Meibomian Glands and Ocular Surface Inflammation

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ABSTRACT The purpose of this review was to systematically analyze publications related to the role of meibomian gland disease in ocular surface inflammation, with special reference to meibomitis as an inflammatory form of meibomian gland dysfunction (MGD). Meibomian gland inflammation is often present with the ocular surface inflammation in conditions such as blepharokeratoconjunctivitis, ocular rosacea, and phlyctenular keratitis, but its contribution is often overlooked, especially in younger subjects. This can result in misdiagnosis, mistreatment, and, sometimes, severe visual impairment. We identified a related disease entity, seen predominantly in young patients, of ocular surface inflammation associated with meibomitis, which we termed *meibomitis-related keratoconjunctivitis*. Its specific clinical features are similar to those observed in the above-mentioned diseases, and the inflammatory form of MGD was found to be closely involved in the ocular surface inflammation seen in those four diseases, based on our statistical evaluation. The diagnosis and management of meibomitis, an inflammatory form of MGD, is vital for the successful treatment of the induced ocular surface inflammation. We propose that the ocular surface and the adnexal meibomian glands should be considered as one unit, i.e., the "meibomian gland and ocular surface" (MOS), when encountered in the clinical setting.

KEY WORDS blepharokeratoconjunctivitis, meibomian gland, meibomian gland dysfunction, meibomitis, meibomitis-related keratoconjunctivitis, ocular rosacea, phlyctenular keratitis

I. INTRODUCTION

We systematically analyzed the published reports related to the role of meibomian gland disease in ocular surface inflammation, with special reference to meibomitis as an inflammatory form of meibomian gland dysfunction (**MGD**). Although meibomian gland inflammation is often recognized with ocular surface inflammation in conditions such as blepharokeratoconjunctivitis (**BKC**), ocular rosacea, and phlyctenular keratitis, its contribution is often overlooked, especially in children, adolescents, and young adults, resulting in misdiagnosis, mistreatment, and sometimes severe visual impairment. As the findings of this review illustrate, focusing on the diagnosis and management of meibomian gland inflammation is critical for the successful treatment of ocular surface inflammation induced by the above-mentioned diseases.

II. THE MEIBOMIAN GLAND AND ITS ABNORMALITIES

According to a 1942 report by Scobee,[1] meibomian glands were first described by the German physician Heinrich Meibom in 1666, although their existence had been suggested by Julius Casserius in 1609. They are large, modified sebaceous glands that are embedded in parallel rows in the tarsal plates of the eyelids, numbering 30-40 in the upper lid and 20-30 in the lower lid.[2,3] Each meibomian gland consists of grape-like clusters of acini situated on either side of a central duct, the terminal part of which opens onto the cutaneous side of the lid margin.

Meibomian glands synthesize and secrete a mixture of lipids, termed meibomian oil or meibum,[4] which is delivered as a clear liquid via orifices located directly in front of the mucocutaneous junction. This facilitates the delivery of meibum to the tear film lipid layer and its spread during the upstroke of the blink over the aqueous subphase. The tear film lipid layer plays a critical role in retarding the evaporation of tear fluid from the preocular tear film, thereby protecting it from desiccating stress. It also enhances tear film stability by

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OUTLINE

lowering surface tension and preventing contamination of the tear film by sebum.[5] Disturbances of meibomian gland function that alter the quality and quantity of meibum can lead to tear film instability and evaporative dry eye.[6]

In 1980, Korb and Henriques introduced the term *meibomian gland dysfunction* to describe a condition of meibomian gland obstruction that is responsible for reduced delivery of meibum to the lid margin.[7] This term has been generally adopted to describe a condition that may or may not have inflammatory features, depending on its stage of development.[8,9] Historically, the concept of MGD was that of a hypersecretory disorder with obvious signs of infection and inflammation.[5,6,10,11] However, the current concept of MGD includes its initiation as a less obvious or nonobvious type of hyposecretory obstructive MGD, where signs of inflammatory pathology may be absent.[12] There are two forms of obstructive MGD: 1) simple, obstructive MGD, and 2) cicatricial MGD.[5,10] Simple MGD is primarily caused by a terminal duct obstruction due to hyperkeratinized duct epithelial cells and qualitative/quantitative changes in the meibum.[8,9] Cicatricial MGD is chiefly the result of traction on the terminal ducts and orifices by a scarring process in the tarsal plates, which occurs in diseases such as benign cicatricial pemphigoid and trachoma. MGD can result in symptoms of eye irritation, alteration of the tear film, clinically apparent inflammation of the lid margin, and ocular surface diseases.[13] In addition, MGD has received particular attention over the past two decades as the primary cause of both blepharitis and evaporative dry eye.[13]

According to a comprehensive review article published in 2009 regarding blepharitis in the U.S.,[14] the term *blepharitis* encompasses conditions that result from pathology associated with the pilosebaceous unit of the anterior lid and/or the meibomian glands of the posterior lid. Hence, blepharitis is clinically subdivided into two types: anterior and posterior. Anterior blepharitis is most often a product of bacterial overgrowth (in which case it is accompanied by collarettes around the eyelashes) and/or sebaceous gland disorder. The related inflammation may spread to the posterior lid margin, thus resulting in secondary MGD. Conversely, posterior blepharitis is almost always associated with MGD, yet may have different etiologies such as allergic or infectious conjunctivitis, drug toxicity, or acne rosacea.[10]

An additional meibomian gland disease of importance is the chalazion, also known as meibomian gland lipogranuloma, whose clinical features were well described in the 19th century.[15] The association between chalazia and meibomian gland disease was first theorized by Addaria in 1888, and it is now widely accepted that chalazia are primarily caused by the retention of the secretion of a meibomian gland.[16] Typically, no meibum can be expressed at the site of a chalazion due to obstruction of the associated meibomian gland orifices. This results in a secondary, granulomatous reaction in the acinar and periacinar tissues in response to meibomian gland lipid constituents.[5,17] MGD is defined as a "diffuse" abnormality of the meibomian gland, and a localized involvement of meibomian glands such as a chalazion is not considered to belong within the context of MGD.[13] However, a chalazion is an important sign of focal inflamed obstructive MGD, although it tends not to cause abnormalities in the ocular surface tear film.

Sebaceous carcinoma is a rare but important meibomian gland disease that occurs more commonly in women and in the elderly and is most usually observed in the upper eyelid. Both clinically and histologically, sebaceous carcinoma may masquerade as benign or less invasive conditions, such as chalazia, blepharitis, meibomitis, basal cell carcinoma, and carcinoma *in situ*, and this occasionally results in delay of diagnosis and treatment.[18]

The subject of this review is the group of acquired, symptomatic, non-neoplastic inflammatory disorders of the meibomian gland, with a special focus on their occurrence in children and young adults. Thus, no further discussion regarding congenital diseases[19,20] and neoplastic disorders[18,21] will be included in this report. An overall summary of the widely acknowledged meibomian gland diseases is shown in Table 1 (modified from the table by Tomlinson et al[22]).

III. DEFINITION OF MEIBOMIAN GLAND INFLAMMATION "MEIBOMITIS (MEIBOMIANITIS)"

There have been discussions in the past as to whether MGD is or is not an inflammatory disease. Prior to 1980, meibomian gland disorder was recognized as the inflammatory state of meibomian glands with hypersecretion that occurred in middle-aged subjects, often associated with seborrheic blepharitis primarily caused by bacterial infection (especially *Staphylococcus aureus [S. aureus]*).[16] McCulley et al reported that primary meibomitis appears not to be a primarily infectious entity but represents a facet of generalized sebaceous gland dysfunction that it is found in association with seborrheic dermatitis or acne rosacea.[23] However, the presence of obstructive MGD without inflammation