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Case Report

Novel Meibomian Gland and Tarsal Conjunctival Changes Associated with Trastuzumab, Pertuzumab, and Anastrozole Treatment for Metastatic HER2 Positive Breast Cancer: A Case Report and Literature Review

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Anti-HER2 biological therapy anastrozole · Meibomian gland dysfunction · HER2+ breast cancer · Trastuzumab

Abstract
The aim of the study was to report a case of severe meibomian gland dysfunction (MGD) and conjunctival changes associated with trastuzumab, pertuzumab, and anastrozole therapy in a HER-2 positive breast cancer patient. A 57-year-old white woman was treated with trastuzumab and pertuzumab biological and anastrozole endocrine therapy for metastatic breast cancer for several months. She suffered from intense eye pain and foreign body sensation. On the ocular surface, severe MGD developed without corneal lesions. On the tarsal conjunctiva, circumscribed lesions evolved 6 months after receiving anticancer therapy. After biopsy, the histological assessment excluded metastasis or chalazion. The lesion consisted of subepithelial lymphocytic infiltrates surrounding lipid-laden CD68-positive macrophages. Besides the redundant lipid accumulation, no acute necrotic reaction was seen. Noncontact infrared meibography visualized ductal drop-out in the upper and lower lids, and functional tests confirmed severe MGD. During the 18-month follow-up, the patient received treatment for MGD and no new conjunctival lesions developed, subjective symptoms subsided, and

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ocular surface morphology remained unchanged. The novel HER2-inhibitor trastuzumab and pertuzumab biological therapy and anastrozole endocrine therapy were associated with the disruption of the ocular surface milieu. The new histological aspect of tarsal conjunctiva changes may give a hint to understand the potential underlying molecular mechanisms of anticancer therapy-associated severe MGD. Since anticancer therapies may substantially interfere with the ocular surface milieu, awareness of this side effect leads to improved care of oncology patients.

Introduction

In the USA, over 1.91 million new cancer cases are predicted for 2022 [1]. Cancer therapies are getting more and more effective at preventing cancer-related deaths; however, the ophthalmic side effects appear to be around 20% and might deteriorate the quality of life [2–5]. The most common severe adverse events included severe conjunctivitis (1–13%), "visual disturbances" (0.8–64%), corneal perforation, and retinal vascular occlusion (<0.1%). The ocular side effects are often underreported or overlooked [2–5].

This publication reports a brand new observation with a 1-year follow-up of a metastatic breast cancer patient treated with chemotherapy, anti-HER2 biological therapy, and anastrozole (AI) adjuvant endocrine therapy. As of now, no human histopathological findings are reported of the meibomian gland dysfunction (MGD) associated with anti-HER2 and AI therapy.

Trastuzumab (Herceptin™, HER) and pertuzumab (Perjeta™, PER) are humanized monoclonal antibodies that bind the extracellular juxtamembrane domain of the HER2 protein. They are approved for HER2 positive tumors, like breast cancer, lung adenocarcinoma, or gastric carcinomas. The binding of these monoclonal antibodies inhibits cellular proliferation and differentiation of cancer cells and may interfere with non-cancer but HER2 protein-bearing cells as well. Only a few reports of ocular surface disorders are associated with oncologic therapy: spectrum of corneal changes [6], or increased lacrimation (21%), and severe conjunctivitis (2.4%) are reported in patients treated with HER, whereas the agency label lists dry eye and increased lacrimation among common (1–10%) ocular adverse events. PER treatment was associated with increased lacrimation in more than 10% [2–4, 6].

Understanding the side effects is critical for early recognition and prompt management, since the preservation and the protection of the ocular surface balance provide many times the paramount importance for the well-being of oncology patients. Our case corroborates the importance of ophthalmological screening and follow-up of cancer patients.

Meibomian Gland Dysfunction

Oncological Treatment

A 57-year-old white woman was diagnosed with a LumB-HER2 positive, T4N1M1 metastatic ductal breast carcinoma without BRCA1/2 mutation. The Semmelweis University Oncology board advocated her treatment regime in April 2019.

At baseline, the patient had no ocular symptoms. The ocular surface was checked with a pen light and no ocular change was noticed.

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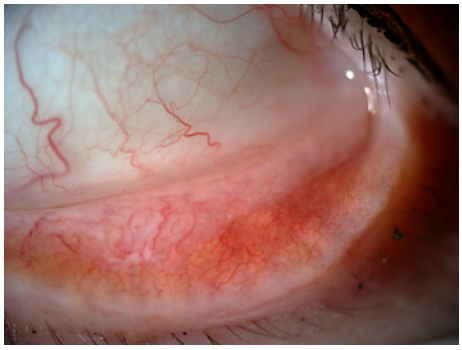

Fig. 1. Slit lamp photo of ocular surface changes associated with HER, PER, and AI therapy.

The patient was treated according to the ESMO Clinical Practice Guidelines. First, she had been treated with chemotherapy and biological triplet therapy, consisting of docetaxel (TXT), HER, and PER (HER + PER) from December 2019. Unfortunately, the TXT therapy resulted in severe side effects, i.e., nausea, numbness in her feet, hair and nail loss, fatigue, anemia, diarrhea, and skin and mouth dryness, and therefore, TXT therapy was abandoned in May 2020. In June 2020, AI endocrine hormone therapy was initiated, coupled with her ongoing HER + PER therapy.

Since the third 3-weekly dose (in the 10th week) of PER + HER, she started to experience ocular discomfort and increased lacrimation bilaterally. At this stage, no ocular examination was carried out by an ophthalmologist or no topical eye medication was administered. In July 2020, after the TXT stopped, the patient re-reported fluctuating moderate to severe eye discomfort worsened. Ocular symptoms had peaked between the 3rd and 8th day following each dual PER + HER infusion. As eye symptoms further deteriorated during the HER + PER + AI regime, in July 2020, the patient's well-being allowed an ophthalmic evaluation. This took place after the 8th circle of the HER + PER infusion, when the patient suffered from her constant stabbing eye pain.

Ocular Findings

The patient reported that her symptoms evolved gradually, in temporal association with the HER + PER treatment. Symptoms included bilateral foreign body sensation, photophobia, increased lacrimation, and severe eye pain, leaving the patient with sleeping disorder. The maximum symptom severity was reached between the 3rd and 8th days of the PER + HER infusion.

Her best corrected visual acuity was 1.0 (decimal Snellen) in both eyes for near and far. Intraocular pressures were normal. The Schirmer test without topical anesthesia showed low tear secretion (8 mm for the right and 11 mm for the left eye). Tear meniscus height measured with fluorescein dye was low; lid parallel conjunctival folds (Lipcof) were higher than her tear meniscus height in concordance with her dry eye symptoms.

Slit lamp microscopy revealed diffuse conjunctival injection and lid margin telangiectasias with increased vascularity. Meibomian gland expressibility was very limited (grade 3 or absent) with meibomian gland orifice drop-out (Fig. 1). The duct appearance showed orifice atresia, indicating a severe MGD with a globular or abnormal color fringe lipid pattern with tear interferometry (LacryDiag Ocular Surface Analyzer; Quantel). Furthermore, the middle part of the lower tarsal conjunctiva showed a couple of yellowish spherical lumps scattered around. Their size differed between 1 and 4 mm, having a shiny, streaked appearance with circumscribed thickening without fluorescein staining. Bulbar conjunctiva showed some staining, but the cornea remained intact (Oxford scheme 1). Bacterial swabs did not confirm bacterial overgrowth of the conjunctiva. The pupil assessment, the anterior eye examination, and dilated fundoscopy revealed no abnormality.

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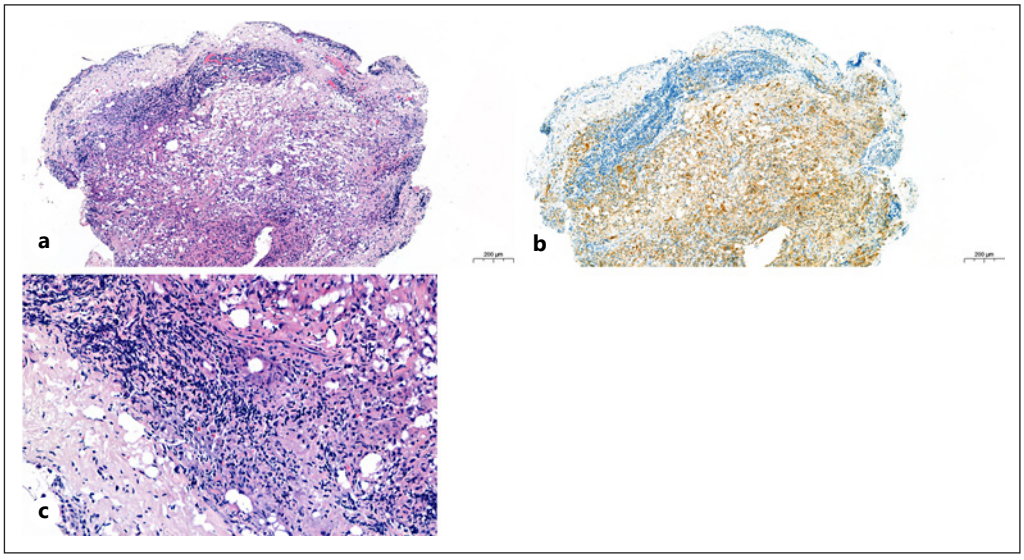

Fig. 2. Histological and immunohistochemical characterization of the excised conjunctival lesion. **a** Low magnification (×50) hematoxylin and eosin stain of biopsy demonstrating a thinned epithelial cell layer. In the stroma, a massive, band-like lymphoid layer was seen, composed of inflammatory infiltrates and dilated capillaries. **b** Low magnification (×50) of immunohistochemical findings confirmed large groups of CD68 positive macrophages. Their cytoplasm contained dissolved lipids with large vacuoles. **c** High magnification (×200) shows lipid-laden macrophages.

Histopathological Findings

Because of the long-lasting, unbearable ocular foreign body sensation and the suspicious tarsal conjunctival elevated lesions, conjunctival biopsy was carried out under local anesthesia. Histopathology (Fig. 2) showed thinned conjunctival epithelium. Dense, band-like inflammatory infiltrate composed of lymphoid cells was observed with dilated capillaries. Next to the lymphoid elements, large groups of CD68-positive macrophages were detected with vacuolated cytoplasm containing dissolved lipids. We do not describe this lesion as a chalazion since no chronic granulomatous reaction with numerous lipid-filled giant cells was revealed. The nuclei of the macrophages were not located around a central foamy cytoplasmic area. No acute necrotic reaction with polymorphonucleae cells were found. The specimen showed no HER-2 positivity, though normal conjunctival epithelial epidermal growth factor receptor (EGFR) positivity was detected with immunohistochemistry. No malignant cells were seen.

Follow-Up

Follow-Up of the Oncologic Patient

After 24 months of oncology treatment, the PET-CT showed stable disease on the first line therapy. ECOG PS: 0, Karnofsky index 95%

Ophthalmological Follow-Up

The patient was followed up regularly during a period of 18 months: in the first 4 months 6 weekly, later 3 monthly. Hot compress and lid hygiene, a conventional treatment for MGD, were suggested to the patient coupled with topical lipid-supplementing lubricants. The state of the orifices slightly improved, vascular engorgement decreased, but the presence of local gland dropouts did not change. After 2 months, the ocular surface balance improved, no

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corneal problems emerged, and the sight-threatening ocular adverse events were avoided. It was not necessary to discontinue the anticancer treatment since the subjective symptoms subsided as well. During the HER + PER + AI therapy administration, no new conjunctival elevated lesions appeared on the tarsal conjunctival surface. The anti-MGD therapeutic approach altered the meibomian gland function essentially. After 12 months of MGD treatment, the infrared meibography still showed about 40% of meibomian gland dropouts bilaterally; however, the TBUT improved to 10 s.

Discussion

The systemic chemo-, biological-, and endocrine therapies improved survival in metastatic malignancies [1] but may cause severe ophthalmic adverse events, too [2–8]. MGD is the leading cause of dry eye worldwide. The DEWS II report [9] summarized the tests for diagnosing and monitoring. During MGD, not only the insufficient lubrication but also the consecutive local inflammation impair the ocular surface's homeostasis. In turn, a primary ocular surface inflammation may induce abnormal meibomian gland function. The meibocytes (acinar cells) constantly differentiate from proliferating, non-lipid producing basal cells to nonproliferating, but lipid-accumulating mature cells. Through the holocrine secretion process, the hypermature cells rupture, and their content, the meibum, gets to the lid margin through a central excretory duct.

The most common mechanism for the development of MGD is the "ductal-centric" hypothesis [10]. The ducts suffer from cystic dilatation, and the acini undergo secondary atrophy. The stasis of the meibum is caused by the obstruction of the duct orifice through epithelial hyperkeratinization. By contrast, Hwang et al. [11] suggest a mechanism that is independent of the state of the ductal epithelium and emphasizes the differentiation and renewal of meiocytes. Acini are renewed by a single stem cell adjacent to individual acini, and proper function of meibomian glands depends on proliferation of its acinar cells. The continual loss of cells, stimulation of epithelial cell proliferation is important, and during biological therapy, the HER2 inhibition may result in inadequate cell differentiation.

The ErbB receptor family contains four members; its excessive signaling is associated with the development of a wide variety of solid tumors. ErbB1 is the first member of the EGFR family, namely EGFR. It is expressed in human meibomian gland epithelial cells as well, and its signaling increases the proliferation but not the differentiation [12]. EGFR activation promotes proliferation and inhibits differentiation of meibomian gland epithelial cells, and decreases processes related to fatty acid metabolism [13]. The HER2 receptor is the 2nd member of the EGFR family and can be involved in the regulation of epithelial cells; it may control cell growth, differentiation, or apoptosis (lateral signal transduction) [13]. HER2-inhibitors (HER, PER) get cells arrested in the G1 phase; therefore, survival and angiogenesis is suppressed. HER2 receptors are widely expressed both in the conjunctival epithelium and in the lacrimal gland [14]. The meibomian gland is a holocrine gland where apoptosis is needed for meibum production in acinar cells. During HER2 suppression, these apoptotic signals are not properly mediated, resulting in a lower grade of apoptosis, decreased meibum production, and very narrow orifices.

Our conjunctival specimen showed excessive conjunctival lipid accumulation accompanied by inflammatory cells including CD68-positive macrophages. It is known that MGD may be coupled with chronic ocular surface inflammation, so the meibomian gland may be the target of immune cells and immunotherapy as well. HER activates the FcgammaRIII antibody receptors on myeloid cells; therefore, antibody-dependent cell-mediated cytotoxicity is part of the antitumor activity [12, 13]. We may assume that HER causes inflammation

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around orifices, which may subsequently cause keratinization and fibrosis, leading to obstruction and subsequent tissue damage of the meibomian glands. However, there have been no detailed investigations pertaining to the effects of HER on the meibomian glands. Macrophages may be abundant in the conjunctiva due to allergic inflammation as well, but in our case, there was no sign of allergy on the ocular surface.

The oncologic therapy protocol often includes several different drugs, as in our case. There is some literature available regarding AI-related ocular diseases and TXT [4, 5, 15], but no HER or PER data. However, large prospective studies are lacking. In our case, TXT therapy may not be a sustaining factor since MGD deteriorated after it was stopped. Furthermore, the conjunctival mass evolved only after skipping TXT and was not a chalazion. The conjunctival biopsy excluded conjunctival metastasis and eliminated severe foreign body sensation. Since the anti-MGD treatment avoided severe pain and corneal ulcers, we highlight the importance of ophthalmic care in this patient population. This patient's example brought us new details of the pathophysiology of anticancer treatment associated with MGD and prompted us to implement new routines in the large population of cancer patients.

In case of no preexisting MGD or DED, close monitoring is suggested. In case of MGD, the patient should start dry eye therapy such as lipid-containing artificial tear drops, eyelid hygiene, and other MGD treatment. Close communication between oncologist and eye specialist may avert to seek alternative therapy or temporary drug holiday.

Our patient administered topical lipids supplementing artificial tear drops and performed lid care on a regular basis, and no new conjunctival lesions developed; however, the MGD was maintained and proven by meibography as well. Interferometry is an established technique for objective noninvasive clinical examination that allows visualization of the kinetics of the oily layer of the tear film and the morphology of meibomian ducts.

To our knowledge, there is no human report available regarding histopathological changes on the tarsal conjunctiva in association with anticancer therapy of humanized monoclonal antibodies. Considering the high incidence of cancer diseases and treatment-related ophthalmic adverse events, dialogue between oncologists and eye care providers is essential. The incidence and severity of ocular side effects are not known. Besides this lack of information, improved tumor patient survival calls for eye evaluation prior to initiating anticancer therapies, e.g., careful examination of the patient's ocular surface, including the meibomian glands. Our knowledge is guarded about who is more susceptible for ocular complications or how e.g., the individual ErbB receptor family genotype predisposes to ocular vulnerability during biologic treatment.

The present case report has some limitations. First, before the initialization of the anticancer therapy, no ocular slit lamp examination or meibography was performed. Although the patient could not recall any symptoms dating back to her pretreatment period, we may still have missed some preexisting ocular changes. Second, using a combination of compounds in anticancer therapy, different pathways are targeted, therefore a synergistic or potentiation effect could yield difficulties to address the potential associations between the treatment and the ocular changes. Our finding prompts us to plan a prospective study with a periodical ocular follow-up protocol to uncover the real prevalence and the underlying mechanisms leading to severe MGD in HER + PER + AI therapy.

Conclusions

To the best of our knowledge, this is the first report on HER2-receptor antagonist trastuzumab and PER therapy being associated with severe MGD with excess lipid accumulation and topical inflammatory response in the subconjunctival layer. Based on the literature, we

expect MGD to be more common, but because of the primer cancer disease, it takes a back seat and we do not recognize it. 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, they deteriorate the patient's quality of life and should be given more attention by oncologists, especially in patients with a promising long-term prognosis. We believe that prescribing anticancer agents 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.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

No conflicting relationship exists for any authors. There is no financial/personal interest or belief that could affect objectivity.

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Author Contributions

Amarilla Barcsay-Veres wrote the paper, carried out ocular examination of the patient, carried out conjunctival biopsy, and is the corresponding author. Zsuzsa Szilagyi carried out ocular examination of the patient and follow-up examinations. Jeannette Toth and Anna Maria Tokes revised the paper and carried out histological assessment. Eva Katalin Toth conducted the internal examination of the patient and anticancer therapy assessment. Zoltan Z. Nagy supervision of the paper. Anna Horvath revised the paper, conducted the internal examination of the patient, conceived the study design, and supervised.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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