

OCULAR ROSACEA AND ZONOTIC DEMODICOSIS

By

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Abstract

Among the temporary skin ecto-parasites, *Demodex folliculorum* is a worm-like mite that infests hair follicles in various mammals including man. Rosacea is a common skin disorder that may occur in adults of all ethnic backgrounds, but is most commonly diagnosed in individuals with fair skin. Ocular rosacea may present independently or in association with cutaneous subtypes of rosacea. This study clarified the correlation between ocular rosacea and demodicosis *folliculorum* in family patients; two females of them were superimposed with secondary bacterial infection. The patients acquired in zoonotic infestation from their pet dog. The pet dog was sent to the Governmental Veterinary Hospital at Abbassia and was treated with Ivermectin[®].

Specific ocular infections often required etiological diagnosis of combined consultant ophthalmology and microbiology

Key words: Patients, Ocular rosacea, *Demodex folliculorum*,

Introduction

Rosacea is a chronic inflammatory facial disease occurring world-wide. Pathogenesis of rosacea is not completely understood, but neurovascular and immunologic mechanisms are involved (Alexis *et al*, 2019). This dermatologic condition was classified by the National Rosacea Society into four subtypes based on the clinical features: 1- erythematotelangiectatic rosacea, 2- phymatous rosacea, 3- papulopustular rosacea, and 4- ocular rosacea (Wilkin *et al*, 2002). Ocular manifestations were defined as one of the secondary criteria leading to morbidity, if not well diagnosed and managed (Vieira and Mannis, 2013). Ocular rosacea may occur in the presence or absence of other dermatologic forms, its features include foreign body sensations, blepharitis, lid margin telangiectasia, tear abnormalities, meibomian gland inflammation, frequent chalazion, conjunctivitis, and rarely, corneal ulcers or vascularization (Stone and Chodosh, 2004). Wollina (2019) reported that rosacea may develop as a manifestation of systemic diseases with a significant morbidity and even mortality as obesity, *Helicobacter pylori*, smoking, and inflammatory bowel disease, metabolic, psychiatric, and neurologic disorders and certain types of cancer showed a significant association with rosacea.

Ocular rosacea (roe-ZAY-she-uh) is inflammation that causes eye redness, burning and itching, often developed in people who have rosacea, a chronic skin condition that affects the face. Rosacea is a multifactorial chronic inflammatory disease with various clinical manifestations. Primarily, it is seen as a dermatological condition, but common to develop ophthalmological implications affecting eyelids, cornea and conjunctiva, but sometimes ocular rosacea is the first sign & that patient may later develop the facial type (Trufanov and Shakhbazyan, 2018). Patients with rosacea may develop severe sebaceous gland growth accompanied by papules, pustules, cysts, and nodules. Inflammatory lesions develop in the areas of erythema and appear identical to the inflammatory lesions of acne vulgaris, with the exception of a lack of comedones in rosacea (Quarterman *et al*, 1997). Some patients experience burning or stinging sensations. Ocular symptoms occur in many patients with rosacea, most commonly in combination with skin symptoms, but occasionally alone (Akpek *et al*, 1997). Eye involvement may include foreign body sensation and burning, telangiectasia and irregularity of lid margins, meibomian gland dysfunction (posterior blepharitis), keratitis, conjunctivitis, and episcleritis (Oltz and Check, 2011). The cause of vascular dilatation

in rosacea is unknown, although factors that trigger innate immune responses may worsen symptoms (Yamasaki *et al*, 2007). The hair follicle mites *Demodex folliculorum* and *D. brevis* played a role in the pathogenesis of the inflammatory lesions; increased numbers of mites in the rosacea patients' skin compared with unaffected individuals (Roi-hu and Kariniemi, 1998). On the other hand, in a study of patients with rosacea treated with tetracycline for one month, mite counts did not decrease despite an improvement in rosacea symptoms (Bonnar *et al*, 1993).

This study aimed to clarify the correlation between ocular rosacea and the hair follicle mites in a family members and their pet dog.

Materials and Methods

A family of six members, father, mother, three girls and one boy were referred with signs and symptoms of redness, burning, feeling like something is stuck in their eyes, and clogging of the eyelids oily glands. Besides, the mother and the three girls suffered from swelling on their eyelids and at the base of eyelashes.

All the patients underwent complete ophthalmic examination under a slit lamp biomicroscope. Examinations of ocular manifestations were performed on the eyelids (erythema, telangiectasia, and meibomian gland secretion), conjunctiva (injection and papillary hypertrophy), and cornea (erosion, opacity, and other corneal abnormalities). The tear film break-up time and the Schirmer test measured the amount of tears, using topical anesthesia to avoid reflex tearing by ocular irritation due to corneal erosion or physical contact with the Schirmer strip.

The Schirmer test was performed 5 minutes after the application of the anesthetic. Then, they underwent epilation of eight eyelashes (two eyelashes in both upper and lower eyelids) and the number of follicular mites was counted with an optical research microscope. The lashes were epilated with cylindrical dandruff around the root of the lash as deeply as possible and examined for mites.

Results

The identification of the follicular mites proved to be *Demodex folliculorum*. The patients were diagnosed rosacea due to demodicosis with density highly exceeded the normal fauna (>5 mites/cm²). To identify bacteria on the eyelids relative to the presence of *Demodex*, bacterial cultures were done for the six patients. After squeezing the meibomian gland, the discharge was scraped with a sterile cotton tip without touching the eyelid skin. On blood agar plate the discharge proved to contain *Staphylococcus aureus*, and antibiotic sensitivity test was done (Sharma *et al*, 2002).

Discussion

Generally, the ocular involvement occurred in more than 50% of patients with rosacea (Ghanem *et al*, 2003). Ocular rosacea may be preceded by 20%, followed by 50%, or occurred concurrently with cutaneous disease (van Zuuren *et al*, 2011). Nevertheless, both adults and children may be affected (Chamaillard *et al*, 2008).

In the present study, *D. folliculorum* was accompanied with *Staphylococcus aureus* secondary infection only in the mother and her old daughter. Ocular infections may be caused by bacteria, fungi, parasites, or viruses, and each of these may produce a spectrum of disease and exogenous infections are most common, eye infection may develop by spreading from neighboring organs or hematogenously (Mohammed *et al*, 2017). Jacob *et al*. (2019) stated that human demodicosis was linked to bacterial folliculitis, rosacea, and other common skin conditions.

Demodex mites are the commonest microscopic ecto-parasite infesting human skin. This is apart from others parasites infesting human skin especially the eyelashes as ocular myiasis (Morsy, and Farrag, 1991), pubic lice (Morsy and El-Ghazali, 1999), or scabiasis (Morsy *et al*, 2000a).

Demodex infestation rate increased with age, up to 84% of population aged 60 and in 100% of those older than 70 years (Post and Juhlin, 1963). Apart from its higher density

in rosacea patients (Forton *et al*, 2005), the *Demodex* mites also caused skin diseases such as pityriasis *folliculorum*, perioral dermatitis particularly in immunocompromised patients (Morras *et al*, 2003), scabies-like eruptions, facial pigmentation, eruptions of the bald scalp, demodicosis gravis, and even basal cell carcinoma (Erbagci *et al*, 2003).

Eyes are surrounded by protruding body parts as nose, brow, and cheek; and not as accessible as the face to daily cleansing hygiene (Kamoun *et al*, 1999). Thus, *Demodex* infestation spread and flourished in eyelids leading to blepharitis (Heacock, 1986). The ecto-parasite *Demodex* is the most common parasite in humans. It inhabits the eyelids, cilia, meibomian glands, face, and external optic tract. These obligate mites are transparent, elongated in shape, and divided into head-neck and body-tail parts, with eight short legs attached to the anterior body segment (Kheirk-hah *et al*, 2007).

Generally speaking, there are many species of *Demodex*, but only *D. folliculorum* and *D. brevis* are found on the human body especially eyelashes (Gao *et al*, 2005). *D. folliculorum*, 0.35 to 0.4mm in length, lives in lash follicles, and *D. brevis*, 0.15 to 0.2 mm in length, lives deep in the meibomian glands and the sebaceous glands of the lash (English and Nutting, 1981). They eat skin cells, hormones, and oils accumulated within hair follicle (Karincaoglu *et al*, 2004).

Dermatologically, *Demodex* colonizes the normal human skin everywhere; *Demodex* population was approximately $\leq 5/\text{cm}^2$ of skin in the adult population (Aydingöz *et al*, 1997). They did not cause of any dermatologic problems, but when the mites penetrate the dermis, they caused diseases, such as acne, rosacea, and folliculitis, when the population increases (Forton *et al*, 2005). Ophthalmologically, *Demodex* is an etiological factor in chronic blepharitis, conjunctival inflammation, and meibomian gland dysfunction (Li *et al*, 2010). Moreover, rosacea predisposes the patients to blepharitis mainly by creating the skin environment to congest all

the oil-producing glands necessary for a healthy dermis and epidermis (Wilkin, 1981). Other factors may change the environment to encourage mites' proliferation, such as the skin photo-type, sunlight exposure, alcohol intake, smoking, stress, hot beverages, spicy food, and abrupt changes in temperature (Bernstein, 1982). *Demodex* mites developed in patients whose local or systemic compromised immune status by topical or systemic steroids or other immunosuppressive diseases such as leukemia and HIV (Kulac *et al*, 2008), particularly children (Morras *et al*, 2003) and polycystic ovary syndrome (Eser *et al*, 2017). *Demodex* can block hair follicles causing 'blackhead-like' condition or roseaceous skin rash (Alexander, 1984). Also, they were found in ear canals and other areas of human body (Chen and Plewig, 2014). Besides, demodicosis present on the nipple was transmitted easily by skin-to-skin contact, initially during mother-to-infant nursing (Elston and Elston, 2014).

In Egypt and abroad the endemicity of human demodicosis was reported by many authors. Some were given here within.

Morsy *et al*. (1995) recovered *D. folliculorum* above the sebaceous glands level from a boy and his pet dog, they suffered from intense irritation and dermatitis and successfully treated with permethrin

Abd-El-Aal *et al*. (1997) examined sixteen female patients (35-55years old) with papulopustular rosacea (PPR) and sixteen cross sectioned normal healthy ones to assess *D. folliculorum* pathogenesis. They used mite density in a standard skin surface biopsy 10.5cm^2 from different designated six face areas, SEM and total IgE level. They treated patients with Crotamiton cream 10% with special program. All patients and 15 controls (97.22%) harbored mites, with mean counts of 28.6 & 6.9 on cheeks, 14.5 & 3.0 on forehead and 6.8 & 0.8 on chin in patients and controls respectively. Total mean mite count in patients was 49.9 dropped to 7.9 after treatment, and in controls was 10.7 dropped to 10.6. Total IgE was 169.4 & 168.4 and

96.3 & 98.4 in patients and controls respectively. SEM examination showed that all the mites were pointing in one direction, and some contained bacteria inside their gut and on their skin. They concluded that *D. folliculorum* has pathogenic role in rosacea.

Morsy *et al.* (2000b) reported marked pathologic infestations caused by *D. folliculorum* in five immunocompetent children, whom were successful treated with 2% permethrin cream.

El-Shazly *et al.* (2001) reported significant difference in rosacea patients (aged 11-50 years old) 44% were infested with *D. folliculorum* compared to normal ones (23.0%). The mean \pm SD of mite density ranged between 13.2 \pm 0.9 to 18.2 \pm 1.2 as compared to normal controls with mite density ranged between 1.4 \pm 0.25 to 2.4 \pm 0.3. Mite infestation in rosacea patients was 66.1% in squamous, 66.7% in erythematotelangiectate and 83.3% in papulo-pustular rosacea. The highly infested site was cheek (27.3%) with mean mite density of 25.3 \pm 1.3, followed by the area around the orbit (23.4%) with a density of 19.0 \pm 1.2, the area around the nose (19.5%) with mite density of 7.1 \pm 1.5, then chin (15.6%) with a density of 8.2 \pm 1.4 and lastly the area around the mouth (14.1%) with a mite density of 14.2 \pm 1.3. Undoubtedly, infestation with *D. folliculorum* particularly in large number causes rosacea.

Morsy *et al.* (2002) reported that follicular or demodicid mite was a zoonotic obligatory parasite with clinical manifestations ranged from normal infestation to complicated ones. They successfully used camphor oil (100%, 75% & 50%) with or without glycerol dilutions in treating human facial demodicidosis without side effects.

El-Shazly *et al.* (2004) reported *D. folliculorum* in fifteen females with erythematotelangiectatic rosacea. The patients were successful treated by daily topical application of camphor oil in glycerol (1:3) and 500mg metronidazole orally for two weeks.

El Bassioni *et al.* (2005) evaluated 40 patients (26 females & 14 males) aged 48.57 \pm -

15.33years with facial skin lesions and *D. folliculorum* density $> 5/cm^2$ by SSSB for immune response by counting T-cell subsets (CD3-CD4-CD8) and NK cells (CD16) numbers and IgG, M, D concentrations in peripheral blood in relation to DF mite density. The mean DF mite density (MD) was 11.82 \pm 3.72/cm² in patients compared to 1.77 \pm 2.39/cm² and 47.5% prevalence in controls. A significant decrease in absolute numbers of lymphocytes, T-cell subsets and NK cells was patients as compared to controls. They concluded that *D. folliculorum* modulated the host cellular immune response to their advantage, as T-cell subsets and NK cells target of immuno-suppression, favoring dermatosis development.

Salem *et al.* (2013) treated 120 patients with skin lesions and anterior blepharitis, whose infestation was treatment-resistant and who had a *Demodex* count >5 mites/cm² for skin lesions or ≥ 3 mites at root of each eyelash. They used ivermectin and combined ivermectin-metronidazole therapy in treating *D. folliculorum* in ocular and skin lesions and followed up. They reported significant difference in the mite count between patients given ivermectin and combined therapy during all follow-up visits. At the last visit, 1.7% patients given combined therapy did not show clinical improvement, 26.7% showed a marked clinical improvement, and 71.6% showed complete remission. In patients given ivermectin, 21.7% did not show clinical improvement, 33.3% showed a marked improvement, and 45% showed complete remission. They concluded that combined therapy was superior in decreasing mites count in all patients and reduced mites to normal level in rosacea and in anterior blepharitis as well in acne and peri-oral dermatitis lesions.

Salem *et al.* (2020) stated that canine demodicosis is a zoonotic parasitic skin infection with impact on acute-phase proteins and oxidant-antioxidant balance. They reported that among 14 demodicosis infested pet dogs, there was significant elevation in malon-

dialdehyde, total antioxidant capacity, superoxide dismutase, and C-reactive protein levels along with significant reduction in glutathione peroxidase and catalase levels.

Abroad, Liu *et al.* (2010) in China divided *Demodex* blepharitis anatomically into anterior and posterior blepharitis. The former infested eyelashes and follicles by *D. folliculorum*, clustering to the root of lashes, whereas *D. brevis* preferentially infested the meibomian gland. They used tea tree oil with either 50% lid scrubs or 5% lid massages in eradicating mites and reducing ocular surface inflammation.

Nicholls *et al.* (2016) in Austria reported that *Demodex* species was implicated in the blepharitis pathogenesis, and confirmed by microscopic examination of epilated eyelashes. All patients responded to treatment (5% tea tree oil) regarding to change in subjective symptoms utilizing a symptom-based patient questionnaire assessment, but 91% showed some symptoms improvement. They added that treatment improved of symptoms in patients with long standing external ocular disease and underlying ocular mites, infestation.

Nicholls *et al.* (2017) in Austria reported that *D. brevis* and *D. folliculorum* were implicated in the pathogenesis of external ocular diseases reflecting an imbalance in the external ocular ecology. They added that the *Demodex* spp. role as a commensal parasite should not be overlooked and treatment should not be aimed at total eradication of the mite but rather restoring the ocular ecology to a balanced state.

Fromstein *et al.* (2018) in USA reported that *D. folliculorum* and *D. brevis* infested human eye and in excess, led to a wide range of anterior segment findings, implicated in anterior and posterior blepharitis, blepharoconjunctivitis, blepharokeratitis, and beyond. They added that definitive diagnosis was made with lash sampling, and the commonest treatment is with tea tree oil in varying concentrations.

García *et al.* (2019) in Spain that *D. follic-*

ulorum and *D. brevis* inhabit the skin of humans and alternated the ocular surface, such as, dysfunction of Meibomian glands, blepharitis, chalazion...etc. Ocular demodicosis is characterized by pathognomonic presence of cylindrical dandruff at the base of eyelashes and various symptoms including, amongst others were itching, lacrimation, and hyperemia. They concluded that patients with blepharitis or other infectious diseases of the ocular surface, unresolved with antibacterial treatment, the search for *Demodex* spp. infestation should be considered.

Juliandri *et al.* (2019) in China stated that rosacea (erythema or papulo-pustular or ocular or phymatous) is a highly prevalent, chronic inflammatory disease, which treatment remains a challenge to dermatologists. Therapies include skin care, medications, lasers, and various combinations of these modalities. They concluded that proper diagnosing and choosing the appropriate treatment depended on clinical types and patient's various clinical symptoms, but must be based generally on anti-*Demodex*, anti-inflammatory, and anti-angiogenesis.

Redd and Seitzman (2020) in USA stated that ocular rosacea has several associations with many significant systemic diseases that can cause permanent blindness if well treated. Variations in local and systemic microbiome, including demodicosis, played a role in pathogenesis, severity, and in explaining rosacea different phenotypes. They concluded that continued advances in the understanding its epidemiology and pathogenesis, randomized controlled trials specific for ocular rosacea remain more or less lacking, and there was overall consensus that rosacea and ocular one especially require chronic maintenance treatment strategies involving combination topical and systemic therapies.

Conclusion

Little study has been done on human eyelash and the great attention was directed to research on hair for people suffering from scalp hair loss. Eyelashes are an integral part of lid margin anatomy, much like the meio-

mian glands, eyelid skin and biofilm, each contributing to the overall homeostasis of the ocular surface.

In this study, *D. folliculorum* (>5 mites/cm²) was detected in six family members who acquired infection from the infested pet dog. Common interventions for demodicosis included metronidazole-based therapies, permethrin, benzoyl benzoate, crotamiton, lindane, and sulfur. Efficacious treatment options may include permethrin, crotamiton, benzyl benzoate, camphor oil with or without glycerol, and oral metronidazole; however, long-term efficacy has not been established.

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