

Demodicosis

Demodikoz

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Received: 19.12.2018
Received in revised form: 25.03.2019
Accepted: 01.04.2019
Available online: 02.04.2019

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ABSTRACT Demodicosis is the term applied to cutaneous diseases caused by *Demodex folliculorum* and *Demodex brevis*. Demodex mites are acquired shortly after birth. They are saprophytic ectoparasites that are found primarily in areas rich in sebaceous glands, like face, scalp, neck. While human demodicosis is a skin disease sui generis, it can mimic many other inflammatory dermatoses. Therefore demodicosis are commonly underdiagnosed, and are masked behind other diagnoses such as papulopustular rosacea, erythematotelangiectatic rosacea, seborrheic dermatitis, perioral dermatitis, contact dermatitis, atopic dermatitis, phyma, seborrhea, etc. Human demodicosis is classified into a primary and secondary form by Chen and Plewig. Absence of pre-existing or concurrent inflammatory dermatosis (acne, rosacea or perioral dermatitis), abnormal increase in mite colonization in active lesions, and remission of the lesions following adequate treatment with topical or systemic acaricides/arachnicides, but not with antibiotics with antiinflammatory effects are diagnostic criteria of primary demodicosis. Secondary demodicosis is defined to skin lesions associated with an abnormal increase of Demodex mites in patients with other known skin or systemic diseases. Clinically, demodicosis has a wide range of variants and may manifest as folliculitis (Pityriasis folliculorum), papulopustular erythema (Rosacea-like demodicosis), blepharconjunctivitis (demodectic blepharitis), and granulomatous rosacea-like demodicosis (Demodicosis gravis). The pathogenesis of human demodicosis remains largely obscure. Here, we discuss the clinical manifestations, pathogenesis of demodicosis, and treatment strategies.

Keywords: Demodicosis; pathogenesis; clinical manifestations; treatment

ÖZET Demodikoz; *Demodex folliculorum* ve *Demodex brevis* tarafından oluşturulan deri hastalığını tanımlamak için kullanılan bir terimdir. Demodeksler saprofitik ektoparazitlerdir ve yüz, skalp, boyun gibi sebese bezlerden zengin alanlarda bulunurlar. Demodikoz, çok sayıda inflamatuvar dermatozu taklit edebilir. Bu nedenle sıklıkla tanısı atlanır ve hastalar papülopüstüler rozase, eritemato telenjiyektazik rozase, seboreik dermatit, perioral dermatit, kontakt dermatit, atopik dermatit, fima, sebore gibi tanılar alır. İnsan demodikozu Chen ve Plewig tarafından primer ve sekonder olarak sınıflandırılmıştır. Primer demodikoz tanısı; eşlik eden inflamatuvar bir dermatozu (akne, rozase, perioral dermatit) olmayan, aktif lezyonlarda artmış parazit varlığı gösterilen ve tablonun antiinflamatuvar etkili antibiyotikler ile değil, topikal veya sistemik akarisit tedaviyle düzeldiği hastalar için kullanılır. Sekonder demodikoz ise bilinen bir deri veya sistemik hastalığı olan hastalarda demodeks yoğunluğunun artmasına denilir. Demodikozun çeşitli klinik varyantları vardır. Bunlar follikülit (pitriyazis follikulorum), papülopüstüler eritem (rozase benzeri demodikoz), blefarokonjunktivit (demodektik blefarit) ve granülatöz rozase benzeri demodikozdur (demodikoz gravis). Hastalığın patogenezi tam olarak aydınlatılmamıştır. Bu derlemede demodikozun klinik özellikleri, patogenezi ve tedavisi anlatılmıştır.

Anahtar Kelimeler: Demodikoz; patojen; klinik belirtiler; tedavi

The human Demodex mites are *Demodex folliculorum* and *Demodex brevis*, resided in the follicular infundibulum, and sebaceous ducts/meibomian glands, respectively.¹⁻³ Demodex mites are acquired shortly after birth. They are saprophytic ectoparasites that are found primarily in areas rich in sebaceous glands, like face, scalp, neck and de “col-

lete” and feed on the nutrients in the sebaceous glands. Colonization increases with age, and the mites can be found in nearly all adults although mite density is low.^{1,4-6} Demodex mites remain usually asleep and harmless, rarely inducing immunological or allergic reactions and are believed to become pathogenic when present in excessive numbers, and also penetration into the dermis can lead to pronounced inflammatory reaction.^{7,8} “Demodex density, (Dd)” of fewer than five mites per square centimeter is considered “normal” skin flora, with 20%-100% of adults reported to have detectable mites. A count of more than five mites per square centimeter is defined as demodicosis.¹

Human demodicosis can be seen in primary or secondary forms (Chen and Plewig).⁷ Absence of pre-existing or concurrent inflammatory dermatosis (acne, rosacea or perioral dermatitis), abnormal increase in mite colonization in active lesions, and remission of the lesions with topical or systemic acaricides/arachnicides treatment, but not with antibiotics with antiinflammatory effects are diagnostic criteria of primary demodicosis.⁷ Secondary demodicosis is defined to skin lesions associated with an abnormal increase of Demodex mites due to skin or systemic diseases. It occurs significantly in immunosuppressed patients with leukaemia, human immunodeficiency virus infection or those being treated with topical or systemic immunosuppressants.^{7,9-12} Other conditions associated with secondary demodicosis are summarized in (Table 1).^{1,7,13-17} Primary demodicosis is usually seen after the fourth decade and periorificial involvement (perioral, periorbital or periauricular) is typical. The lesions are usually asymmetrically distributed. The lesions are follicle bound and usually asymptomatic or mildly pruritic. Clinical manifestations of rosacea (erythema, telangiectasias or transient flushing) are absent in patients with primary demodicosis. On the other hand, secondary demodicosis can occur in younger patients, facial involvement is more diffuse, the trunk can be affected, and inflammation is more extensive when compared with the primary form. In the secondary form, past history and the clinical signs of the un-

TABLE 1: The conditions and diseases associated with demodicosis.

Human immunodeficiency virus infection
Leukaemia
Immunosuppressant treatments (topical calcineurin inhibitors, topical or systemic glucocorticoids etc)
Rosacea (especially papulopustular and granulomatous)
Perioral dermatitis
Seborrhoeic dermatitis
Blepharitis
Papulo-pustular lesions of the scalp
Treatment with epidermal growth factor receptor inhibitors
Skin tumours
Chronic renal failure
Ultraviolet phototherapy

derlying disease, such as perioral dermatitis or rosacea, are generally evident.⁷

In contrast to Chen and Plewig, Forton et al suggested a more simplified classification based on the description of the clinical picture: i) non-inflammatory and (ii) inflammatory demodicosis. If demodicosis is not concomitant with another dermatosis, it is called “isolated”, and if otherwise, “associated”.¹⁸

CLINICAL MANIFESTATIONS

Clinically, demodicosis has a wide range of variants and may manifest as folliculitis (Pityriasis folliculorum), papulopustular erythema (Rosacea-like demodicosis), blepharoconjunctivitis (demodectic blepharitis), and granulomatous rosacea-like demodicosis (Demodicosis gravis).^{3,5,6} Forton et al. showed that the most frequently encountered demodicosis was Pityriasis folliculorum (54%) and papulopustular erythema (37%).¹⁹

Pityriasis folliculorum (Figure 1a) is one of the most typical skin manifestations of Demodex, and is characterized by facial erythema with follicular plugs and scales producing a “nutmeg-grater” or “sandpaper-like” appearance.² In practice, patients come to the dermatologist with mainly subjective complaints (such as a sensation of pruritus, dry skin, hypersensitive skin, irregular or rough skin) and the dermatologist is able to observe this very



FIGURE 1: a) Pityriasis folliculorum, b) Rosacea-like demodicosis.

discrete picture only on close examination.⁸ Rosacea-like demodicosis (Figure 1b) is another representative eruption characterized by follicular scaling, sudden onset, rapid progression, and no history of flushing.^{2,20} Meibomian gland dysfunction and keratoconjunctivitis may occur as eye lesions.^{2,21} Notably, there may be eyelid involvement, called demodectic blepharitis. Demodicosis gravis represents a more severe form of demodicosis and shows intriguing granulomatous rosacea.^{2,20}

According to Chen and Plewig, primary demodicosis is classified as (i) spinulate demodicosis (ptyriasis folliculorum) which involves sebaceous hair follicles without marked inflammation, characterized by fine, discrete, whitish-yellowish pointed changes affecting primarily facial sebaceous hair follicles, the lesions may be isolated or grouped, may be accompanied by faint erythema or little inflammation (ii) papulopustular/nodulocystic or conglobate demodicosis affecting most commonly perioral and periorbital areas with pronounced inflammatory lesions (iii) ocular demodicosis causing chronic blepharitis, chalazia or keraconjunctivitis; and (iv) auricular demodicosis presenting with external otitis or myringitis.⁷

PATHOGENESIS

The pathogenesis of human demodicosis is not fully understood.⁷ Chen and Plewig underlined that transition from a noninflammatory to an inflammatory state is critical in the initial stage.^{7,18} It is hypothesized that an unknown break in immune

tolerance or other potential favouring factor, results in Demodex proliferation, corresponding to pityriasis folliculorum; in a second stage, possibly when some mites penetrate the dermis, the immune system is suddenly stimulated which gives rise to an exaggerated immune response towards the Demodex, resulting in the papules and pustules of rosacea.^{1,18}

Other different mechanisms are thought to play a role in the pathogenesis. The mites or the reactive hyperkeratosis can block hair follicles or sebaceous ducts; the host's humoral and cellular immune reactions can be stimulated by the mites and/or local damage caused by their products; a foreign body granulomatous reaction to the mite's chitinous skeleton; and a possible vector role for bacteria are all thought to be responsible.^{1,6,8} Lacey et al reported that antigenic proteins related to *Bacillus oleronius* isolated from demodex folliculorum mites are capable of stimulating an inflammatory response in patients with papulopustular rosacea.²²

DIAGNOSIS

The diagnosis of demodicosis is complicated by the fact that Demodex are normal skin fauna and their numbers increase as we age. A definite diagnosis of demodicosis, therefore, requires both a compatible clinical picture and a density of more than 5 mites/follicle or 5 mites/cm² of standardized skin surface biopsy (SSSB) specimen in the lesional skin (Figure 2).^{6,7,23} The density of Demodex mites can



FIGURE 2: Demodex mites.

be studied by direct microscopic examination (DME) of fresh secretions from sebaceous glands.^{6,23}

According to Aşkın and Seçkin, standardized skin surface biopsy (SSSB) is a superior diagnostic method for the measurement of demodex density (Dd) when compared with the direct microscopic examination (DME) method.²³ In this technique, a drop of cyanoacrylate adhesive on a glass slide is placed on the skin and removed in approximately 60 s, when the glue has solidified.¹⁰

However, there are some limitations of the standardized skin surface biopsy (SSSB) technique. It is not appropriate for determining the prevalence of Demodex mites, as only a limited skin sample, both in surface area and depth, is obtained.^{23,24} In addition to, false negative results at the first standardized skin surface biopsy (SSSB) may be a result of bad adherence of the mites to the slide as a layer of hyperkeratosis or sebum protects them from direct contact with the glue.^{23,25} It has been suggested that when the clinical suspicion is strong, it would be useful to perform a second standardized skin surface biopsy (SSSB) at the same site in order to avoid false negative results.⁶

Dermatoscopy, confocal laser scanning microscopy or high definition optical coherence to-

mography seem to be effective diagnostic techniques based on the results of preliminary studies, but further studies must be performed to determine the precision, validity and clinical practicability of them.^{4,26,27} Reflectance confocal microscopy is a fast, direct and noninvasive method for Demodex-associated diseases and it is superior to standardized skin surface biopsy (SSSB) for Demodex mite detection.⁴

Standard punch biopsy technique can also be used to demonstrate the mites and any accompanying inflammatory reaction. Accuracy of detection and quantitation with this method depends on the number of follicles included in the biopsy as well as the use of serial sections.¹⁰ Histological examination is characterized with a massive colonization of the follicle with hair-gland mites and a strong inflammatory reaction due to the extrafollicular mites after follicle rupture are typical findings.⁵

TREATMENT

Treatment of human demodicosis is mainly based on single case reports.⁷ Most of demodicosis patients (62%) did not use soap to wash their faces.⁶ Washing with water and soap seems to be effective in elimination of mites by chemical (soap), and mechanical action. To wash the skin twice a day with a gentle soap, lukewarm water and face cloth is recommended for patients with demodiosis.¹⁹

Ivermectin is an acaricidal agent, and has proven to be effective in the treatment of human demodicosis.^{5,7} The recommended dose of oral ivermectin in humans is 0.2 mg/kg, administered in a single dose.^{3,28,29} The usefulness of systemic metronidazole (500-750 mg/day, 2 weeks to 8 months) for therapy of demodicosis is doubtful.^{5,29,30}

Topical drugs, such as permethrin 5%, benzyl benzoate 10–25%, crotamiton 10%, metronidazole 2%, hexachlorocyclohexane, lindane 1% or malathion 0,5%, has been suggested although topical therapy alone is often not sufficiently effective.^{7,9,10,19,31}

Forton et al. recommend applying a topical acaricidal treatment (crotamiton 10% in the morning and crotamiton 10% plus benzyl benzoate 12% in the evening), in a thin layer, all over the face,

except the eyelids, until normalization of demodex density (Dd) (2-12 months); then, if necessary, the night cream continued 3 times/wk to keep demodex density (Dd) normal. This treatment cannot be used directly on irritated skin, and must be well explained to the patient.¹⁹ Koo H et al. suggest to the tea tree oil eyelid scrub treatment is effective for eliminating ocular Demodex and improving subjective ocular symptoms.³² Use of ivermectin in combination with topical permethrin to treat severe *Demodex* infestation has also been reported.¹⁰

Whether the therapeutic effect of systemic low-dose tetracycline or macrolide antibiotics, 15-20% topical azelaic acid or 0.75-2% topical metronidazole is mainly due to the anti-inflammatory or partially acaricidal properties of these agents is controversial. Although it has been suggested that tetracyclines may affect the proliferation of Demodex mites by targeting endosymbiotic *B. Oleronius*, this hypothesis style is still not confirmed.³³

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Ayça Cordan Yazıcı, Guliz İkizoglu; **Analysis and/or Interpretation:** Ayça Cordan Yazıcı, Guliz İkizoglu; **Literature Review:** Ayça Cordan Yazıcı; **Writing the Article:** Ayça Cordan Yazıcı, Guliz İkizoglu; **Critical Review:** Ayça Cordan Yazıcı, Guliz İkizoglu.

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