation marker
- C-reactive protein (CRP): a nonspecific acute-phase reactant
- Complete blood count (CBC) with differential: may show anemia, leukocytosis, or eosinophilia
- Comprehensive metabolic panel (CMP): basic organ function and electrolyte status

More specific tests may be ordered based on ocular manifestations of suspected systemic disease.

UVEITIS AND SCLERITIS

- Human leukocyte antigen (HLA)-B27: associated with ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and IBD-related arthritis
- Angiotensin-converting enzyme (ACE): elevated in sarcoidosis
- Lysozyme: elevated in sarcoidosis
- QuantiFERON-TB Gold or T-SPOT: can rule out tuberculosis (TB), especially in posterior uveitis or panuveitis
- Rapid plasma reagin (RPR)/Fluorescent treponemal antibody absorption (FTA-ABS): syphilis screening (can mimic many ocular inflammatory conditions)
- Chest x-ray or CT scan: evaluates for sarcoidosis, TB

SEVERE DRY EYE AND SJÖGREN SYNDROME

- Anti-Ro(SSA) and anti-La(SSB): Sjögren-specific antibodies
- ANA: often positive in cases of Sjögren syndrome
- RF: often elevated in primary or secondary Sjögren syndrome

THYROID EYE DISEASE

- Thyroid stimulating immunoglobulin (TSI): specific for Grave thyroid disease and found in thyroid eye disease
- Thyroid peroxidase antibodies (TPOAb): autoimmune thyroiditis

ADDITIONAL CONTEXT-SPECIFIC TESTING

- Antineutrophil cytoplasmic antibodies (ANCA; pANCA, cANCA): vasculitis syndromes, such as granulomatosis with polyangiitis/Wegener and microscopic polyangiitis
- Anti-double stranded DNA (Anti-dsDNA): SLE
- Complement levels (C3, C4): SLE or immune complex disease
- Hepatitis B and C serologies: important to rule out before starting immunosuppression; also linked to some forms of uveitis
- HIV: can present with infectious or inflammatory ocular manifestation

> FOR OCULAR SURFACE MANIFESTATIONS OF AUTOIMMUNE DISEASE, THE ARSENAL OF TREATMENTS AT OUR DISPOSAL REVOLVES AROUND IMPROVING TEAR QUALITY AND PRODUCTION, AS WELL AS MANAGING INFLAMMATION AND OTHER INVADERS (WE'RE LOOKING AT YOU, *DEMODEX* MITES).

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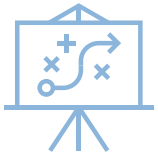
tear meniscus height, ocular surface staining, tear breakup time, meibography, testing the functionality of the meibomian glands, osmolarity, and certain inflammatory markers. In the case of Sjögren syndrome, performing a salivary gland biopsy to identify lymphocytic infiltrates may also be necessary. (For more information about testing to order for a possible autoimmune disease, see *Rheumatalogic and Autoimmune Screening Panels*.)



MANAGEMENT STRATEGIES

Managing the ocular manifestations of autoimmune diseases typically involves both local and systemic approaches; the patient's systemic disease must be under control in order to successfully manage the ocular surface.

Biologic agents have been particularly useful in targeting B cells, T cells, and specific inhibitors. Anti-tumor necrosis factor, anti-CD20 therapy, interleukin-17 and interleukin-6 inhibitors, and monoclonal antibodies that block IGF-1R are all available options. Janus kinase (JAK) inhibitors are a class of medications being used increasingly in rheumatology to manage rheumatoid and psoriatic arthritis. By targeting the Janus kinase pathway, these inhibitors reduce the production and function of cytokines that regulate immune responses. This results in diminished activation of T cells and suppression of B cell-mediated antibody production, thereby modulating immune activity.[2]

For ocular surface manifestations of autoimmune disease, the arsenal of treatments at our disposal revolves around improving tear quality and production, as well as managing inflammation and other invaders (we're looking at you, *Demodex* mites). These treatments may involve lubrication, punctal occlusion, canalicular occlusion with filler, neurostimulation, antiinflammatory medications such as steroids and immunomodulators, mite eradication, pulsing light therapies, and meibomian gland evacuation.

Pipeline therapeutics such as reactive aldehyde species inhibitors and JAK Inhibitors may soon become exciting additions to our arsenals.

IDENTITY THE ROOT OF OCULAR SYMPTOMS

Ocular rheumatology encompasses a diverse array of autoimmune diseases, each with distinct mechanisms and implications for the eye. DED, as a prominent feature in many of these conditions, highlights the role of B cell- and T cell-mediated inflammation in ocular pathology. Advances in targeted immunotherapy may offer the potential for reducing ocular morbidity and preserving vision in individuals who are affected by autoimmune diseases. ■

1. Stern ME, Theofilopoulos AN, Steven P, et al. Immunologic basis for development of keratoconjunctivitis sicca in systemic autoimmune diseases: role of innate immune sensors. *Ocul Surf*. 2024;32:130-138.
2. Moura RA, Fonseca JE. JAK Inhibitors and modulation of B cell immune responses in rheumatoid arthritis. *Front Med (Lausanne)*. 2021;7:607725.

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