Editorial

Demodex Mites as a Cause of Human Disease

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The article in this issue by Sanfilippo and English[1] reports a case of scalp folliculitis with associated *Demodex* infestation. Although the folliculitis proved refractory to clindamycin 1% gel, it responded to sulfacetamide 10% plus sulfur 5% cream used in conjunction with selenium sulfide 2.5% shampoo. The authors believe the mites were pathogenic in their patient. I believe they are correct, but despite many case reports and decades of debate, the role of *Demodex* mites in human disease is still controversial because causation is difficult to prove. *Demodex* mites are quite common in patients with inflammatory facial lesions, as well as the general population.

Sanfilippo and English[1] suggest that *Demodex* mites played a pathogenic role in causing the patient's symptoms because of the persistence of the folliculitis despite previous treatment, the finding of *Demodex* mites on microscopic examination, and the rapid clearing after therapy with sulfacetamide 10% plus sulfur 5% cream and selenium sulfide 2.5% shampoo. This is circumstantial evidence. In a court of law, motive and opportunity are not sufficient evidence for a conviction. In a court of science, circumstantial association does not fulfill Koch postulates. Of course, Koch postulates were designed to assess the pathogenicity of bacteria rather than arthropods. Even in the realm of bacterial infection, they have limitations. Some organisms, such as Hansen bacillus, cannot be grown in pure culture in the laboratory and other laboratory methods of identification like polymerase chain reaction are imperfect. The postulates form a common framework for an analysis of pathogenicity and require the following: the organism must be present in every case of the disease, the organism must be isolated in pure culture, pure culture inoculated into healthy hosts must reproduce the disease, and the organism must be recovered from the now diseased host.

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Not all accepted pathogens fulfill the postulates; opportunistic pathogens break Koch postulates because they do not produce disease in healthy hosts. Other organisms produce flares of disease through mechanisms other than direct tissue invasion. An example of this is guttate psoriasis related to streptococcal infection. We have little trouble accepting the association, though Koch postulates are not met.

In the case of rosacea, some data suggest a statistical association with *Demodex* mites. A study of 49 rosacea patients using 1-cm square skin surface biopsies demonstrated a mean mite density of 10.8/cm^2. Control patients had a significantly lower density (0.7/cm^2; $P<.001$).[2]

Demodex mites are common in the general population. In a consecutive series of skin biopsy specimens, *Demodex folliculorum* and *Demodex brevis* were found in 117 (10%) of 1124 skin biopsies and 198 (12%) of 1692 follicles.[3] The prevalence of both species increased with age, but *D brevis* had a lower prevalence and a wider distribution on the body, though both species were most common on the face. Males were more heavily infested than females with both species, but the difference was greatest for *D brevis*.[3] In a study of healthy white New Zealanders, 17 of 88 subjects (19%) were infested with *Demodex* mites (8 subjects had single species infestation of *D brevis,* 7 had *D folliculorum* infestation, and 2 were infested with both species).[4] Among Australian aborigines, the incidence of infestation is higher (12 [66.6%] of 18 males and 4 [80%] of 5 females).[5] A high rate of infestation (26%; 15/58) has also been noted in autopsy technicians.[6]

With high background rates of infestation, it is not surprising that not all studies have shown a greater prevalence of mites in patients with skin lesions. The inability to demonstrate a statistical association does not disprove causation. In many cases, it is difficult for studies to sufficiently prove an association, but this does not mean a causal association does not exist. The issue is further clouded by the possibility that some diseases are

not caused by mites themselves but by bacterial organisms that infect mites. With rosacea, it has been suggested that *Wolbachia* organisms may incite the inflammatory reaction in a similar fashion to their pathogenicity in Mazzotti reactions.[7] Disease manifestations in the human host may not simply relate to having mites but to having "sick" mites. Future studies incorporating polymerase chain reaction probes will help support a statistical association.

I have a strong personal bias regarding the pathogenicity of *Demodex* mites. I am a believer. The ability of *Demodex* mites to incite an inflammatory response and produce alopecia or demodectic mange in other species is incontrovertible.[8-10] A convincing case of human demodectic alopecia with features similar to animal mange was published in *Cutis*® in 2001.[11] As a dermatopathologist, I regularly see spongiosis and lymphoid inflammation in hair follicles heavily colonized by mites, while adjacent follicles without mites show no signs of inflammation. My mentor, Wilma Bergfeld, MD, is such a strong proponent of the importance of *Demodex* mites that she has dubbed her former fellows as the "*Demodex* society." Coming from this background, how could I not believe? However, for this editorial, I will set aside my personal faith in the competence of the mite and concentrate on recent published evidence. Sanfilippo and English[1] present a thorough discussion of the mite's likely causative association with the most common dermatologic diseases. I will expand on their discussion by reviewing other recent relevant literature.

The immune system's response to *Demodex* mites varies based on HLA type.[12] Those who lack the HLA-A2 phenotype have lower numbers of $CD8^+$, lower functional activity of leukocytes, and higher concentrations of immunoglobulin A, and are more likely to have deep papular and papulopustular lesions associated with *Demodex* mites. Those with the HLA-Cw2 phenotype also appear to be more susceptible to demodicosis.[12]

Chronic blepharitis has been associated with *Demodex* mites, with some evidence suggesting that increased numbers of *Demodex* mites in eyelashes are strongly associated with cylindrical dandruff. By washing the eyelid with shampoo, the mite counts are reduced and clinical symptoms are improved.[13] The prevalence of mite infestation in eyelashes increases with age. Czepita et al[14] reported that *Demodex* mites were found in roughly 2 (13%) of 16 patients aged 3 to 15 years, 66 (34%) of 194 patients aged 19 to 25 years, 52 (69%) of 75 patients aged 31 to 50 years, 58 (87%) of 67 patients aged 51 to 70 years, and 79 (95%) of 83 patients aged 71 to 96 years. The prevalence of infestation is higher among people taking care of the elderly and medical school students. Fifty-eight percent (150/257) of the individuals with mites also had chronic blepharitis.[14] Although the concept of demodectic blepharitis is fairly well accepted in ophthalmologic literature, not all studies have shown a statistically significant association with advancing age or blepharitis.[15]

External otis with chronic pruritus has been associated with *Demodex* infestation of the external ear in humans, as well as other species. Among 613 college students, 71 (11.58%) were found to have *D folliculorum* or *D brevis* in the external auditory canal. The presence of mites correlated with symptoms of itching.[16]

The most common skin manifestations relating to *Demodex* mites are clinical lesions that resemble rosacea and perioral dermatitis.[17] Specifically, a high frequency of *Demodex* mite infestation has been described in patients with symptoms of papulopustular rosacea.[18] It has been suggested that *D folliculorum* is associated with a primary erythematous and scaly eruption in the facial T-zone, and *D brevis* is characterized by a symmetrical malar and papulopustular eruption in those who already have underlying skin disease.[19] In the setting of perioral dermatitis, the density of *D folliculorum* is strongly associated with topical steroid therapy.[20] Although tacrolimus ointment has been used to treat steroid-aggravated rosacea and perioral dermatitis, it also has induced similar clinical lesions. Biopsy in such cases has revealed an abundance of *Demodex* mites in some patients.[21] *D folliculorum* also has been associated with pityriasis folliculitis, a condition characterized by apparent follicular spines that correspond to the posterior portions of numerous mites protruding from the skin surface. *Demodex* mites also are common among patients who present with nonspecific symptoms, such as facial itching, with or without erythema.[22]

In patients with human immunodeficiency virus, *Demodex* mites have been associated with pruritic eruptions of the face and the presternal and interscapular areas. Ivermectin has resulted in clinical cure. Demodicosis is more likely to occur with clinical acquired immunodeficiency syndrome with a CD4 count lower than $200/mm^3$.[23] According to Seyhan et al,[24] the intensity of mite infestation is statistically greater ($P=.00$) among adults with leukemia or lymphoma than normal controls, with the highest incidence among patients with acute myelocytic leukemia. Demodicosis also

appears to be associated with facial eruptions in this population.[24]

Treatment of *Demodex*-associated skin disease can be difficult. Like Sanfilippo and English,[1] I have found topical sulfur to be an excellent initial approach to treatment. In my experience, it is superior to permethrin and ivermectin. Facial *Demodex* infestation also has been shown to respond to topical dilute camphor oil with oral metronidazole.[25] A recent report described a man with confluent erythematous papules, pustules, and abscesses of the face with many *D folliculorum* mites in the abscesses and in skin scrapings. The skin manifestations progressed for 5 years despite repeated oral administration of ivermectin and external application of lindane, permethrin, and benzoyl benzoate. Oral metronidazole resulted in rapid and lasting response.[26] Given these 2 reports of metronidazole efficacy, it is interesting to speculate on this drug's mechanism of action in rosacea. I believe that future research should focus on the statistical association between mites and disease, the effect of therapy on the mite population, and the role of commensal organisms.

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