Acta Derm Venereol 2002; 82: 3–6

Taylor & Francis
healthsciences

MINI REVIEW

Demodicidosis Revisited

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Demodex mites are common commensals of the pilosebaceous unit in mammals. In humans, only two species (*Demodex folliculorum* and *D. brevis*) have been identified and have been implied to play a role in at least three facial conditions: pityriasis folliculorum, rosacea-like demodicidosis and so-called "demodicidosis gravis". However, there is no consensus to what degree the mites are causative of the skin pathology and how they might contribute to the disease. This review presents a demodicidosis case, discusses the clinical features of Demodex infestation in man and reviews its pathogenetic implications and the therapeutic options. *Key words: Demodex mites; pityriasis folliculorum; rosacea-like demodicidosis*.

(Accepted December 13, 2001.)

Acta Derm Venereol 2002; 82: 3–6.

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Follicle mites live in the hair follicles or sebaceous glands in mammals. The species of major importance to domesticated animals belong to the genus Demodex. They are common parasites of cats (*Demodex cati*), dogs (*D. canis*), horses (*D. equi*), cattle (*D. bovis*), swine and sheep (*D. ovis*). In healthy animals, follicle mites do not cause skin deterioration, but in weak or diseased animals demodectic mange can develop. Heavily infested dogs, for instance, initially manifest scaling and wrinkling of the skin, along with a change of colour from normal to red or bruised-looking ("red mange"). Furthermore, pustules and inflammatory nodules develop, which usually reflects the development of secondary bacterial infection (esp. Staphylococcus) of the follicles. In both conditions, itching appears and can be severe (1). Some animals seem to be genetically predisposed to demodicidosis by a specific T-cell abnormality, and generalized mange has been associated with depressed T-cell response to a variety of mitogens (2).

In humans, only two species: *Demodex folliculorum* (DF) and *Demodex brevis* (DB) have been identified (3). They inhabit the pilosebaceous unit and utilize sebum as nourishment. DF mites are found in the infundibular portion of hair follicles, while DB burrow deeper into the sebaceous glands and ducts. The prevalence approximates 100% in middle-aged and older adults; in healthy skin, however, mite density is normally low (4). Dermatologists have not been able to reach agreement concerning the pathogenetic potential of the mites. The question whether they are mere commensals coincidentally found in diseased skin or a real cause of rosacea remains controversial.

CLINICAL FORMS OF DEMODEX INFESTATION IN MAN

Ayres (5, 6) originally described two clinical forms of Demodex infestation in humans: pityriasis folliculorum and rosacea-like demodicidosis. Since that time, Demodex mites have been reported in connection with clinical entities such as pustular folliculitis (7), papulopustular scalp eruptions (8), perioral dermatitis (9) and hyperpigmented patches of the face (10).

Pityriasis folliculorum primarily affects women and presents with diffuse but faint facial erythema, itching and burning sensations as well as fine follicular plugs and scales which give the face a "nutmeg-grater", "sandpaper-like" or "frosted" appearance. A history of infrequent washing and application of heavy creams and make-up helps to confirm the diagnosis (5). Histologically, a diffuse and perivascular lymphocytic infiltrate is present in the dermis, without the formation of granulomas (11).

Rosacea-like demodicidosis with erythema, scaling and papulopustules (6) clinically mimics the picture of common rosacea. However, the scaling in Demodex infestation is follicular and the lesions are superficial and tend to be small papulovesicles and vesicopustules. In contrast, common rosacea presents with papulopustules, and the scaling, if present, is rather flaky (10). Additionally, sudden onset, rapid progress and no history of flushing, persistent erythema or photosensitivity, sebostatic skin type, burning and itching sensations, the absence of significant teleangiectases as well as (more infrequently) asymmetrical distribution, involvement of the eyelids (demodectic blepharitis) (12), previous steroid usage and poor general health (e.g. diabetes mellitus) help in establishing the diagnosis of demodicidosis. A definite diagnosis can be made by examining scale scraps after macerating with 40% KOH under low power magnification (13), by standardized skin surface biopsy (SSSB) (14) or by a punch biopsy. SSSB with the application of cyanoacrylate glue is preferred because it is a non-invasive sampling method that allows the superficial part of the horny layer and of the follicle

 ISSN 0001-5555

content – the site where the DF mites reside – to be collected. The technique also enables the DF population to be monitored during treatment. The finding of an occasional Demodex mite is of no significance, but five or more of them in a single low-power field (13) or more than 5/cm^2 in SSSB (14) has definite pathogenic implications. Histological examination reveals mononuclear, mainly perifollicular inflammatory infiltrate, which occasionally can assume a granulomatous pattern. Georgala et al. (15) showed that the infiltrate consists mainly of CD4 positive T lymphocytes, CD8 positive T cells representing less than 5%. This study also showed that around the infested follicles CD1a positive macrophages (Langerhans' cells) could be found.

The third form of demodicidosis in humans, reported by De Dulanto & Camacho-Martinez (16), is called 'demodicidosis gravis' and presents a clinical picture similar to severe granulomatous rosacea with dermal granulomas containing mite remnants phagocytized by foreign-body giant cells and showing central necrosis (caseation). Which form the demodicidosis will take in a particular individual depends on the degree of Demodex infestation, the duration of the disease and the patient's age and general health.

THE PREVALENCE OF DEMODEX IN MAN

Demodex is believed to be sparse in children and in adolescents (4). The newborn presumably become infested soon after birth by direct contact, but because of low sebum production in childhood Demodex density remains low (17). Kligman & Plewig (4) stated that they had never observed mites in acne comedones or in papulopustules. Why mites do not colonize acne patients in spite of the abundance of sebum remains a puzzle. It is possible that the changes in sebum composition reported in adolescent acne sufferers (18) make it impossible for the mites to flourish. The few reports of demodicidosis in children connected it with leukaemia (19) or HIV infection (20). Recently, however, Patrizi et al. (21) reported 8 immunocompetent children (aged 10 months to 5 years) with pityriasis folliculorum and rosacea-like demodicidosis. The reason for this unusual infestation was not found, but in all cases the lesions cleared after 3–4 weeks of local therapy with 1% metronidazole.

Several pathogenic mechanisms have been postulated: (i) blockage of follicles and sebaceous ducts by the mites and by reactive hyperkeratinization and epithelial hyperplasia, (ii) a vector role for bacteria, (iii) a foreign body granulomatous reaction to the mite chitinous skeleton, and (iv) stimulation of the host's humoral and cell-mediated immune reactions by the mites and their waste products (17). Georgala et al. (15) put forward an interesting hypothesis that a delayed hypersensitivity reaction (type IV immune response) to an unknown antigen of follicular or mite origin, could occur in Demodex infestation. Roihu & Kariniemi (22) studied the prevalence of Demodex mites in facial biopsies from patients with rosacea, eczema and discoid lupus erythematosus (DLE). In the rosacea group, the mites were found more frequently (51%) than in the rest of the study population (eczema 28%, DLE 31%). Vollmer (23) examined 24 large sections of skin with histologic folliculitis and demonstrated DF in 42% follicles with inflammation, but in just 10% without inflammation. Furthermore, 83% of follicles with Demodex showed inflammation. The probability that this result could occur by random chance alone is less than 0.1% (23). Although it does not prove that DF causes clinical or histologic folliculitis, it must be concluded that DF and follicular inflammation are preferentially associated. Since Ayres's (5, 6) and Spickett's (34) studies on demodicidosis, it is known that the pathogenicity of Demodex mites is a quantitative matter. Bonnar et al. (17), using surface skin samples (SSSB), showed that the average mite count of patients with rosacea was significantly higher than the count of healthy individuals.

THERAPEUTIC OPTIONS

Since the first descriptions of demodicidosis, clinicians have reported the therapeutic efficacy of salicylic acid (10), selenium sulphide (24), metronidazole (21, 25), crotamitone (14, 26), lindane (10, 11), sublimed sulphur (10), oral ivermectine together with topical permethrin (27) and oral or topical retinoids (11). However, it is difficult to study any possible long-term effects of drugs on mite viability because of the inability to culture Demodex. It might be that in mild demodicidosis cases topicals that promote desquamation (e.g. salicylic acid and retinoids) alone could be effective because they prevent follicular plugging and accelerate shedding of the epidermis, thus enabling elimination of the mites and their waste products. Regular cleansing with mild soap and water and avoidance of potentially occlusive agents is also important. In Demodex blepharoconjunctivitis, yellow mercury ointment 1% or topical metronidazole gel 2% (28) have been recommended.

In the case presented (Figs. 1–3), our patient was treated with oral metronidazole, which is also effective in common rosacea. This could point at a relationship between the two clinical entities. However, the mechanism of the therapeutic response brought about by metronidazole is not known. It cannot be attributed to its antiparasitic activity against Demodex because *in vitro* the mite can survive in such a high concentration of metronidazole that cannot be achieved *in vivo* (29). However, this does not exclude the possibility of a metronidazole metabolite as an active anti-mite agent.

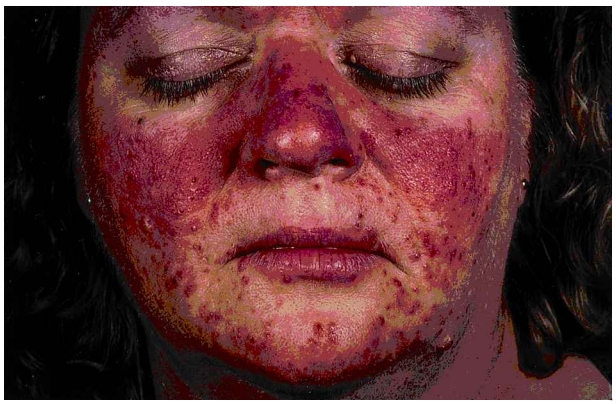

Fig. 1. A 44-year-old woman presented in our outpatient department with a 4-year history of itching and skin lesions in the central region of the face. Previous medication included oral tetracycline, which was ineffective, and oral isotretinoin, which led to a remarkable improvement but had to be discontinued because of gastrointestinal complications. On physical examination, the patient presented papulopustules and fine keratotic follicular papules against a vivid background erythema localized on the nose, cheeks, chin and forehead. Comedones and teleangiectases were missing. The patient did not report flushing episodes or any kind of photosensitivity. Past medical history included severe acne in adolescence. The patient was put on a 0.5 g/day dose of oral metronidazole for 2 weeks (see Fig. 2).

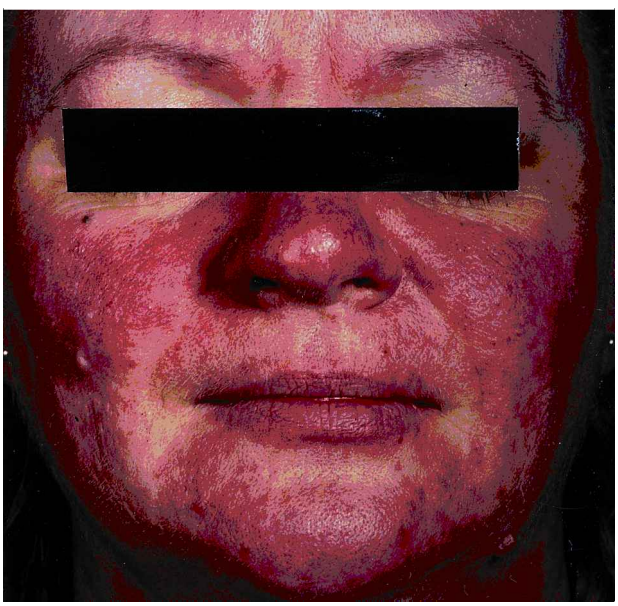

Fig. 2. After 2 weeks of metronidazole therapy: an almost complete remission with only some residual erythema, patches of post-inflammatorial hyperpigmentaion and a few excoriations on the chin. To prevent a recurrence the patient received an additional 14-day therapy with metronidazole orally (0.5 g/day).

Metronidazole is degraded *in vivo* into at least 5 metabolites with potent biological activity (e.g. its 2-hydroxymethyl derivative is one-third to 10 times more active as an antibacterial agent than metronidazole itself) (30). It has also been suggested that metronidazole can have an anti-inflammatory influence on T lymphocytes and adhesion molecules (29). Further, it has been shown

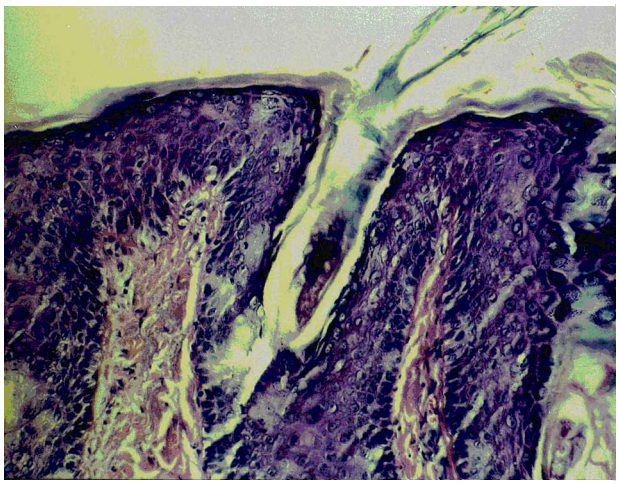

Fig. 3. A punch biopsy from the patient's left cheek revealed sparse lymphohistiocytic perivascular infiltration in the upper dermis. Within the follicular infundibula and sebaceous glands, multiple Demodex mites can be seen. Direct immunofluorescence examination was negative.

that metronidazole has an inhibitory effect on H_2O_2 and $OH\cdot$ generation by neutrophils in a dose-dependent manner (32). The alteration of neutrophil function and metronidazole's antioxidant effect could explain why metronidazole is effective against papulopustular rosacea where inflammatory neutrophils are involved (33). However, Palotta et al. (26) reported that in rosacea-like demodicidosis a therapy attempt with oral metronidazole was unsuccessful, while topical crotamitone cleared the lesions. Similarly, Shelley et al. (33) observed that oral metronidazole suppressed the disease but did not reduce the Demodex population. Treatment with topical crotamiton, however, eliminated DF and was curative. Forton et al. (14) recently investigated the efficacy of 6 different topical treatment modalities in 34 patients with high DF density in SSSB (> 5 mites/cm^2). This randomized study did not show any acaricidal activity of metronidazole 2%, sublimed sulphur 10%, permethrin 1% or lindane 1%, but confirmed the efficacy of crotamitone 10% (when used once daily) and benzyl benzoate 10% (used twice daily).

CONCLUSION

Common rosacea is essentially a cutaneous vascular disorder with a varied degree of sun damage (solar elastosis) of the upper dermis and a history of reactive, photosensitive skin. Demodex mites are not causative of rosacea, but they may aggravate the disease. Furthermore, when the mites get the opportunity to multiply above a certain limit, which is dependent on the immunological status of the patient, they are the aetiologic factor of rosacea-like demodicidosis. The disease shows a remarkable similarity to common rosacea, yet can be distinguished from the latter on clinical and

histopathological grounds. Rosacea patients with persistent lesions that do not respond to conventional therapy, as well as patients presenting unusual patterns of rosacea, should be checked for mites.

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