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Patient with Malignancies Calls for Eye Care Providers

Anna H[1], Szilagyi Z[2] and Barcsay-Veres A[2]*

[1]Department of Internal Medicine and Hematology, Semmelweis University of Medicine, Hungary

[2]Department of Ophthalmology, Semmelweis University of Medicine, Hungary

Abstract

Severe Meibomian Gland Dysfunction (MGD) is less known among clinical oncologist, although it causes great discomfort to their patients. This review helps to recognize and understood MGD and assist to be familiar with the therapy as well. Meibomian gland dysfunction is very common all over the world, the incidence is in the Caucasian population is up to 20%, and in the Asian population it is around 60%. Based on the literature, we expect MGD to be more common among patients with malignant diseases, but because of the primer cancer disease, it takes a back seat and we do not recognize it. Among patient with malignancies the MGD and tarsal conjunctival changes with excess lipid accumulation and topical inflammatory responses in the subconjunctival layer are not only caused by hormonal changes, but chemo-, radio- and biological therapy, too. However, ocular surface toxicity is becoming increasingly relevant in the management of patients on these agents. Although ocular adverse events are not directly life-threatening, but they are related to the patient's quality of life and should be given more attention by oncologists and hematologists, especially in patients with a promising long-term prognosis. We believe that prescribing any anticancer agent is enough to merit ophthalmic referral in order to establish an ophthalmic baseline and to lower the incidence of ocular adverse drug reactions with proper management plans.

Keywords: Meibomian gland dysfunction; Quality of life; Ocular adverse events; Solid tumors

Introduction

Meibomian gland dysfunction is very common all over the world, in the Caucasian population the prevalence of MGD is up to 20%, and in the Asian population it is up to 60% [1], it can cause everyday discomfort, dry eye, sever pain, itch to infections.

The function of the meibomian gland in the upper and lower eyelids is critical to maintaining homeostasis at the ocular surface. It is well known that meibomian gland dysfunction is the leading cause of evaporative dry eye disease and is one of the most common conditions encountered by eye care providers. The disorder is characterized by obstruction of the meibomian gland terminal ducts and/or changes in their glandular secretion, resulting in changes in tear film stability, inflammation, and symptoms of irritation.

The pathophysiology-based classification of the meibomian gland diseases includes the MGD. Any change in the amount or quality of the meibum alters the physiological role in the protection of the ocular surface. The low delivery form can be divided into hyposecretory or obstructive forms. Hyposecretion may occur primarily or secondarily to medications. There is a large number of ophthalmic and systemic medications related to MGD, e.g., antidepressants, antihistamines, isotretinoin therapy etc. The meibomian gland obstruction may occur as a result of cicatrization as well, as in trachoma, atopy or ocular pemphigoid. High delivery rate leads to dysfunction of the holocrine gland, as hypersecretion is the leading clinical sign in seborrheic dermatitis or acne rosacea. In conclusion, too much, too less, or altered quality of the meibum interferes with the microbiome predisposing the ocular surface to inflammation and infection. Furthermore, the tear film's physical parameters deteriorate with poor quality meibum; consequently, the ocular surface is more exposed to drying. Overall, MGD leads to eye irritation, clinically apparent inflammation and ocular surface disease, including dry eye.

Meibomian gland is considered as a hormonal target organ [2,3], estrogen level changes and DHEA (dehydroepiandrosterone sulfate) in both genders are diagnostic factors for MGD. Estrogen and progesterone are implicated in meibomian gland metabolism and regulate gene expression and lipid production in these holocrine glands [3]. Anti-androgens, postmenopausal hormone replacement therapy is associated with abnormal meibomian gland function. Subjective symptoms

Correspondence:
Horváth Anna, Department of Internal Medicine and Hematology, Semmelweis University of Medicine, 1085 Budapest, Maria u. 39, Hungary, Tel: +36-206632319;
E-mail: horvath.anna@med.semmelweis-univ.hu / annahorvath.bohus@gmail.com

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include foreign body sensation, puffy eyelids, irritation, grittiness, photosensitivity, blurred vision. Clinical signs depend on which progression stage the MGD is. First, the fibrotic process causes lid margin hyperemia with the opacity of the orifice. Later, the atrophic process results in periductal fibrosis accompanied with epithelial ridging, orifice's notching and absorption.

Thickened secretion under expression insufficiently covers the cornea, mostly producing meibomian foam at the lid margin. The toothpaste-like, thick meibum is unable to cover the ocular surface and promotes topical overgrowth of bacteria. Another preclinical sign is the appearance of the lids. Starting with hyperemia, later lid thickening and lid margin notching can still be asymptomatic. Later stages show distortion of the orifices anteriorly or complete dropout without any secretion; in neglected cases even loss of vision may result.

Even preclinical signs can be detected easily to screen oncologic patients. Should the patients have certain preclinical signs of MGD, special topical treatment may avoid a severe ocular surface disease? Thus, oncological medication related MGD is preventable in many cases if clinicians bear in mind this possibility.

Highly specialized meibocytes within the gland must differentiate and accumulate intracellular lipid droplets that are released into the tear film following rupture of the cell membrane [4]. Proteases and their inhibitors have been recognized as key players in remodeling extracellular matrices and in promoting the normal integrity of glandular tissue. They modulate a wide range of biological processes, such as cell proliferation and differentiation, and can contribute to disease when aberrantly expressed, or can be caused by malignancies or by their therapies as well [5,6] MGD caused by intrinsic factors (aging, ocular and general diseases) and by extrinsic everyday influences like contact lens wear and extended periods in front of computer screens, DES (resulting in TF instability, visual disturbances and chronic ocular discomforts are the major ophthalmic public health diseases of the present time affecting the quality of life of 10% to 30% of the human population worldwide [7]. MDG appears more often if there is a malignancy at the background, even more if the patient received therapy to cure it such as chemo-, radio-, endocrine- and biological therapy.

Chemotherapy

After iv chemotherapy high incidence of accompanying meibomian gland loss in cases of Lacrimal Drainage System (LDS) obstruction, reflex tearing by meibomian gland dysfunction should also be considered for proper management of tearing was observed. Early recognition and management of LDS stenosis could result in patients undergoing surgery with a lower burden [7]. Orally given anticancer chemotherapy combination as tegafur, gimeracil, and oteracil potassium can cause MGD, too [8].

Radiotherapy

Eyes that received periocular radiotherapy exhibited relatively high tear film instability induced by meibomian gland dysfunction, contributing to the high severity of dry eye symptoms [9-11].

Hormonal Therapy

In breast cancer treatment, the subsequent hormonal therapy, the subsequent hyperandrogenism and the early sudden menopause, may be responsible for ocular surface system failure and its clinical manifestation as dry eye disease. This local dryness is part of the breast cancer iatrogenic dryness, which affects overall mucosal tissue in the fragile population of those with breast cancer. The role of sex hormones on dry eye pathogenesis is most likely the result of a strict crosstalk between the protective androgens effects and the androgen-modulating effects of estrogens on the meibomian glands. Patients with a pathological or iatrogenic hormonal imbalance, such as in the case of breast cancer, should be assessed for dry eye disease, as well as systemic dryness, in order to restore their social and personal quality of life [12]. Women undergoing aromatase inhibitor treatment (AI) for early-stage breast cancer had worse meibum expressibility score and increased pain perception compared to an untreated group of women [13,14]. The first signs can be seen as early as the third month of AI therapy, and longer duration with higher tear osmolarity may increase the risk of DED and MGD [15].

Androgen levels were associated with significant changes in relative meibomian gland function. Subjective symptoms, such as dryness and foreign body sensation, were more obvious in prostate cancer patients receiving ADT, which may be caused by MGD and demodex infection. More attention is recommended to be paid to the ocular surface in prostate cancer patients taking ADT by performing examination of NI-BUT (Non-Invasive Break-Up-Time) and meibomian gland morphology and function with a view to providing more comprehensive prevention and treatment protocols [16].

Biological Therapy

Tyrosinase inhibitors, monoclonal antibodies, mTOR inhibitors, antibody-drug combinations and several targeted agents have been found to be associated with ocular side-effects due to their specific targeting of activities in the eye. We mention a few here. Cetuximab causes corneal lesions, meibomian gland dysfunction, periorbital and lid dermatitis, blepharitis and conjunctivitis [11]. Erlotinib, Gefitinib tyrosine kinase inhibitor that inhibits the activity of tyrosine kinase at the Epidermal Growth Factor Receptor (EGFR) and has been widely used to treat non-small-cell lung cancer is related to various ocular toxicities, mainly on the ocular surface, and perifosine has been reported to be associated with severe keratitis. EGFR is expressed in various ocular structures, including hair follicles, meibomian glands and corneal, limbal, and conjunctival epithelium. In hair follicles, the EGFR cascade regulates the transformation from anagen or the growth phase to catagen or the regressive phase. For meibomian gland morphogenesis, EGFR signaling activation stimulates meibomian gland epithelial cell proliferation. EGFR signaling pathway functions through multiple downstream signals such as ERK, Rho/ROCK and integrin and is regulated by a variety of upstream signals including ADAM17, GPR48 and FGFR signaling [17].

Trastuzumab is a humanized monoclonal antibody that acts by binding to the extracellular juxtamembrane domain of Human Epidermal growth factor Receptor type 2 (HER 2). By down-regulating downstream signaling cascades, trastuzumab is useful in inhibiting proliferation and the survival of HER2-dependent tumors, mainly breast cancer and advanced gastric cancer. *In vivo*, trastuzumab was found to inhibit corneal neovascularization [18] and MGD of trastuzumab in human subjects [19]. In a study on a related compound, trastuzumab-DM1, a HER2 antibody-cytotoxic conjugate, adverse ocular effects were reported to be 31% such as dry eyes, increased lacrimation, mild subjective blurring of vision and conjunctivitis [20].

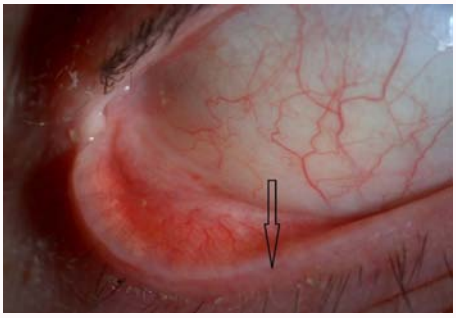


Figure 1: Early Meibomian gland's changes. On slit-lamp photo at the lid margin plugged and blocked meibomian gland's orifices can be seen. Beside hypersemia the lid margin is notched, the mucocutaneous junction is displaced retrogradely.

Table 1: Expressibility and the quality of meibum and the grading of MGD [21].

Grade	Expressibility = the expressed volume	The quality
0	normal	clear (normal)
1	2-3 times increased	cloudy
2	>3 times increased	cloudy with particles
3	>10 times increased	inspissated

Preclinical Signs of MGD

Preclinical signs can be detected through gland expression. Applying pressure to the eyelid margins helps to assess the texture of the meibum (Figure 1). Normal gland expression yields an easily spreadable, clear, smooth lipid layer sufficiently covering the cornea. Expressibility of meibum helps grading the severity of MGD and the expressed meibum quality grade [21] gives another aspect to grading the progression of MGD (Table 1).

Thickened secretion under expression insufficiently covers the cornea, mostly producing meibomian foam at the lid margin (Figure 2), moderate MGD. The toothpaste-like, thick meibum is unable to cover the ocular surface and promotes topical overgrowth of bacteria.

Another preclinical sign is the color change appearance of the lids (Figure 1). Starting with hyperemia, later lid thickening and lid margin notching can still be asymptomatic. Later stages show distortion of the orifices anteriorly or complete dropout without any secretion. Before further signs develop, slit-lamp examination is a preferable device to detect changes on the ocular surface, lid margin and the tear film layer.

Non-invasive meibography uses infrared light to visualize the glands. Partial or total dropout is visible *via* transillumination with white light or infrared imaging. Extensive dropout indicates increasing dryness as a consequence of evaporative water loss from the eye. There are clinical grading scales, e.g., Five-grade meiboscale [22] to help the clinical practitioner the objective clinical record keeping (Table 2). Grading the severity of MGD with the help of meibography measuring the area of acini and ducti, such scales are used for diagnosing (Table 3), monitoring of the disease and monitoring the effectiveness of a therapy, too.

In the everyday ophthalmology practice, more comprehensive grading is presented according to Tomlinson [23] includes the morphologic features (eyelid margin, orifices, main duct and acini) with the help of combining the measures an aggregate MGD score can be generated. Assessing the eyelashes and the skin, the lid margin tear film stability and lipid layer appearance can be graded with the help of slit-lamp or special devices. The ocular surface staining is for checking the viability of the ocular surface epithelial layer. At the end the digital gland expression helps differentiate the quality and quantity of Meibom.

Table 2: MGD grading the severity with meibography measuring the percentage loss of acini and ducti area [22].

Degree	Area of Loss:
0	0%
1	<25%
2	26%-50%
3	51%-75 %
4	75%<

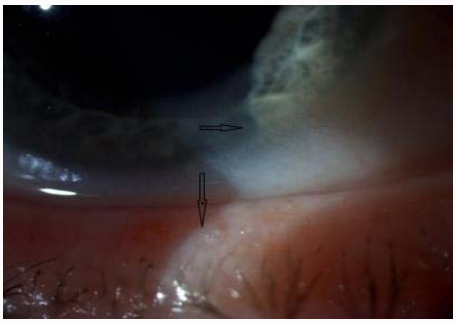


Figure 2: Moderate Meibomian gland dysfunction. This slit-lamp photo demonstrates progressed changes on the conjunctiva and the lid margin. Vertical arrow is pointing to lid margin's irregular vascular engorgement. The expressed meibum is cloudy. Horizontal arrow shows widened limbal vascular arcades indicating subclinical ocular surface inflammation.

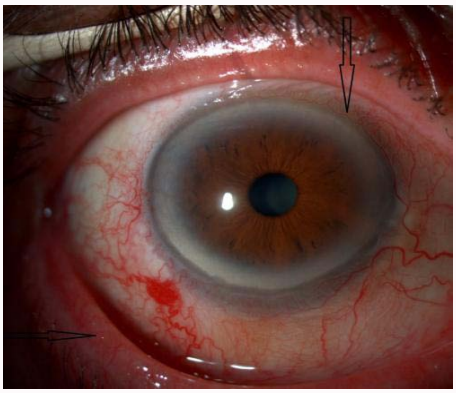


Figure 3: Severe Meibomian gland dysfunction with related ocular surface inflammation. At the slit-lamp photo the lid margin is thickened, the secretion is also thickened and decreased (horizontal arrow). Perilimbal capillaries widened, engorged extensively (vertical arrow). The ocular surface suffers from clinically apparent inflammation accompanied with severe subjective symptoms and visual deterioration.

A clinician first must assess the symptoms, and observe the ocular surface (Figure 1, 2) and send the patient to the ophthalmologist. Do not wait till the patient severe ocular surface inflammation related to severe Meibomian gland dysfunction transforms to chronic disease! The neovascularization can progress and the conjunctival vasculature overgrowth to the cornea causes scarring and severe, permanent visual deterioration (Figure 3, 4). Severe MGD-related ocular surface inflammation causes permanent visual deterioration (Figure 5).

Table 3: Clinical grading of MGD.

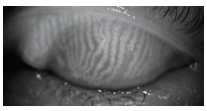
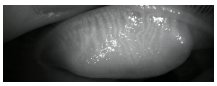
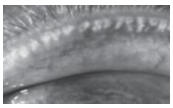
Grade of MGD	Clinical signs	Meibom gland change	Meibography
preclinical signs	● hyperemia the lid margin is notched ● the mucocutaneus junction is displaced retrogradely	● expressibility of meibum is normal ● the meibum is clear (normal)	● 0% loss of acini and ducti area 
mild signs	● hyperemia the lid margin is notched, ● the mucocutaneus junction is displaced retrogradely ● irregular vascular engorgement ● widened limbal vascular arcades ● subclinical ocular surface inflammation	● expressibility of meibum is 2-3 times increased ● the meibum is cloudy	● <25% loss of acini and ducti area 
moderate signs	● extended lid margin inflammation, ● dilated conjunctiva ● vessels overgrowing to the cornea resulting in a deforming pannus ● ocular surface inflammation	● expressibility of meibum >3 times increased ● the meibum is cloudy with particles	● 26%-50% loss of acini and ducti area 
severe clinical signs	● extended lid margin inflammation, ● dilated conjunctiva ● vessels overgrowing to the cornea resulting in a deforming pannus ● Permanent visual deterioration. substantial irregular astigmatism	● expressibility of meibum >10 times increased ● the meibum is inspissated	● >50% loss of acini and ducti area 

Table 4: Treatment options of MGD based on clinical signs.

Grade of MGD	Causative treatment	Active treatment	Supportive treatment
preclinical signs	stop using predisposing make-up products/procedures stop blockage of the orifici	support wetting the ocular surface with artificial tear drops	introducing Mediterranean diet reducing screen time or interrupting it on a regular basis enhance the secretion of Meibomian glands with massage
mild signs		above measures plus tea tree oil/ terpinen-4-ol treatment lipid supplementing artificial tear drops	moist hot enhancing the purging of orifici
moderate signs		above measures plus anti-inflammatory eye drops mild steroids, tear gels and combined tear products	intense pulsed light therapy Rexon eye® treatment LipiFlow treatment
severe clinical signs	above measures ± if it possible change or suspend the anticancer medication	above measures plus anti-inflammatory steroid, ciclosporin or lifitegrast eye drops systemic/local azithromycin	intense pulsed light therapy Rexon-eye® treatment LipiFlow treatment

Treatment for MGD

The best treatment for MGD is prevention. Beyond diagnostic lid margin expression, the therapeutic expression results purging. Either with fingers or with cotton swabs or a Meibomian paddle a forceful expression of the glands helps to release the obstructive material from the gland. A forceful blinking on a regular basis is a less effective but easy way to maintain the continuous purging of the orifici. During the manual expression one has to squeeze the lids against each other or push the lid margin against a rigid object (e.g., cotton swab). The rigid object protects the eyeball from pressure/pressing and provides resistance in order to express the glands properly.

Heat facilitates the release of secretion, therefore dry heat or moist heat enhances the effect of therapeutic expression also proven clinically.

There is no gold standard treatment for meibomian gland dysfunction, but rather a diversity of options (Table 4) for current

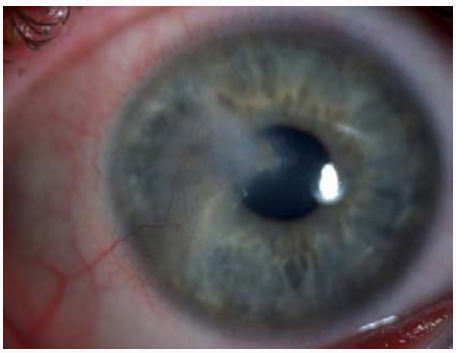


Figure 4: Severe ocular surface inflammation with non-reversible cornea complication originating from severe Meibomian gland dysfunction. Aggressive, clinically apparent ocular surface inflammation was related to severe Meibomian gland dysfunction. The neovascularization progressed and the conjunctival vasculature overgrowth to the cornea causes scarring and severe, permanent visual deterioration.

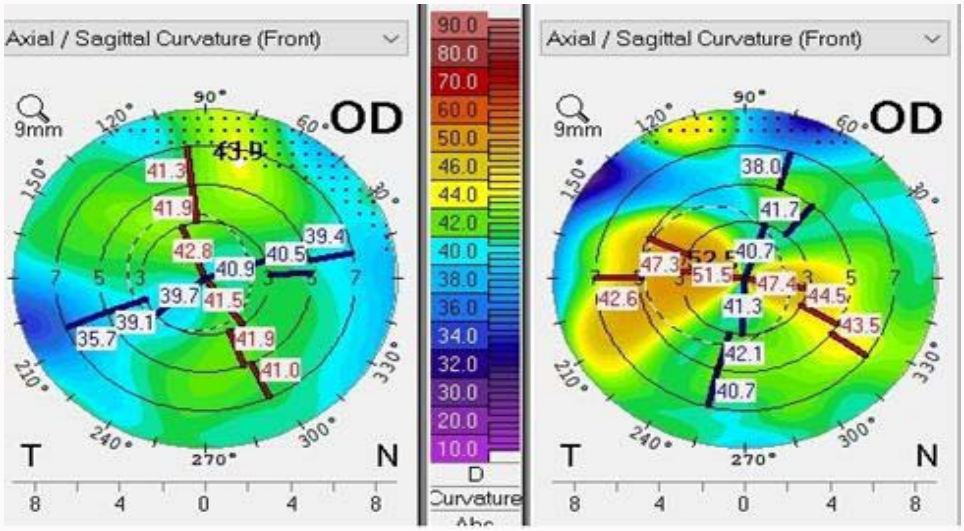


Figure 5: Severe MGD-related ocular surface inflammation causes permanent visual deterioration. Pentacam® ocular device measures the cornea curvature, density describing the anterior segment biometry. On the left panel the post inflammatory state left the patient's right eye with substantial irregular astigmatism. In this case the visual acuity cannot be improved not even with glasses or contact lenses. The right panel shows the same eye during the acute phase of severe ocular surface inflammation. The front axial curvature of the cornea enlarged because of the inflammation of the cornea and the overgrowing vessels resulting substantial visual distortion and blurred vision.

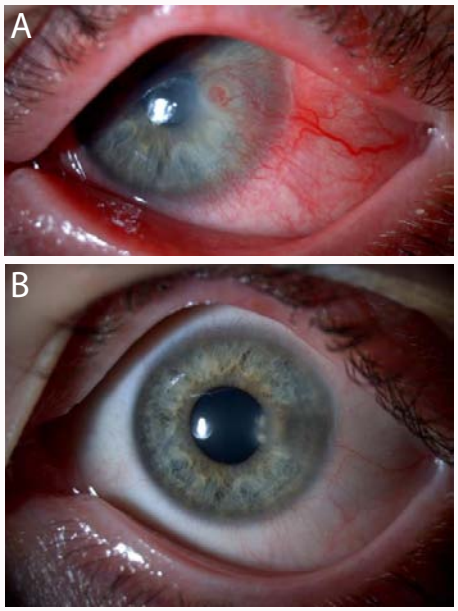


Figure 6: Severe ocular surface inflammation before and after treatment with ciclosporin eye drops. A) Active state with extended lid margin inflammation, dilated conjunctiva vessels overgrowing to the cornea resulting in a deforming pannus. B) Inactive state with white ocular surfaces without lid margin inflammation. The cornea bears a superficial scar involving the center as well leaving the patient with permanent visual deterioration.

treatment of MGD. Conservative measures include warm compresses and lid hygiene, but there is growing interest and need for medical treatments and procedures. Potential medical treatments include antibiotics, nonsteroidal and steroidal anti-inflammatory agents, essential fatty acid supplementation, hormone therapy. Tea tree oil is applied topically to the eyelid in the form of a scrub *via* eyelid wipes to control ocular Demodex infestations. Procedures include intraductal meibomian gland probing, the use of electronic heating devices, intense pulsed light therapy, and intranasal neurostimulation. Intense Pulsed Light (IPL) is a non-laser high-intensity light source in the wavelength range of 515 nm to 1200 nm that has shown to play a valuable role in dry eye disease. IPL is applied to the periocular area and the emitted light is absorbed by oxyhemoglobin in blood vessels on the surface of the skin. The raised skin temperature coagulates the red blood cells leading to thrombotic changes. Beside that IPL eradicates the parasitic and bacterial growth on the lids. Treatments are recommended on a regular basis, mostly 4 to 6 weeks apart. Recent evidence from various research works has shown that IPL modifies the mechanism of Meibomian Gland Dysfunction (MGD), which helps to relieve the symptoms of Dry Eye Disease (DED) [24].

The majority of clinical cases are mild or moderate where daily lid care routine and tear film supplementation alleviate the symptoms and signs. Even with subtle inflammatory signs Cyclosporin A (CsA), Lifitegrast (LG), or dexamethasone corticosteroid drops help to repress the key enzymes involved in the initiation or maintenance of the inflammatory response. To avoid the vicious circle of topical inflammation orally given Matrix Metalloproteinase (MMP) inhibitors stop the trigger effect of MMPs to worsen inflammation.

Different growth factors, like EGF, TGF, NGF, IGF, PDGF naturally constitute the tear fluid and the serum as well. For example, tear fluid contains EGF 0.2 ng/ml to 0.3 ng/ml, and the serum 0.5 ng/ml. Furthermore, the human serum contains many other growth factors in similar or even higher concentration compared to the human tear fluid. Diluted serum applied as eye drops offers a therapeutic benefit in corneal wound healing or ocular surface inflammation. Not only whole human serum, but amnion membrane extract (also instilled as an eye drop) may offer a good opportunity to enhance ocular surface regeneration. Amnion membrane extract contains fibronectin, EGF, TGF, collagen I, III, and V. to improve healing epithelial defects) [25].

Therapeutic effect can be guided by clinical signs or objective measurements, e.g., InflammaDry (Rapid Pathogen Screening, Inc., Sarasota, FL) which is a disposable, single-use, non-invasive, in-office assay that allows the measurement of the tear levels of MMP-9 [26,27].

As a new promising treatment intra-MG injection of the anti-VEGF agent bevacizumab- it demonstrates that the treatment is effective and safe in eliminating eyelid-margin vascularity, improving MG function and relieving clinical signs and symptoms of MGD [28], but do not forget, that bevacizumab could potentially disrupt intrinsic ocular circulation and lead to the development of thromboembolic events; there are rare reported cases of optic neuritis or optic neuropathy [29].

MGD even in very severe form can be successfully treated (Figure 6).

Conclusion

Severe meibomian gland and tarsal conjunctival changes can appear in any stage among patients with cancer. The hormonal changes (estrogen, androgen), the chemotherapy, the radiotherapy (head and neck) and the biological therapy can lead to collapse of homeostasis at the ocular surface. The patient's complaint in early stadium only dry eye later grows to visual problems. Although ocular surface analysis in hematological patients before and after allogeneic hematopoietic stem cell transplantation: An implication for daily clinical practice 3, it is not for every patient with malignancy yet, but it should be. We all know ocular adverse events are not directly life-threatening; they are directly related to the patient's quality of life and should be given more attention to by oncologists and hematologists, especially in patients with a promising long-term prognosis. We believe that prescribing anticancer agents is enough to merit ophthalmic referral to establish an ophthalmic baseline and to lower the incidence of ocular adverse drug reactions with proper management plans.

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