Clinics in Dermatology (2014) **32**, 739–743

Clinics in Dermatology

Demodex mites☆

Carly A. Elston, BA[a], Dirk M. Elston, MD[b,*]

[a]*The Commonwealth Medical College, Scranton, Pennsylvania*
[b]*Ackerman Academy of Dermatopathology, 145 East 32nd Street, 10th Floor, New York, NY 10016*

Abstract *Demodex* mites are normal inhabitants of human hair follicles. *D folliculorum* is found predominantly in the follicular infundibulum of facial skin and is typically present in small groups. *D brevis*, the smaller of the two species, predominates on the trunk, typically as solitarily mites within the sebaceous glands and ducts. In a wide variety of animals, *Demodex* mites are recognized as a cause of mange. The role of *Demodex* mites as agents of human disease has been more controversial, but evidence favors their involvement in acneiform eruptions, folliculitis, and a range of eruptions in immunosuppressed patients.

Introduction and background

Mites were first described in the hair follicles of humans in 1841 by Henle and Berger and were classified into two distinct species in 1963.[1] *Demodex* spp mites are considered to be part of the normal skin fauna, residing within the pilosebaceous unit. *D folliculorum* (Figure 1) is the larger of the two species. It predominates on the face and is typically found in clusters of 10 to 15 organisms within the keratin and debris of the follicular infundibulum. *D brevis* (Figure 2), the smaller of the two species, resides as a solitary organism and is typically found within the sebaceous glands and ducts. It can occur anywhere but often predominates on the trunk. *Demodex* mites are ubiquitous commensals in dogs and other mammals and are well established as a causative agent of mange. Whereas sarcoptic mange affects previously healthy dogs, demodectic mange typically affects dogs already suffering from malnutrition, immunosuppression, or illness. Similarly, in humans a wider variety of manifestations are found in immunosuppressed patients compared with immunocompetent adults. It is ironic that despite the acceptance of their pathogenicity in the veterinary literature, the role of the *Demodex* mites as agents of human disease remains somewhat controversial. This is because it is difficult for a commensal organism to fulfill Koch's postulates. Though their presence is clearly correlated with inflammatory facial lesions and other eruptions, absolute proof of causation is difficult to achieve. The strongest evidence that these organisms are pathogenic is prompt response to therapy. This paper discusses the epidemiology of *Demodex* mites, clinical manifestations, and treatment strategies.

Epidemiology

Demodex mites are acquired shortly after birth. Because they are found on the nipple, it is likely that mother-to-infant transmission first occurs during nursing. Their numbers increase as their food supply becomes more abundant with sebaceous gland proliferation during puberty. The percentage of individuals who are infested also increases with age, peaking in the fifth and sixth decades of life. The prevalence of *Demodex* infestation is nearly 95% in individuals older than 71 years. They spread easily by skin-to-skin contact and

☆ Images were produced while the senior author was a full time federal employee. They are in the public domain.

* Corresponding author. Tel.: +1.800.553.6621.
E-mail address: delston@ameripath.com (D.M. Elston).

http://dx.doi.org/10.1016/j.clindermatol.2014.02.012
0738-081X/

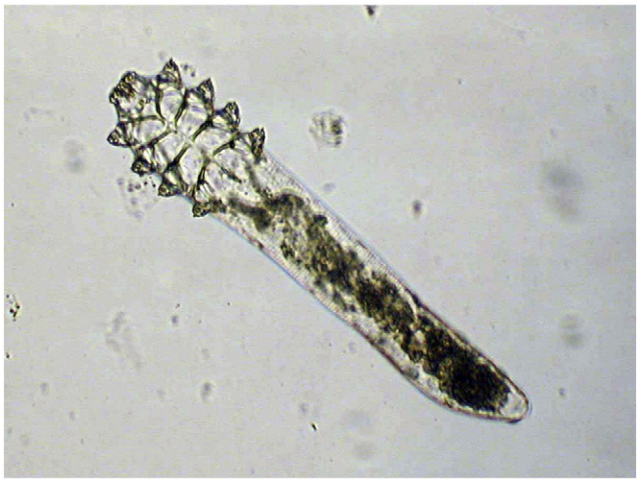

Fig. 1 *Demodex folliculorum* mite.

are therefore more prevalent in individuals who care for the elderly. They are found in 69% of 31 to 50 year olds, are less common in children, and are seen in only 13% of patients ages 3 to 15 years.[2]

Both species can be found in normal skin biopsies with a rate of recovery of about 10%. Of the two, *D folliculorum* is more prevalent and is also present in greater numbers within individual follicles, especially those on the face. Within these biopsies they are present in 12% of hair follicles. *D folliculorum* and *D brevis* are most prevalent on the face, especially the forehead, cheeks, nasolabial folds, and nose because of the high density of sebaceous glands in these areas. *Demodex* mites, especially *D brevis*, may also be found in the ear canals and are also distributed on the trunk and pubis. Normal rates of colonization within the population range from 20% to 80%, with men typically more heavily infested than women in most studies.[3–5] Presumably, this is a direct result of greater androgen-induced sebum production in men. It should

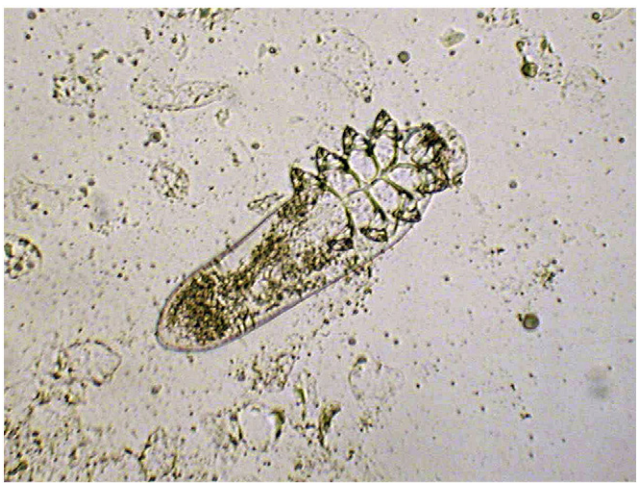

Fig. 2 *Demodex brevis* mite.

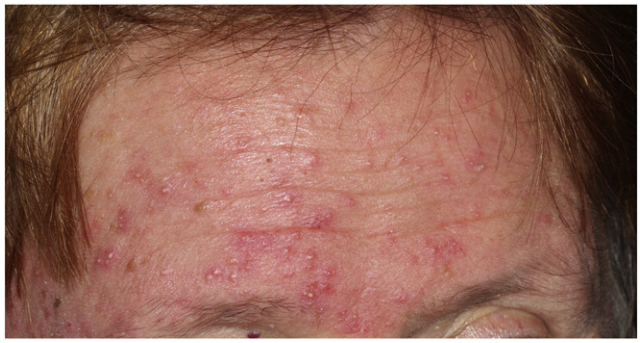

Fig. 3 Demodectic folliculitis that responded to topical sulfur.

be noted that applications of exogenous lipids in cosmetics may also affect the growth of *Demodex* mites.

Demodex-associated skin disease

Demodex mites have been implicated as the cause of chronic inflammatory eruptions of the skin that resemble bacterial folliculitis (Figure 3), rosacea, perioral dermatitis, and otitis externa.[6–8] Demodectic alopecia similar to animal mange has been reported in humans and has responded to antidemodectic therapy.[9,10] The signs and symptoms of papulopustular rosacea correlate with the frequency of *Demodex* mite infestation.[11] In a study assessing skin surface biopsies from 49 rosacea patients, affected individuals had a mean mite density of 10.8/cm^2, compared with healthy controls who demonstrated only 0.7/cm^2 ($p < .001$).[12] Another study evaluating 48 rosacea patients reported *D folliculorum* in a larger percentage of samples compared with healthy controls (96% versus 74%, $p < .01$). Mites were also 5.7 times denser in individuals with rosacea.[13]

The presence of follicular spines caused by the protrusion of mites and keratin from the follicle is referred to as pityriasis folliculorum (Figure 4). The presence of large quantities of mites may appear as spiny follicular papules and is correlated with pruritus with or without visible inflamma-

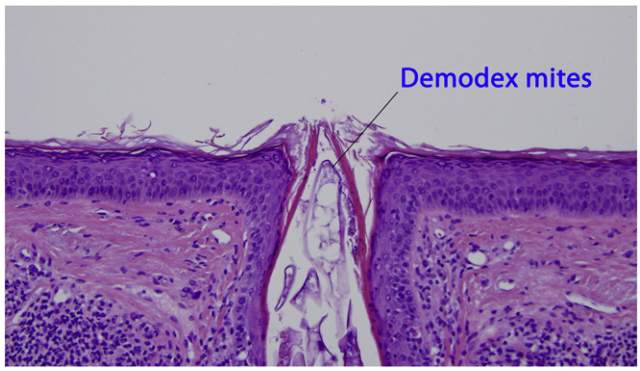

Fig. 4 Pityriasis folliculorum is characterized by follicular spines composed of *Demodex* mites and keratin debris.

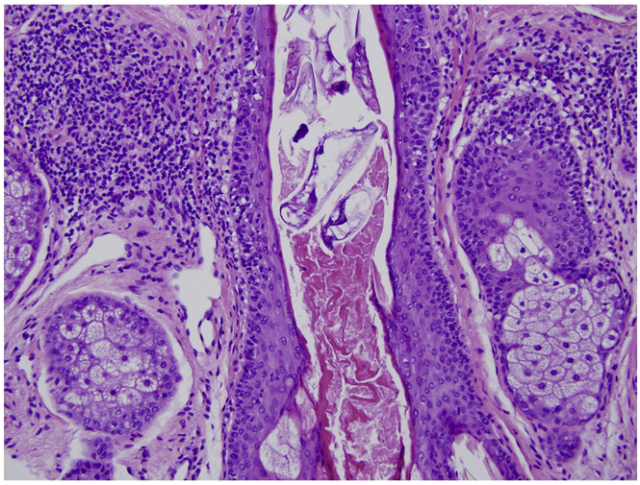

Fig. 5 Demodectic folliculitis is characterized by follicular spongiosis and a perifollicular lymphoid infiltrate.

tory lesions.[14] The primary species of mite causing the infestation can affect the clinical presentation. *D brevis* mites are more likely to cause a symmetric papulopustular eruption in a malar distribution over existing diseased skin. *D folliculorum* mites, however, are more commonly associated with scale and erythema over the forehead and nose.[15]

Various treatments have been used for *Demodex*-associated skin eruptions, including topical sulfur products, permethrin, and ivermectin. Although each can be effective, our experience favors sulfur as the most effective intervention for facial eruptions. Facial *Demodex* infestations have also been treated with dilute topical camphor oil and with oral metronidazole.[16] A patient with facial abscesses refractory to ivermectin, lindane, permethrin, and benzyl benzoate ultimately responded to oral metronidazole.[17]

Blepharitis and otitis

Demodex mite infestation is associated with chronic blepharitis, although data are mixed as to whether the severity of symptoms correlates with the density of mite infestation. The increase in prevalence of chronic blepharitis with age parallels the expansion of the mite population, but although nearly all individuals have evidence of mite infestation by the age of 71, only 58% of these individuals experience clinical blepharitis.[18–20]

As with rosacea symptoms, the species of infesting mite determines the clinical manifestation of blepharitis. Anterior blepharitis with eyelash involvement is more often associated with *D folliculorum*, whereas posterior blepharitis with dysfunction of the meibomian glands and keratoconjunctivitis is more likely to be associated with *D brevis* infestation. Topical treatment with 50% tea tree oil as a lid scrub or 5% tea tree oil as a lid massage effectively decreases the mite population and ocular surface inflammation, but the safety of this intervention has not been established.[21] Oral ivermectin can be curative in cases of refractory blepharitis. In one study, ivermectin successfully reduced the number of *D folliculorum* found in lashes and statistically improved tear film breakup time after treatment.[22] *Demodex* mites have also been associated with chronic ear pruritus and external otitis. A study of a population of Chinese students found 11.6% to have *Demodex* mite infestation of the external auditory canal associated with these symptoms.[23]

Immune response to *Demodex* mites

Demodex mites elicit a vigorous immune response. Spongiosis and lymphocytic infiltrates are often found in histologic sections, surrounding follicles infested with *Demodex* mites (Figure 5) but not around non-infested follicles. Polymerase chain reaction (PCR) evaluation of tissue from rosacea patients has found upregulation of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1b (IL-1b), and interleukin 8 (IL-8), especially those with papulopustular rather than erythematotelangiectatic rosacea (Casas 2012). The immune response varies somewhat based on HLA type. Individuals with the Cw2 phenotype are more susceptible to infestation. The HLA A2 phenotype, on the other hand, appears to be protective. Individuals without this allele have less functional leukocyte response, recruit fewer CD8+ lymphocytes, and develop a humoral response with higher IgA concentrations. They are more likely to develop deep papular and papulopustular lesions that involve larger swaths of skin.[24]

Demodex mites as opportunists: Infestations in the immunocompromised host

Considerable evidence exists to support the pathogenicity of *Demodex* mites in the setting of immunosuppression. In immunocompetent hosts, they are regularly associated with cutaneous eruptions on the eyelids and face and can be isolated from these lesions. These conditions respond to agents like topical sulfur and oral ivermectin aimed at reducing the infestation of mites, suggesting that the mites are pathogenic. Like other opportunistic pathogens, *Demodex* mites break Koch's postulates. They do not regularly induce illness in healthy hosts and are much more likely to produce illness in those whose immune system is not intact.

Immunocompromised patients are more likely to present with problematic eruptions of *Demodex* mites than are immunocompetent individuals. HIV positive patients may present clinically with demodicosis, usually with a pruritic eruption on the face, when CD4+ counts drop

below 200/mm^3.[25] The interscapular and presternal areas may also be involved. The eruption has been shown to respond to ivermectin therapy, suggesting pathogenicity of the mites.

High-density *Demodex* mite infestation has also been reported as a cause of facial eruption in patients with lymphoma or leukemia, especially those with myelocytic leukemia.[26] One report described a patient with leukemia and demodecosis misdiagnosed as graft-versus-host (GVH) disease. The eruption occurred while the patient was recovering from an allogenic bone marrow transplant, leading to misinterpretation of the eruption as a sign of GVH. *Demodex* infestation has been cited in the literature as an important diagnostic consideration in bone marrow transplant recipients presenting with facial erythema.[27]

A higher density of *Demodex* mites has been reported in diabetic individuals. In one study, *D folliculorum* eyelash infestation in 42 diabetic patients with documented diabetic retinopathy was found to be significantly more prevalent compared with age-matched controls (54.8% versus 38.1%, $p = .048$).[28] Individuals receiving immunosuppressive therapy have also presented with symptoms of demodecosis. Patients with epidermal growth factor receptor inhibitor–associated cutaneous eruptions demonstrated significant *Demodex* infestation in their skin lesions compared with that of the healthy population (4.7/cm^2 versus 0.7/cm^2), suggesting that the use of these drugs may impair necessary defense mechanisms.[29] In individuals with perioral dermatitis, the density of *D folliculorum* mites is associated with topical steroid use.[30] Topical calcineurin inhibitors such as tacrolimus may also increase the density of mites.[31] This finding is of interest because these drugs have produced rosacea-like eruptions but have also been used to treat perioral dermatitis.

Demodex mites as vectors

Demodex mites, like many other parasites and commensals, serve as vectors for other pathogenic organisms. *Demodex*'s bacterial parasites most commonly belong to the genus *Wolbachia* and are thought to play in a role in producing the inflammatory response in rosacea patients. They are known to play a similar role in the Mazzotti reaction that often follows treatment of onchocerciasis where their antigens are responsible for neutrophil chemotaxis and Th1-mediated immune response.[32] Recently, *Bacillus oleronius* was isolated from *D folliculorum* associated with papulopustular rosacea. The bacterium produced two antigens, one largely homologous with heat shock proteins, the other similar to a protease involved with carbohydrate metabolism. The antigens caused proliferation of peripheral blood mononuclear cells more often in patients with rosacea than in those without (16 of 22 versus 5 of 17, $p = .0105$), suggesting that they may be involved in pathogenesis of the disease.[33]

Conclusions

Demodex are part of the human condition because they represent normal skin fauna acquired at a young age. Their numbers increase as we age, and the prevalence of mites roughly parallels that of several skin diseases. Because inflammation is commonly found in follicles that house the mites, it is likely that they are a cause of clinical folliculitis. It has been shown that antigens from bacteria found within *Demodex* mites can stimulate lymphocyte proliferation. As lymphocyte stimulation is more likely in patients with rosacea than in normal controls, there may be a genetic predisposition to the pathogenic properties of the mite. In immunosuppressed hosts, a greater range of disease manifestations is related to *Demodex* infestation and a high index of suspicion should be maintained.

References

1. Aylesworth R, Vance JC. Demodex folliculorum and Demodex brevis in cutaneous biopsies. *J Am Acad Dermatol.* 1982;7:583-589.
2. Czepita D, Kuzna-Grygiel W, Kosik-Bogacka D. Investigations on the occurrence as well as the role of Demodex follicuforum and demodex brevis in the pathogensis of blepharitis. *Klin Oczna.* 2005;107:80-82.
3. Andrews JR. The prevalence of hair follicle mites in Caucasian New Zealanders. *N Z Med J.* 1982;95:451-453.
4. Nutting WB, Green AC. Pathogenesis associated with hair follicle mites (Demodex spp.) in Australian Aborigines. *Br J Dermatol.* 1976;94:307-312.
5. Ozdemir MH, Aksoy U, Sonmez E, Akisu C, Yorulmaz C, Hilal A. Prevalence of Demodex in health personnel working in the autopsy room. *Am J Forensic Med Pathol.* 2005;26:18-23.
6. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51:327-341.
7. Lee JY, Hsu CK. Granulomatous rosacea-like demodicidosis. *Dermatol Online J.* 2007;13:9.
8. Allen KJ, Davis CL, Billings SD, Mousdicas N. Recalcitrant papulopustular rosacea in an immunocompetent patient responding to combination therapy with oral ivermectin and topical permethrin *Cutis.* 2007;80:149-151.
9. Elston DM, Lawler KB, Iddins BO. What's eating you? Demodex folliculorum. *Cutis.* 2001;68:93-94.
10. García-Vargas A, Mayorga-Rodríguez JA, Sandoval-Tress C. Scalp demodicidosis mimicking favus in a 6-year-old boy. *J Am Acad Dermatol.* 2007;57:S19-S21.
11. Forton F, Germaux MA, Brasseur T, et al. Demodicosis and rosacea: Epidemiology and significance in daily dermatologic practice. *J Am Acad Dermatol.* 2005;52:74-87.
12. Forton F, Seys B. Density of Demodex folliculorum in rosacea: A case-control study using standardized skin-surface biopsy. *Br J Dermatol.* 1993;128:650-659.
13. Casas C, Paul C, Lahfa M, et al. Quantification of Demodex folliculorum by PCR in rosacea and its relationship to skin innate immune activation. *Exp Dermatol.* 2012;21:906-910.
14. Karincaoglu Y, Bayram N, Aycan O, Esrefoglu M. The clinical importance of demodex folliculorum presenting with nonspecific facial signs and symptoms. *J Dermatol.* 2004;31:618-626.
15. Akilov OE, Butov YS, Mumcuoglu KY. A clinico-pathological approach to the classification of human demodicosis. *J Dtsch Dermatol Ges.* 2005;3:607-614.

16. El-Shazly AM, Hassan AA, Soliman M, Morsy GH, Morsy TA. Treatment of human Demodex folliculorum by camphor oil and metronidazole. *J Egypt Soc Parasitol.* 2004;34:107-116.
17. Schaller M, Sander CA, Plewig G. Demodex abscesses: Clinical and therapeutic challenges. *J Am Acad Dermatol.* 2003;49: S272-S274.
18. Czepita D, Kuźna-Grygiel W, Czepita M, Grobelny A. Demodex folliculorum and Demodex brevis as a cause of chronic marginal blepharitis. *Ann Acad Med Stetin.* 2007;53:63-67.
19. Gao YY, Di Pascuale MA, Li W, et al. High prevalence of demodex in eyelashes with cylindrical dandruff. *Invest Ophthalmol Vis Sci.* 2005;46:3089-3094.
20. Kemal M, Sumer Z, Toker MI, Erdogan H, Topalkara A, Akbulut M. The prevalence of Demodex folliculorum in blepharitis patients and the normal population. *Ophthalmic Epidemiol.* 2005;12:287-290.
21. Liu J, Sheha H, Tseng SC. Pathogenic role of Demodex mites in blepharitis. *Curr Opin Allergy Clin Immunol.* 2010;10:505-510.
22. Holzchuh FG, Hida RY, Moscovici BK, et al. Clinical treatment of ocular Demodex folliculorum by systemic ivermectin. *Am J Ophthalmol.* 2011;151:1030-1034.e1.
23. Ding Y, Huang X. Investigation of external auditory meatus secretion Demodex folliculorum and Demodex breuis infection in college students. *Lin Chuang Er Bi Yan Hou Ke Za Zhi.* 2005;19: 176-177.
24. Mumcuoglu KY, Akilov OE. The role of HLA A2 and Cw2 in the pathogenesis of human demodicosis. *Dermatology.* 2005;210: 109-114.
25. Clyti E, Sayavong K, Chanthavisouk K. Demodecidosis in a patient infected by HIV: successful treatment with ivermectin. *Ann Dermatol Venereol.* 2005;132:459-461.
26. Seyhan ME, Karincaoglu Y, Bayram N, Aycan O, Kuku I. Density of Demodex folliculorum in haematological malignancies. *J Int Med Res.* 2004;32:411-415.
27. Román-Curto C, Meseguer-Yebra C, Cañueto J, et al. Demodicidosis simulating acute graft-versus-host disease after allogeneic stem cell transplantation in one patient with acute lymphoblastic leukemia. *Transpl Infect Dis.* 2012;14:387-390.
28. Yamashita LS, Cariello AJ, Geha NM, Yu MC, Hofling-Lima AL. Demodex folliculorum on the eyelash follicle of diabetic patients. *Arq Bras Oftalmol.* 2011;74:422-424.
29. Gerber PA, Kukova G, Buhren BA, Homey B. Density of Demodex folliculorum in patients receiving epidermal growth factor receptor inhibitors. *Dermatology.* 2011;222:144-147.
30. Dolenc-Voljc M, Pohar M, Lunder T. Density of Demodex folliculorum in perioral dermatitis. *Acta Derm Venereol.* 2005;85:211-215.
31. Antille C, Saurat JH, Lubbe J. Induction of rosaceiform dermatitis during treatment of facial inflammatory dermatoses with tacrolimus ointment. *Arch Dermatol.* 2004;140:457-460.
32. Brattig NW. Pathogenesis and host responses in human onchocerciasis: Impact of Onchocerca filariae and Wolbachia endobacteria. *Microbes Infect.* 2004;6:113-128.
33. Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br J Dermatol.* 2007;157:474-481.