Commentary: Demodex – Microscopic residents of the ocular biome

"Blepharitis acarica," a clinical entity characterized by relentless eczematous blepharitis was one of the initial reported ocular diseases caused by the mite *Demodex*.[1] The prevalence of the disease is reported to be 25–30% in patients with blepharitis, however, the prevalence is seen to increase with age and affects men and women alike.[2] *Demodex* is known to incite inflammatory and allergic reactions by mechanical blockage of hair follicles in patients of rosacea in whom the mite density is found to be higher.[3] Similarly, mite density is reported to be higher in patients suffering from Sjogren's syndrome and other immunocompromised states such as Human immunodeficiency virus (HIV). In addition to populating the skin, they are found abundantly in the eyelash follicles, enveloping them in the characteristic cylindrical dandruff-like fashion (Demodex folliculorum), or in the sebaceous glands (Demodex brevis) of the eyelids.

Ocular demodicosis is an umbrella of various clinical scenarios caused by *Demodex*. The range of clinical manifestations of ocular demodicosis is wide and the course of the disease is often unabating. Demodex mite has been reported to cause meibomian gland dysfunction, chronic anterior blepharitis, blepharokeratoconjunctivitis, trichiasis, madarosis, tear film instability, dry eye, recurrent chalazion, conjunctival inflammatory nodule, and has also been reported to mimic sebaceous gland carcinoma.[4] The corneal findings are characterized by peripheral or central stromal infiltration with neovascularization, limbitis, superficial punctate keratopathy, and corneal perforation. Keratitis is more commonly bilateral and characteristically associated with blepharitis. Demodex brevis is hypothesized to have higher keratotoxicity as compared to Demodex folliculorum which is demonstrated by Langerhans cell infiltration in the corneal tissue and change in tear cytokine levels, Interleukin-17 (IL-17) in particular.[5,6]

The association between ocular surface inflammation and demodex appears to be bidirectional. While *Demodex* is known to incite the inflammatory cascade which leads to corresponding ocular surface manifestations, it is increasingly reported to be co-existent in patients with pre-existing ocular surface issues such as herpetic stromal keratitis, atopic keratoconjunctivitis, and severe dry eye.[7] *Demodex* acts as a catalyst in the vicious cycle of inflammation in these patients. It seems to aggravate the hypersensitivity immune responses such as type I hypersensitivity response in atopic keratoconjunctivitis and types III and IV hypersensitivity responses in herpetic stromal keratitis. This can explain why often treating an HSV or allergic keratitis as per recommended clinical guidelines does not provide gratifying results because of our inattention toward diagnosis and treatment of the concomitant lid affliction caused by *Demodex* in these patients.

Kim *et al*.[7] report a significant decrease in tear concentrations of IL-1β and IL-17, which was correlated with substantial clinical improvement following treatment of demodex blepharitis with tea tree oil. IL-1 is a potent inducer of inflammatory cytokines such as IL-6, IL-8, Tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GMCSF). It is known to stimulate the production of collagenase and matrix metalloproteinase (MMP) enzymes which cause destruction of extracellular matrix and ocular surface inflammation.[8]

While IL-1 is involved in various immunological paths and processes, IL-17 secreted by an activated helper T cells subset called "Th17," is a key mediator specifically in inflammatory and autoimmune conditions. Developmentally distinct from Th1 and Th2, Th17 are IL-17 secreting cells that propagate production, distribution, and activation of neutrophils.[9] IL-17 further activates T cells to produce a variety of cytokines, adhesion molecules and causes upregulation of gene expression. IL-17 is also a potent inducer of angiogenic chemokines such as vascular endothelial growth factor-A (VEGF-A), vascularization being a prominent clinical finding in demodex-associated blepharokeratoconjunctivitis.[10] Reduction in tear levels of IL-17 after Demodex treatment has been shown to correlate with both a decrease in vascularization and ocular surface inflammation. The review article by Pan *et al*.[11] in the current issue describes a similar scenario in patients with meibomian gland disease (MGD) which can be explained by the complex game of inflammatory mediators at the cellular level.

While the inflamed eye fixates our attention, we recommend careful examination of the eyelashes in all patients. Simple epilation along with rotating of lashes before epilation as described by Mastrota *et al*.[12] and evaluation under light microscopy or *in vivo* confocal microscopy can largely aid in spotting the mite. Following positive results, lid scrubs with an equal concentration of tea tree oil and olive oil and two doses of oral ivermectin (200 ug/kg, 1 week apart) are advised along with tapering doses of soft steroids and lubricants.[13] Correct diagnosis and targeted therapy of demodex can significantly

cut short ocular morbidity in these patients and prevent sight-threatening sequelae.

Aastha Singh, Manisha Acharya, Umang Mathur

Department of Cornea and Anterior Segment Services, Dr. Shroff's Charity Eye Hospital, New Delhi, India

Correspondence to: Dr. Manisha Acharya, Department of Cornea and Anterior Segment Services, Dr. Shroff's Charity Eye Hospital, 5027, Kedarnath Marg, Daryaganj, New Delhi - 110 002, India. E-mail: macharya@sceh.net

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