12 Cicatrizing Disorders of the Ocular Surface

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Maintenance of corneal clarity and integrity depends upon the sustained health and homeostasis of elements that are of intimate relation to the ocular surface, including the eyelids, conjunctiva, lacrimal apparatus, and other accessory structures. Pathology involving cicatricial changes to conjunctiva has been well known to lead to blindness by way of progressive scarring and neovascular changes to cornea and, in severe cases, loss of the eye altogether. Cicatrizing conjunctivitis is characterized by chronically active inflammatory disease starting with subepithelial inflammatory cell infiltrate, later progressing to subepithelial fibrosis, foreshortening of the fornices, symblephara formation, and, finally, ankyloblephara via keratinization of lid and mucosal surfaces. This, in turn, leads to secondary complications like corneal neovascularization and scar formation, goblet cell depletion, severe ocular surface dryness, high risk of secondary infectious infiltrate, limbal stem cell deficiency, contractile entropion, trichiasis and distichiasis, canalicular stenosis, and obliteration of eyelid anatomy [1]. These conditions may arise from various local and systemic causes, making it absolutely essential to identify the etiology early to avoid not only severe vision loss but also the potential morbidity associated with these conditions. Unfortunately, the wide spectrum of causes and typical delayed awareness of the severity of the process involved often lead to more advanced disease prior to the initiation of proper therapy, leading to a large percentage of these patients presenting with various blinding complications when first seen by the ophthalmologist. Also, there is an unfortunate tendency by some investigators to assume that one versus another process is at the root of inflammation without proceeding with necessary testing.

Cicatrizing conjunctivitis is caused by an extremely wide range of pathology including noninfectious or autoinflammatory, infectious, and malignant disorders (Table 12.1). Noninfectious causes include many of the blistering skin disorders, notably ocular cicatricial pemphigoid (OCP), more formally recognized as conjunctival mucous membrane pemphigoid (MMP), and linear IgA disease, which is classified as a subset of MMP [2]; severe atopic disease; severe reactive epithelial diseases such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme (EM); graft versus host disease (GVHD); blepharoconjunctivitis and ocular rosacea; as well as other disorders such as sarcoid, lichen planus, discoid lupus, and secondary (i.e., medication, trauma, radiation) induced inflammation. Infectious etiologies can include ocular trachoma, *Corynebacterium diphtheriae*, adenovirus, and herpetic disease. Masquerade disorders, such as squamous metaplasia or carcinoma, must also be kept in mind. Table 12.1 illustrates a list of

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Table 12.1 Differential diagnosis of cicatrizing ocular surface disorders

Noninfectious
Blistering skin disorders
Cicatricial pemphigoid (MMP/OCP)
Linear IgA disease
Bullous pemphigoid
Epidermolysis bullosa acquisita
Atopic disease
Vernal keratoconjunctivitis
Atopic keratoconjunctivitis
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Erythema multiforme
Graft versus host disease
Ocular rosacea/blepharoconjunctivitis
Sarcoidosis
Lichen planus
Discoid lupus
Systemic sclerosis
Medication-induced
Trauma or radiation
Masquerade syndromes
Squamous cell carcinoma/carcinoma in situ
Mucosa-associated lymphoid tissue lymphoma
Sebaceous cell carcinoma
Infectious
Trachoma
Corynebacterium diphtheriae
Adenovirus
Herpetic disease

these and other disorders that can be associated with cicatricial changes of the ocular surface. With appropriately aggressive investigation including fully comprehensive history taking and review of systems, thorough medical examination, and targeted laboratory testing, one may be able to narrow the broad spectrum of possible causes, even in early stages of disease.

Of note, some of the important topics included in this discussion are covered more thoroughly in other sections of this manuscript; thus focus will not be put on these here.

Epidemiology

Occurrences of diseases of this type are likely underappreciated, as some go unrecognized in their early forms, only to be categorized once the more significant findings of scarring or other secondary complications are seen. OCP is often regarded or reported as the most common cause of presenting cicatricial changes [3]. Early attempts to estimate prevalence place it anywhere from 1 in 8000 to 60,000 [4–7] although it is also noted that this likely represents only progressed cases, with some stating it impossible to accurately assess [7]. Reports generally show the disease has a mean age onset in the sixth to seventh decade [1, 8, 9] but may occur much earlier and has a female predilection of 2:1 or more with no geographic or racial bias noted [1, 8, 10]. Linear IgA is rare, occurring in only a few per million individuals per year [11].

Atopic disease is common, with various forms affecting upwards of an estimated one-fourth of the US population [12], but severe forms such as atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) are sparse. AKC can occur at almost any age, generally reported more in males age 30–50 [13, 14]. VKC occurs more commonly in males in warm climates, a severe but typically self-limiting disease manifesting and resolving in the first two decades in 89% in a large series with long-term follow-up [15]. Thankfully, SJS and TEN are rare, with incidence estimates at only a few cases per million occurring yearly [16].

GVHD is by convention uncommon, manifesting as a complication of allogeneic hematopoietic cell transplantation (HCT). Incidence rates vary widely in both acute (19–90%) and chronic forms (33–80%) depending on age, HLA-matching, and product given [17, 18], with lower rates seen in recipients with better donor parity and those receiving cord blood versus peripheral blood stem cells (PBSC) or bone marrow [19].

Rosacea is seen more commonly in lighter-pigmented populations with prevalence reported from 2–22% [20–23], and speculation of bias toward more easily distinguished facial flushing in this group. Ocular involvement is reported in ranges from 10 to over 50% [24–26], most commonly reported around the fifth decade with a strong preponderance of females [26, 27]. Keratopathy may occur due to several associated

mechanisms; however, the disease severe enough to progress to the level of cicatrizing changes is infrequent [28].

The exact prevalence of sarcoidosis is unknown despite many attempts to classify this, largely due to its occult nature in asymptomatic patients. Screening methods using lung imaging studies have concluded it in the range of 1–50 in 100,000 individuals; however, autopsy studies have estimated it to be much larger in the range or 320–640 per 100,000 [29]. Eye findings are more common in females.

Infectious causes of ocular inflammation tend to be more prevalent in developing regions, primarily in areas of lower socioeconomic status. Ocular trachoma is thought to cause vision impairment in 2.2 million individuals worldwide with over half of these being permanently affected, many being women and children, with cicatricial disease occurring more often in middle age [30].

Diphtheria is much less common in the USA now than in the early twentieth century prior to immunization, and there are recent years where no cases were reported. However, some endemic areas remain with reduced burden compared to prior decades, particularly in the newly independent states formed after the dissolution of the Soviet Union in the 1990s [31].

Adenovirus is an extremely common form of infectious conjunctivitis, typically self-limiting; however, the severe epidemic form is seen much less often, the degree of which is unknown as most cases are managed by local providers and not reported or recognized. Other forms of viral conjunctivitis include those due to the herpes simplex group, which more often causes corneal scarring via a primary keratitis rather than cicatrizing inflammation followed by secondary corneal changes.

Masquerade conditions may mimic, and, in some cases, be very difficult to distinguish from noninfectious inflammatory disease such as OCP, especially when less commonly found in the forniceal rather than bulbar conjunctiva – the former would be more likely to appear like pemphigoid. Squamous cell carcinoma or intraepithelial neoplasia may present in various stages and affect conjunctiva in this manner and is the most common malignancy of conjunctiva occurring in less than 0.02–3.5 per 100,000 yearly in the USA, most often seen around the fifth to sixth decades of life [32]. Incidence is thought to be higher in areas of greater sun exposure as in equatorial regions.

Common Ocular features

In earlier stages, the features of diseases leading to cicatrix are typically indistinguishable from more common forms of conjunctivitis, and may even remain occult for years, disguised as chronic or stubborn “dry eye” in many clinics. Early diagnosis is rare and difficult to come by, often occurring because of clinical suspicion due to other systemic signs or symptoms or by chance in the case of conjunctival resection done for other reasons, i.e., superior resection to treat superior limbic keratoconjunctivitis. There may also be mixed presentations of chronic diseases, and it may be impossible to determine if the disease processes occurred independently or if one was brought on by another.

Patients usually complain of redness, irritation, foreign body sensation, dryness, burning, and light sensitivity. It is usually of indolent onset, many patients regarding the condition as a minor nuisance at first, dealing with symptoms and treating on an as needed basis until symptoms persist to the point of frustration or are significant enough to warrant concern and desire to be evaluated. Early findings include injection and conjunctival thickening, possibly involving a diffuse papillary reaction seen as worse in the superior or inferior palpebral conjunctiva. Large follicles may form and corneal neovascularization may eventually appear. Other differing early features may also be present depending on the etiology, such as bullae, hemorrhage, ulceration, or pseudomembrane formation [33]. Irritation and symptoms may be present in the absence of clinically active appearing disease and may be due to subclinical inflammation but is often concomitant dryness occurring secondarily.

Scarring first appears in the form of lacy white subepithelial fibrotic strands that coalesce and contract, causing a buckling of adjacent conjunctiva into ridges. These changes are often found in a perivascular distribution and in the inferior fornices [1, 34]; however, it is not uncommon for the bulbar and inferior forniceal surfaces to appear fairly uninvolved in a patient who is exquisitely symptomatic but then to evert the lids to find tarsal conjunctiva with significant injection and cicatrix formation, often asymmetric. Progression of disease leads to loss of peripheral architecture, including foreshortening of fornices and shallowing of canthal recesses, at times with obliteration of plica and caruncle. Various stages and depths of forniceal foreshortening may be present. Symblephara or fibrous bands occurring between bulbar and palpebral surfaces may form at any time, including prior to foreshortening, often occult but becoming more prominent when one retracts the lid in the opposite direction of a patient's gaze, superiorly or inferiorly. Ankyloblepharon formation is the hallmark of advanced disease, "end game" in most cases, where fusion of lid to bulbar surface has occurred, typically with marked keratinization of the ocular surface that remains visible, many times involving adhesions from lid to cornea (Fig. 12.1).

Secondary complications of scar formation can be just as damaging, all presenting a threat to sustained corneal clarity. As mentioned above, associated dryness is the most common presenting complication, occurring with loss of goblet cells or irreversible damage to the lacrimal apparatus, including main or accessory salivary glands and ducts. Contraction of fibrosis may cause infolding or irregularity of adnexal borders or lamellae leading to entropion as well as lash follicle misdirection or trichiasis, both leading to constant abrasive scraping of lashes against an already inflamed and irritated cornea. This along with lagophthalmos and exposure may be present, together contributing to worsening corneal neovascularization, limbal stem cell deficiency, and then possible central ulceration, secondary infectious processes, or perforation. There are even suggestions that cicatrix formation in some disease may cause susceptibility to ocular hypertension or glaucoma via failure of normal limbal structures involved in aqueous outflow [35]. Lastly, therapeutic doses of corticosteroid vis-à-vis drops, pills, injectables, or intravenous administration can also predispose to conjunctival thinning or masking of poorly controlled disease, which may be seen to advance despite a lack of injection on examination.

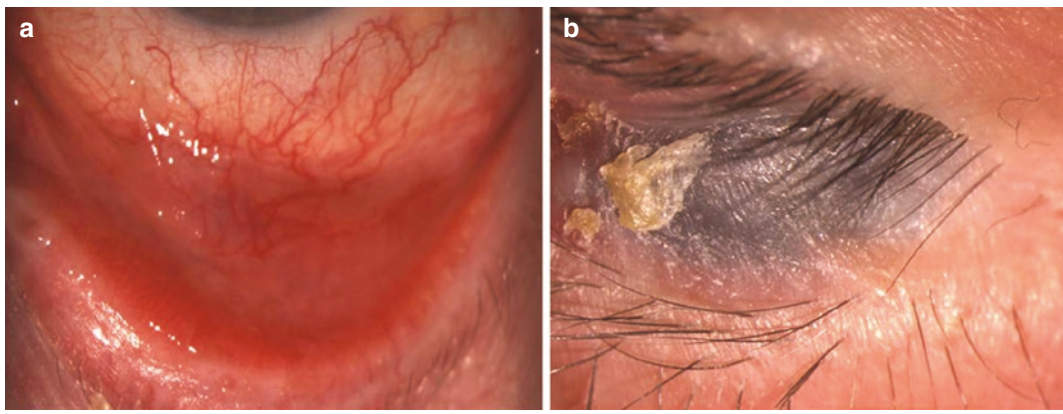

Fig. 12.1 Common ocular features of cicatrizing conjunctivitis including (**a**) subepithelial fibrosis, forniceal foreshortening, symblephara, and (**b**) ankyloblepharon (with complete corneal keratinization)

Distinguishing Features and Pathophysiology

While the abovementioned entities may lead to a similar phenotypic presentation, they are, in fact, quite distinct, stemming from differences in pathogenesis and systemic involvement. In some cases the diagnosis may be obvious; however, findings are often only first discovered after symptoms may have been present for several years. Management varies widely, and a thorough evaluation and attempt to definitively identify the causative disorder is crucial given the significant morbidity of delayed diagnosis or poor or misguided therapeutic approach. It must also be considered that more than one offending entity may be present, co-conspiring in scar formation (Fig. 12.2).

Ocular Cicatricial Pemphigoid/ Mucous Membrane Pemphigoid

Patients with MMP present with blistering inflammation and ulceration of mucosal tissues, most commonly oral cavity [36], but also nasopharynx, esophagus, trachea, and vagina. Cutaneous lesions are less commonly found [1, 9], and it is debated whether this may be an isolated presenting feature (Brunsting-Perry variant) versus a localized variant of another blistering disease, bullous pemphigoid [37, 38], which infrequently affects conjunctiva. Questioning for oral and nasal blisters or hemorrhage, vaginal irritation, hoarseness, heartburn, dysphagia, and respiratory distress is critical; diagnostic screening via endoscopy for nasopharyngeal, esophageal, and tracheal involvement may detect significant active disease even in asymptomatic patients. A consensus of international experts published accepted definitions and outcome measures in an attempt to more reliably compare data from differing studies and meta-analyses in this field; however, it was noted there is not a consensus on how to stage ocular involvement of MMP [39]. Currently, two staging systems are widely referred to for this, including the Foster system [1, 40], which stages disease by progression of clinical signs of cicatrix formation, and the Mondino and Brown system [41], which stages disease by loss of inferior forniceal depth or foreshortening (Table 12.2).

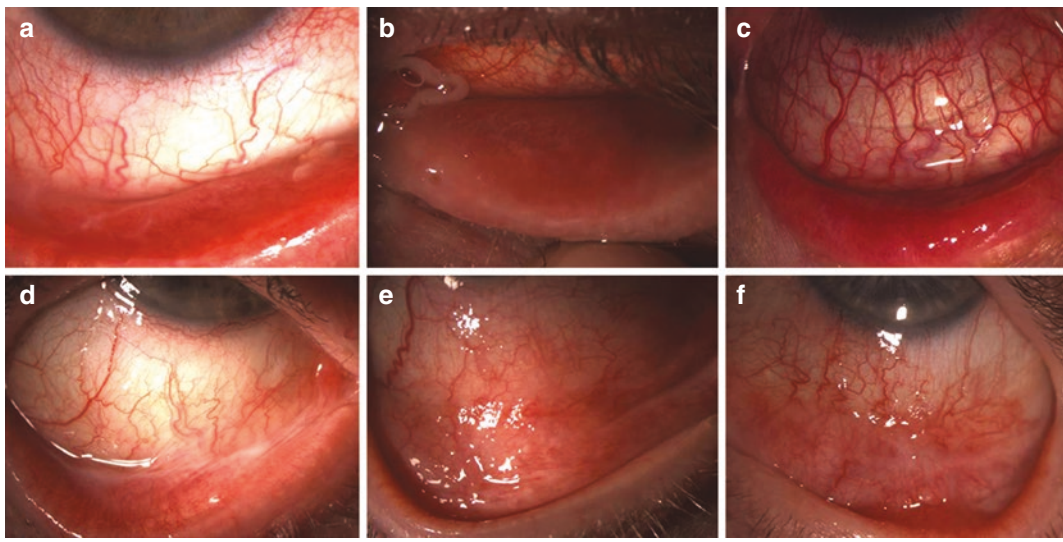

Fig. 12.2 Chronic cicatrizing conjunctivitis manifesting from (**a**) ocular cicatricial pemphigoid, (**b**) atopic keratoconjunctivitis, (**c**) Stevens-Johnson syndrome, (**d**) graft versus host disease, (**e**) sarcoidosis, and (**f**) squamous cell carcinoma in situ

Table 12.2 Staging systems for ocular cicatricial pemphigoid

	Foster	Mondino and Brown
Stage 1	Subepithelial fibrosis	0–25% forniceal foreshortening
Stage 2	Forniceal foreshortening	25–50% forniceal foreshortening
Stage 3	Symblepharon formation	50–75% forniceal foreshortening
Stage 4	Ankyloblepharon formation	75–100% forniceal foreshortening

Inflammation originates within the lamina lucida of the basement membrane zone of mucosal epithelium, with antibodies mostly directed against the cytoplasmic domain of the beta-4 subunit of hemidesmosome integrin [42–44], inciting complement activation and recruitment of varying types of inflammatory infiltrate (including plasma cells, lymphocytes, macrophages, neutrophils, eosinophils) in both acute and chronic diseases. Other targets have also been suggested, including laminin 332 (previously described as laminin 5, epiligrin, kalinin, nicein/BM600), found in disease which presents with pathology indistinguishable from classic OCP but is highly associated with an increased relative risk of malignancies [45]. Several inflammatory markers are elevated in OCP patients such as tumor necrosis factor-alpha (TNF-α), interleukin-1 alpha (IL-1α) and -beta (IL-1β) [46], and interleukin-5 (IL-5) [47], while tumor growth factor-beta (TGF-β) 1 and 3 levels are elevated in conjunctival samples [48]. Patients with the HLA-DQB1∗0301 allele have a demonstrated increased risk of disease, thought possibly to bind to the beta-4 subunit [49]. It is not completely understood how fibrosis is induced specifically here, but it has been shown that conjunctival fibroblasts from OCP patients possess a "profibrotic phenotype" compared to controls [50].

Other blistering diseases, including bullous pemphigoid and epidermolysis bullosa acquisita, also involve inflammation resulting from immune signals interacting with various targets in the hemidesmosome, such as BP180 and collagen VII. Conjunctival involvement is much less frequent in these than MMP. They can usually be clinically distinguished via systemic findings, mostly large or diffuse skin lesions not usually seen in MMP. The final diagnosis may depend on biopsy of affected tissues.

One must also keep in mind the possibility of multiple processes contributing to stubborn or uncontrolled chronic cicatricial disease. A closed-minded provider may miss these, only to struggle in the "unsuccessful treatment" of one problem while actually plagued with the persistence of another. One such example is coexistence of atopic disease with MMP, as in the recent report from our group where 230 consecutive biopsy-proven pemphigoid patients were studied with 33 patients having clinical symptoms of atopic disease (eczema, asthma, hay fever) and 23 patients with evidence of atopy suggested in biopsy specimens, who later successfully responded to antiallergy medications or infusion therapy directed against both diseases [51]. We have also found, in our clinical experience, that evidence of OCP may be suggested via biopsy in individuals with other known disease, i.e., SJS or GVHD, perhaps via epitope spreading, and that these patients may respond to appropriate anti-inflammatory therapy for pemphigoid while their other disease remains inactive. It would seem this may be the mechanism by which OCP, responding to immunosuppressive therapy, is also sometimes found in developmental disorders such as ectodermal dysplasia [52]. Infectious co-conspirators must also be remembered.

Atopic Disease

Systemic manifestations of atopic disease are more obvious, typically making determination of the cause of ocular surface scarring less difficult. Seasonal and perennial allergic conjunctivities do not present with scarring; however the more severe processes vernal keratoconjunctivitis (VKC) and particularly atopic keratoconjunctivitis (AKC) can result in fibrosis and neovascular changes in cornea, with potential permanent irreversible vision loss.

Itching is the most common and suggestive symptom of allergy, though patients also

complain of burning, intermittent blurring, dryness, light sensitivity, lid fullness, and tearing. Early on, congested papillary, or "boggy," conjunctiva commonly found in either superior (more VKC) or inferior (more AKC) tarsal surfaces and fornices or including bulbar surfaces is seen. Thick ropy mucous, which patients often describe pulling out in strings in the "mucous fishing syndrome," is found often in vernal catarrh, and this activity can exacerbate disease. Darkened or scaly periorbital epithelium is often present in AKC as is the characteristic nasal crease from repetitive upward nasal rubbing or wiping, termed the "allergic salute." Corneal findings include shield ulcers (VKC), Horner-Trantas dots (VKC more than AKC) and neovascular pannus, as well as secondary complications of ulceration and infection. Chronic disease may progress to cicatrizing changes in the fornices and eventually the bulbar surface. Allergic rhinitis and hay fever are often seen, and there is a high association of eczema or allergic dermatitis and asthma with both VKC [53] and AKC [54]. Presentation and demographic commonly help differentiate VKC and AKC, with VKC occurring more in young males in warmer tropic climates.

Mast cells are activated and seen in higher numbers in all allergies. They are strikingly present in conjunctival epithelium on light microscopy of biopsy specimens of VKC and AKC, often degranulating alongside eosinophils, neither seen in normal conjunctiva [55, 56]. Fibroblasts and collagen are found in greater abundance, which may stem from a large percentage of mast cells releasing basic fibroblast growth factor (bFGF) [57] and which may lend to the incidence of cicatrix formation by a mechanism as yet still poorly understood. Epithelial hyperplasia with pseudotubule formation is commonly seen. Mechanisms of both Gell and Coombs type I and IV hypersensitivity drive inflammation, with a varied leukocytotic infiltrate and severe ocular surface and corneal damage eventuated by the eosinophil-derived enzymes major basic protein (MBP) and eosinophil cationic protein (ECP). Tears and serum of both patient types contain elevated levels of IgE, and in AKC, ECP, among other important factors in this process. Eosinophils, as well as MBP and ECP, have been isolated in corneal ulceration in AKC but also under intact corneal epithelium [58]. More recent studies are looking into the role of the epithelial nuclear protein interleukin-33 (IL-33), which is upregulated in conjunctiva in AKC and may mediate disease [59].

Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme

These disorders present acutely with distinct findings that are almost never confused with other diseases in this section. Studies including histopathology and serologic evaluation are limited due to the nature of disease; however, those done typically disclose very severe diffuse blistering disease involving skin and mucous membranes, involving microangiopathy, thought to be induced by various medications or infectious processes. One should be mindful, however, of the possibility of a concomitant disease process occurring later on after disease has clearly passed through the acute stages. More on this can be found in the dedicated section in this manuscript.

Graft Versus Host Disease

GVHD occurs in a select population of individuals who have typically received allogeneic HCT for hematologic malignancies and benign disorders and thus is relatively rare. Both acute and chronic stages have been described, which are proposed to have distinct mechanisms of actions. Acute disease models are based mainly on animal studies, while chronic disease is less well understood with hypotheses that are more speculative. In contrast to the proposed 3-phase "cytokine storm" [60] of acute disease consisting of antigen-presenting cell (APC) conditioning, T-cell activation, and target cell apoptosis, chronic GVHD is thought to result from complex development of improper thymic function whereby autoreactive T-cells are no longer

removed. Chronic disease often resembles features of autoimmune disorders; it occurs less often in T-cell depleted marrow recipients [61] and is associated with decreased levels and function of T_{reg} lymphocytes [62].

Target antigens of donor T-cell-mediated inflammation in the acute stages mainly involve recipient skin, gastrointestinal organs, and liver but may also involve lung, oral mucosa, and the eye. Classic symptoms of acute disease include maculopapular rash, nausea, anorexia, diarrhea, cholestasis but may only be conjunctivitis [63]. Various stages of acute and chronic disease have been previously proposed, with more advanced disease involving pseudomembranous and epithelial sloughing in both, but cicatricial changes occur more frequently in chronic disease, along with the common complication of significant keratoconjunctivitis sicca via various secondary mechanisms. Of course, the most agreed upon risk for chronic GVHD is having had acute GVHD. Co-conspiring mechanisms may also include concurrent autoimmune disease, such as OCP, evidence of which we personally have seen in our own conjunctival biopsies taken from chronic GVHD patients.

Ocular Rosacea, Blepharoconjunctivitis

Rosacea and blepharoconjunctivitis are common presenting findings in patients with cicatrizing ocular surface changes, however, are not usually attributed as the direct cause. It may even be that such patients attributed to have this as the cause of their cicatrizing disease may actually have an unrecognized secondary inflammatory etiology, such as atopy, MMP (perhaps with "negative" biopsy), or adverse reaction to topical medications. On top of this, secondary processes often stemming from or associated with lid margin disease, such as phlyctenular keratoconjunctivitis, staphylococcal marginal disease or keratitis, trichiasis and distichiasis, or Demodex infestation, may contribute to corneal changes.

Rosacea is generally classified into four disorders based on morphological characteristics: erythematotelangiectatic, papulopustular, phymatous, and ocular [64]. Cicatrizing changes are uncommon but were found in one study to be the associated with rosacea in MMP-negative biopsies in 12 of 131 patients referred for evaluation of cicatrizing disease [28]. Findings include erythema, telangiectases, papules, and pustules in areas around the face and neck, including the lid margins. Fibrosis is commonly associated with the phymatous form of rosacea, but there may be overlap in these categories in nature. It stands to reason that cicatrizing disease should only be thought attributable to rosacea when other etiologies have been ruled out via thorough history and conjunctival biopsy.

The exact mechanism of this disease is unknown; however, it is felt to be a product of innate immune system or neurovascular dysregulation triggered by one or more of various factors in a genetically susceptible individual [65, 66]. Multiple cell types are thought to be involved, and there is evidence that intercellular adhesion molecule-1 (ICAM-1), transient receptor potential (TRP) ion channels, toll-like receptors (TLRs), and even the angiogenic CD105 (endoglin) may be involved [67]. Innate immune response cascades to epithelial microbial challenge may produce proinflammatory cytokines and antimicrobial peptides such as cathelicidin; the latter is seen to be elevated in rosacea patients, and a cleavage product of this (LL-37) is felt to contribute to all subtypes of rosacea [68]. Type IV hypersensitivity is also thought to be involved [69].

Other Noninfectious Disorders

Several other noninfectious disorders may present with cicatrizing changes of the ocular surface, including sarcoid, lichen planus, discoid lupus, malignancies, as well as those changes induced by medication, trauma, or radiation. Some of these processes are described more in other sections.

Sarcoidosis is a diagnosis typically made by clinical suspicion supported by granulomatous changes seen on biopsied tissues of involved

organs. Systemic features include fever, arthralgia, cough, dyspnea, weakness, and fatigue; however, many patients are asymptomatic. Ocular findings are present in 20–80% of cases [70], and of several possible presenting findings, the most likely is anterior uveitis [71]. Chest imaging with highly suspicious findings in the proper clinical setting will often be enough to make the diagnosis, though biopsy is always more valuable to confirming diagnosis if it is possible to attain.

Lichen planus may present identical to OCP; however, biopsy will reveal absence of immunoreactant deposition and a shaggy appearance of fibrinogen at the BMZ [72]. Etiology is unclear, and it more commonly affects other tissues such as genital or oral mucosa.

Discoid lupus is also a rare cause of conjunctival cicatrix formation, more often affecting oral or anogenital mucosa. An accompanying diagnosis of lupus may already be known, and serologic investigation may reveal typical findings such as antinuclear antibodies (ANA), anti-Ro (SS-A), anti-La (SS-B), and anti-double-stranded DNA (dsDNA) antibodies. Biopsy may show thickening, disruption, or duplication of the BMZ on immunofluorescence studies [73, 74].

Drug-related conjunctivitis is also addressed thoroughly elsewhere in this manuscript but is among the most common reasons for cicatrizing disease of the ocular surface.

As discussed earlier, malignancies have been associated with a less common variant of MMP [45]. Primary malignancies involving conjunctiva may also mimic and sometimes be indistinguishable clinically from, or present concomitantly with, MMP [75]. However, in squamous cell carcinoma and conjunctival intraepithelial neoplasia, histologic evaluation will reveal dysplasia in various degrees of severity, with or without invasion of stromal structures beyond the BMZ. Human papillomavirus (HPV) types 16 and 18 [76] is strongly associated with lesions, and other entities including human immunodeficiency virus (HIV), cyclosporine, and xeroderma pigmentosum have also been implicated in the pathogenesis of CIN. Lesions do not necessarily have to originate at the commonly appreciated site of the limbus. Corkscrew vessels, leukoplakia, and invasion to underlying tissue may make the diagnosis more suspicious. Exfoliative or impression cytology may be performed, as may excisional biopsy in some cases, helping to yield the diagnosis.

Trachoma

Infectious etiologies, as a cause for cicatrizing disease, are much less common in the developed world, but elsewhere still account for a significant amount of vision loss worldwide due to conjunctival scarring and eventual secondary corneal pathology. Transmission of *Chlamydia trachomatis*, an obligate intracellular gram-negative organism, is typically spread to the eye via hand or genital contact from infected individuals, and when suspected, both chlamydial and gonococcal (commonly coinfectious) urine cultures should be obtained. Differing serotypes are associated with types of infection – serotypes A to C are associated with ocular trachoma, serotypes D to K with genitourinary infections, and L1 to L3 with lymphogranuloma venereum. Two components, comprised of the inactive yet infectious elementary body and active yet noninfectious reticulate body, make up the organism. Chronic inflammation results, reinfection is common due to the inability of immune surveillance to eradicate the pathogen completely, then leading to scarring of conjunctiva and cornea.

Active chlamydial conjunctivitis presents in stages, which have been classified in various schemes. The World Health Organization (WHO) scheme is the most recent [77] and documents the development of follicular conjunctivitis in the upper tarsus, which worsens with thickening and eventual fibrosis, trichiasis, and corneal opacification. Both innate and cell-mediated immune responses are thought to contribute to cicatrix formation. Th2 lymphocytes may be more important in scar formation, and increased cytokine formation (IL-1β, TNF-α, TGF-β) has been associated with scarring as well [78]. Histopathology in acute childhood disease reveals epithelial hyperplasia with mixed inflammatory infiltrate involving macrophages, T lymphocytes, and

neutrophils, with plasma cells also being found beneath epithelium and around accessory lacrimal glands. Lymphoid follicles are found in stromal tissue. Cicatricial disease, more frequently seen in adults, is formed by chronic inflammatory infiltrate with squamous metaplasia or atrophy, T lymphocyte predominance, follicles, and subepithelial fibrous membranes [79]. Various available lab tests as well as culture using cycloheximide-treated McCoy cells can also determine the diagnosis.

Corynebacterium diphtheriae

Acute membranous conjunctivitis due to *C. diphtheriae*, a gram-positive bacillus primarily affecting respiratory mucosa, is extremely rare in the USA due to wide and effective immunization. Localized generation of a true membrane from organism, necrotic mucosa, and fibrin is seen which is adherent to underlying stroma and leads to hemorrhage when removed. Epithelial denudation leads to worsening infiltrate and eventual corneal opacification [80]. Systemically, hematogenous spread of exotoxin may cause fever, myocarditis, renal tubular necrosis, and neurodemyelination.

Adenovirus

Adenovirus is the most common cause of infectious red eye and conjunctivitis worldwide [81]. Highly contagious via transmission by fomites, water, and fecal oral contamination, human adenovirus types 8, 19, 37, and 54 are thought to be responsible for most outbreaks of epidemic keratoconjunctivitis (EKC) [82]. Adenovirus is a nonenveloped double-stranded DNA virus which penetrates ocular surface epithelial cells via binding to cell surface integrins, incorporating into vesicles, and eventually releasing viral DNA into cell nucleus. Both innate and cell-mediated immune mechanisms respond to viral infection involving natural killer cells, monocytes and macrophages, as well as Th1 and cytotoxic T lymphocytes. The virus may then lyse the cell, releasing virions that may go on to infect other cells.

Clinical presentation of EKC includes extreme versions of typical follicular conjunctivitis findings, including superficial punctate keratitis and, classically, pseudomembrane formation. However, it has been demonstrated that early angiogenesis and associated chemokine formation are present in these membranes, which may in turn lead to true membrane formation, subepithelial fibrosis, and eventual symblephara [83]. An accompanying lymphadenopathy and pharyngitis may be present. Infiltration of virus into corneal epithelial and, eventually, stromal cells leads to accumulation of lymphocytes, macrophages, and activated fibroblasts [84]. There is no gold standard testing performed in clinical settings; however, some rapid detection kits exist and are used with a significant degree of efficacy [85]. Polymerase chain reaction analysis of infected tears may also confirm viral DNA is present.

Herpetic Disease

A wide variety of pathology may present due to *Herpesviridae* viruses, including conjunctival, corneal, uveal, retinal, optic nerve, and orbital manifestations. The contributions of this family of infectious entities to ocular surface disease are addressed in another section in this manuscript.

Approach to Diagnosis: Conjunctival Biopsy

Perhaps the most important thing to take from this section is the concept of proper approach to diagnostic biopsy, particularly, in MMP, where too often we hear that conjunctival biopsy yield in the diagnosis is poor or inconclusive. Patients may also not respond as expected to therapy when biopsy is performed with limited analyses, yielding the so-called DIF-negative MMP that is then treated as MMP. This likely stems from various deficiencies in the diagnostic approach

taken. Previous thoughts on why this is so have ranged from feelings that antibody levels are low or undetectable, or that DIF in conjunctival specimens is lower than cutaneous samples, or even that there may be a subset of patient who develop T-cell-mediated disease without detectable autoantibody at the BMZ [86–88]. It has even been stated that some have abandoned the use of biopsy in routine management of these patients, rationalized by the notion that all other possible confounding etiologies are always somehow able to be ruled out by other means and that DIF-negative cases would be treated the same way regardless of this using immunosuppressive therapy [89]. It is fair to say, and we would agree, that cases of DIF-negative MMP exist that should be, due to strong clinical suspicion, labeled and treated as MMP despite recommendations by the First International Consensus on Mucous Membrane Pemphigoid [2]. Strangely absent from these discussions, however, despite previously published recommendations [1], is mention of other more likely reasons for why diagnostic yield may be poor.

Easily correctable is the surgical approach. Attention should be given toward a "one-touch" technique with careful handling thereafter of specimen, in an effort to prevent disturbance of the very fragile conjunctival epithelium – epithelium is easily disrupted or displaced from underlying stromal tissue, thus rendering the sample uninterpretable with respect to BMZ. Biopsy should also ideally be taken in an area of or directly next to inflamed or affected tissue, as one might expect a lesser yield during quiescence via disease inactivity or suppression of inflammation by steroid or other anti-inflammatory therapy.

Ideal processing of the specimen has previously been described [1], yet despite common practice we do not wish to discount the existence of an unusually fair amount of biopsied tissue, as seen in our experience done by other providers prior to presentation in our lab, for which DIF was not performed at all, with only histologic evaluation performed under microscopy. DIF, of course, is the standard, during which a characteristic brilliant pattern of IgG in stromal cells is commonly seen, which can also make the sample uninterpretable by way of the inability to recognize and distinguish a distinct linear deposition of IgG at the BMZ. Lastly, there is almost a frank unwillingness to even acknowledge the exceedingly more sensitive approach to detection of autoantibodies or complement at the BMZ by way of avidin-biotin complex immunoperoxidase technique. Admittedly, this is more labor intensive and costly than DIF, but is approximately 1000 times more sensitive, and may detect the suspected low amount of immunoreactant deposition more readily, in addition to other possible confounding features (i.e., observation of high levels of IgE possibly implicating co-conspiracy of atopic disease) (Fig. 12.3).

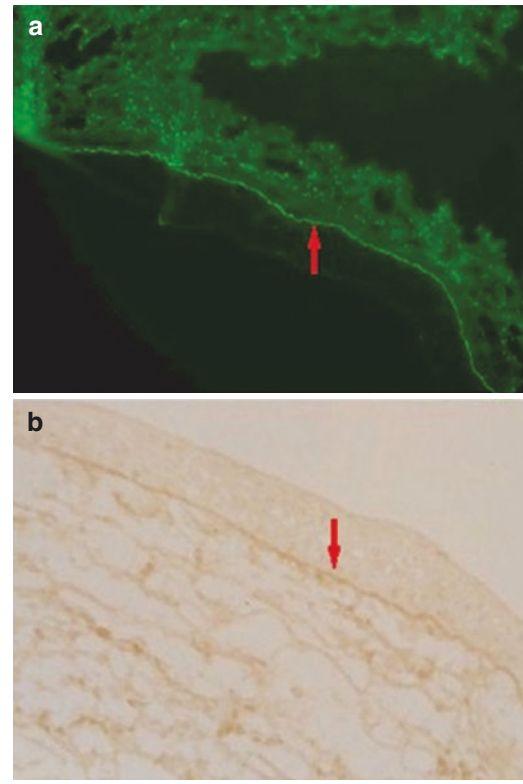

Fig. 12.3 Conjunctival biopsy showing distinct immunoreactant positivity at the BMZ (red arrows) via use of (**a**) direct immunofluorescence and (**b**) avidin-biotin complex immunoperoxidase technique

Medical Management

The goals of treatment in the cicatrizing disorders of the conjunctiva are first, to abort inflammation and prevent further tissue damage; second, to offer symptomatic relief; and third, to improve the ocular surface microenvironment and to restore corneal clarity in order to improve vision. While the treatment of infectious causes is more straightforward, that for the autoimmune disorders is not often clear-cut and may call upon clinical experience. Therapeutic decisions are often made on a case-by-case basis. In OCP, acute inflammation is addressed with topical and systemic corticosteroids, but its inevitable relapse-remission cycle will ultimately result in disease progression if only such therapy is implemented. Thus, the authors advocate for a stepladder approach of steroid-sparing agents. It has been clearly demonstrated by many investigators that systemic immunomodulatory therapy can effectively diminish the tissue-destructive processes caused by inflammation in patients with OCP, in turn saving vision and ocular function [90–93]. In milder cases of OCP, dapsone 50–100 mg daily may offer inflammatory control. However, the majority of cases encountered at our practice are recalcitrant to dapsone alone. If there is no contraindication, methotrexate (MTX) is frequently our first-line therapy for OCP, starting at a dose of 10–15 mg weekly. The dose can be escalated up to 25–30 mg weekly, and it may be switched to subcutaneous administration to increase bioavailability. The two other antimetabolites commonly employed in the treatment of OCP are azathioprine (AZA, 100–250 mg daily) and mycophenolate mofetil (MMF, 1–1.5 g twice daily, which must be taken on an empty stomach). Calcineurin inhibitors such as cyclosporine and tacrolimus are not typically used in OCP as the disease is predominantly B lymphocyte driven. TNF-α inhibitors such as adalimumab and infliximab, while very effective in other ocular inflammatory diseases including uveitis, scleritis, and retinal vasculitis, are not typically used in OCP. In fact, TNF-α inhibitors have been associated with drug-induced bullous pemphigoid in patients with rheumatoid arthritis, psoriasis, and ulcerative colitis [94–97] However, there have been reports of these medications being successful in treating refractory MMP or OCP in the literature [98–100], and we have had some personal success with this as well. On the other hand, rituximab, a B-cell-specific biologic, has proven very effective in inducing remission in OCP [101]. When conventional immunosuppressive therapy fails to bring forth disease remission, the authors recommend a combination of rituximab and intravenous immunoglobulin (IVIg), which is described elsewhere [102]. Finally, oral or intravenous pulse cyclophosphamide is employed in OCP cases not responsive to aforementioned medications, though it carries a higher systemic risk profile.

In severe atopic diseases, topical antihistamine/mast cell stabilizers and corticosteroids are frequently insufficient, and chronic systemic corticosteroids carry inappropriate long-term risks. Tacrolimus dermatologic ointment is available in 0.03% and 0.1% concentrations and is used for periocular dermatitis. Ophthalmic topical preparations of cyclosporine A (up to 1%) and tacrolimus (0.1%) can be specially formulated and may offer relief in less recalcitrant cases. Our experience in severe atopic cases, however, is that systemic immunomodulatory therapy is necessary for long-term inflammatory control without propagation of tissue damage. Although antimetabolites (MTX, AZA, MMF) have demonstrated variable efficacy in atopic diseases, we prefer T-cell inhibition via cyclosporine A (3–5 mg/kg/day divided dose) or tacrolimus (0.1–0.2 mg/kg/day divided dose). Of note, atopic patients have reduced innate immunity and are more susceptible to infections. Hence, concurrent bacterial or herpetic keratitis must be kept in mind and treated appropriately when ocular surface inflammation presents in these patients. Omalizumab, a monoclocal anti-IgE antibody approved by the FDA for allergic asthma, has demonstrated efficacy in AKC and VKC in several reports [103–105]. Monthly infusion of AK002 (Allakos Inc., San Carlos, CA), a fully humanized monoclonal antibody that targets Siglet-8, which is an inhibitory receptor on the surface of mast cells, eosinophils, and some basophils, is currently under investigation in the treatment of a variety of

diseases driven by mast cells and eosinophils, including eosinophilic gastoenteritis, indolent systemic mastocytosis, chronic urticaria, and severe allergic conjunctivitis.

Although the ocular surface inflammation is generally regarded as acute in SJS, we have through the years encountered patients whose inflammation became chronic, with progressive conjunctival cicatrix and corneal blindness the result. Conjunctival biopsy reveals an OCP-like picture, with IgG, IgA, and complement deposition at the basement membrane zone. In these cases, we recommend a therapeutic stepladder as outlined above. The only significant difference is that TNF-α inhibition appears more effective in these "chronic" SJS cases than in OCP.

An effective treatment strategy for severe rosacea blepharoconjunctivitis must implement both topical and systemic measures. We recommend lid hygiene employing effective (lasting, wet compresses typically cool down too quickly) warm compresses and manual expression of meibum, artificial tears containing lipids, and omega-3 supplementation as the foundation of the therapy. Topical tetracycline and cyclosporine can then be used. Short-term corticosteroids are appropriate in acute keratitis to prevent scarring and neovascularization, but long-term topical corticosteroids must be avoided. A specially formulated povidone-dimethylsulfoxide ointment was recently shown to be an effective topical therapeutic for rosacea blepharoconjunctivitis [106]. In the USA, the only FDA-approved oral therapy for rosacea is a modified-release doxycycline (40 mg daily), which has only anti-inflammatory and no antimicrobial properties, and in vivo studies demonstrated no long-term effects on the normal body flora at this dose [107]. However, in severe cases of ocular rosacea resulting in conjunctival cicatrix and corneal neovascularization, we find it necessary to use doxycycline at a higher dose of 50–100 mg twice daily, tapered gradually over a course of at least 6 months. In the pediatric population under the age of 8, oral erythromycin is a first-line therapy and is recommended at a dose of 40 mg/kg/day given over 6 months for moderate rosacea and 12 months for severe cases [108].

Demodex is a parasite that normally lives on the human skin and does not usually cause dermatological issues. However, when it penetrates the dermis, various skin manifestations, including rosacea, can occur. Its prevalence is higher in patients who are elderly or who have poor hygiene and may represent an important cause of chronic blepharoconjunctivitis in patients who fail standard rosacea treatment. A careful examination of eyelashes must be conducted to look for the mites. The treatment for Demodex blepharitis involves improvement in hygiene (washing bed sheets and pillow cases in hot water and drying in high heat), lid scrub with baby shampoo or commercially available cleaning pads, and hypochlorous acid/tea tree oil/shampoo.

Surgical Management

As mentioned above, secondary complications of conjunctival cicatrix can be just as threatening to the corneal integrity and clarity, and trichiasis due to cicatricial entropion must be addressed promptly. This can be done with mechanical epilation with forceps on a regular basis. Epilation can also be accomplished with electrolysis, radiofrequency wave, and argon laser, although these procedures may result in permanent lid scarring and do not necessarily prevent hair regrowth. While cryotherapy has been used for large, confluent areas of trichiasis, it is inappropriate in inflammatory conjunctival cicatrizing disorders as it can worsen symblepharon and entropion. We normally recommend at least 6 months to 1 year of disease quiescence, employing both topical and systemic agents, before entropion surgery, or any significant anterior segment surgery, in fact, is attempted. In patients with aggressive OCP that requires alkylator or biologic therapies, a longer period of inflammatory disease inactivity is desirable, and the clinician must be prepared for postsurgical flare even in the setting of a quiescent eye preoperatively. We recommend perioperative high-dose oral prednisone, starting 1 week before surgery, and tapered after surgery based on degree of postoperative inflammation. What is often striking, and

must be kept in mind by the treating physician in any OCP patient undergoing surgery, is the possible lack of conjunctival inflammation after surgery yet with eventual complete breakdown of corneal epithelium. In these cases, bandage contact lens or amniotic membrane with or without temporary tarsorrhaphy, along with intravenous corticosteroids, may be employed to abort the inflammation.

Once corneal blindness occurs, keratoplasty is required to restore vision. Anterior segment inflammatory disease is a risk factor for corneal graft rejection, owing to increased cytokine production, upregulated expression of HLA-DR in the graft, and facilitation of lymphocytic migration via increased expression of adhesion molecules [109]. Also, penetrating keratoplasty (PKP) alone is associated with poor visual outcomes in the setting of limbal stem cell deficiency. However, limbal stem cell allograft has a better survival rate, with proper systemic and topical immunosuppression, in other causes of conjunctival cicatrix such as chemical injury and AKC [110]. There are various approaches to limbal stem cell transplants, and the details are described elsewhere in this text and the literature.

Therefore, in the majority of cicatrizing disorders that lead to corneal blindness, especially OCP, atopic, SJS, and herpetic diseases, PKP has a lower long-term success rate and worse visual outcomes, in comparison to other indications such as pseudophakic bullous keratopathy and keratoconus. If one were to attempt PKP in the cicatrizing disorders, we recommend achieving disease quiescence with systemic therapy for at least several months (and possibly 1 year or longer in OCP), along with appropriate perioperative systemic and topical corticosteroids. These patients often require a keratoprosthesis (KPro) (Fig. 12.4) rather than a primary PKP in our experience, but this may represent a bias in our tertiary referral center. In patients who still have reasonable tear production and lid function, as well as fornix enough to retain the absolutely required bandage contact lens, we use the Boston KPro type 1 exclusively, because of the relative ease of its insertion and good retention rate. Of course, the viability of the keratoprosthesis is highly contingent upon the eye's inflammatory status and ocular surface health. Unfortunately, even when the surgery is successful and keratoprosthesis retained, the long-term visual outcome is suboptimal, with only 11% of the eyes achieving 20/60 vision [111]. A study at the Massachusetts Eye and Ear Infirmary examining KPro type 1 in OCP patients offers an even grimmer picture: only 1 of the 8 eyes had vision of 20/200 or better after a mean follow-up of 3.2 years [112] Therefore, keratoprosthesis remains a last resort in our practice, being offered only to patients who are on the verge of bilateral blindness. The osteo-odonto-keratoprosthesis (OOKP) and the Boston KPro type 2 may restore vision in those with advanced ocular surface disease, characterized by little to no tear production and poor lid closure, but these procedures are performed by at a limited number of centers in the USA and worldwide.

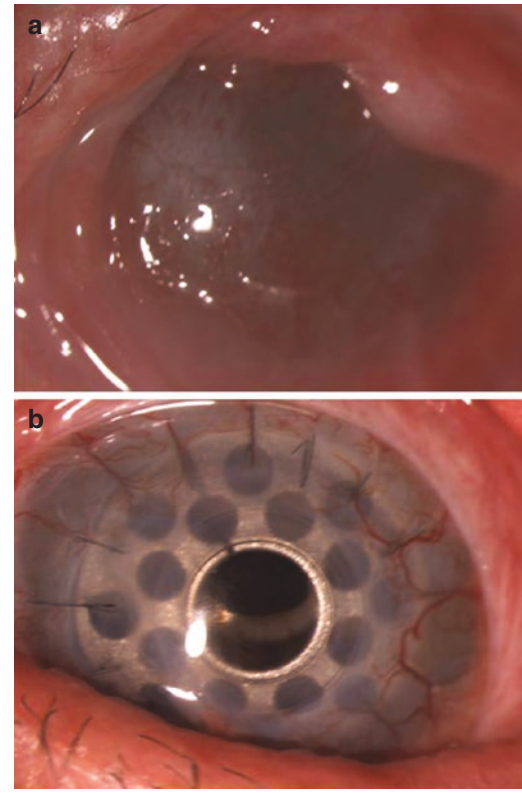

Fig. 12.4 Severe keratopathy, with thick keratosymblephara and neovascularization, in stage 3 OCP (**a**) requiring keratoprosthesis (**b**) for visual rehabilitation

Final Words

Cicatrizing disorders of the ocular surface can present a tremendous challenge to the ophthalmologist both in diagnosis and in management thereafter. It must be emphasized again that not all cicatrizing diseases of the ocular surface, when one fails to recognize the disease process via more definitive diagnostic means, are necessarily going to be cicatricial pemphigoid. A good understanding of the possible causes of this presentation in patients, and the ability to discern when more than one process may be at work, is key in the successful approach to management, especially when disease is particularly severe. The approach to successful management is contingent upon a thoughtful and open-minded yet appropriately aggressive approach, with action taken to preferably avoid secondary complications if possible by optimizing the ocular surface vis-à-vis successful treatment of systemic inflammatory disease as well as accompanying dryness, lid disease, and limbal stem cell deficiency. It is by these means that corneal opacification and neovascular changes may be avoided, which are the lasting and blinding results of uncontrolled cicatricial disease of the ocular surface. Lastly, as these diseases are often systemic in nature, the provider must recognize and address all suspected extraocular manifestations, which in time may present greater morbidity than ocular disease.

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