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Human demodicosis: revisit and a proposed classification

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Summary

Human *Demodex* mites (*Demodex folliculorum* and *Demodex brevis*) hold a high rank in the evolutionary and phylogenetic hierarchy of the skin microbiome, although in most people their presence is of no consequence. While human demodicosis is a skin disease *sui generis*, it can mimic many other inflammatory dermatoses, such as folliculitis, rosacea and perioral dermatitis, leading to unspecific and confusing descriptions in the literature. Here, we propose to classify human demodicosis into a primary form and a secondary form, which is associated mainly with immunosuppression. The clinical manifestations of primary demodicosis may include (i) spinulate demodicosis, currently known as pityriasis folliculorum, involving sebaceous hair follicles without visible inflammation; (ii) papulopustular/nodulocystic or conglobate demodicosis with pronounced inflammation affecting most commonly the perioral and periorbital areas of the face; (iii) ocular demodicosis, inducing chronic blepharitis, chalazia or, less commonly, keratoconjunctivitis; and (iv) auricular demodicosis causing external otitis or myringitis. Secondary demodicosis is usually associated with systemic or local immunosuppression. Treatment is only weakly evidence based, and the most effective concentrations of acaricides remain to be determined. Optimization of an *in vitro* or *ex vivo* culture model is necessary for future studies. Endosymbiosis between certain bacteria and *Demodex* mites in the pathogenesis of demodicosis deserves more attention. Further clinical observations and experiments are needed to prove our hypothesis.

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What's already known about this topic?

- The pathogenicity of human *Demodex* mites in inflammatory skin diseases remains controversial.

What does this study add?

- A new classification is proposed to divide human demodicosis into a primary form and a secondary form associated with other local or systemic diseases.
- The recognition of primary human demodicosis as a disease *sui generis* will enable clinicians to differentiate it from other mimicking inflammatory dermatoses and encourage the development of a specific effective treatment.

First described as a worm by Jacob Henle in Zurich in 1841,[1] and later correctly classified as a mite by the dermatologist Carl Gustav Theodor Simon in Berlin in 1842,[2] human *Demodex* mites (*Demodex folliculorum* and *Demodex brevis*) have intrigued parasitologists, veterinarians and dermatologists for almost 170 years. With regard to taxonomic classification, it is now grouped as *Arthropoda/Chelicerata/Arachnida/Acarina/Demodicidae/Demodex/Demodex folliculorum* or *Demodex brevis*. Compared with other human skin microorganisms, such as *Propionibacterium acnes*, *Staphylococcus epidermidis* and *Malassezia*, *Demodex* mites rank higher in the hierarchy of evolution. In contrast to other human mites such as *Sarcoptes scabiei hominis*, *Cimex lectularius* or *Dermatophagoides pteronyssinus/farinae*, *Demodex* mites remain largely dormant and innocuous, rarely inducing immunological or allergic reactions.[3,4] The diseased state 'demodicosis' in other mammals, such as dogs and cats, can be very extensive and

fatal if left untreated.[5] However, the association between *Demodex* mites and human diseases is much less studied and poorly defined.[3]

This paper aims to emphasize a discrete disease entity *sui generis* in a primary form and, thereby, provide a clear clinical portrait of the disease to distinguish it from other mimicking inflammatory dermatoses. Furthermore, we hope to pave the way for the investigation of the pathogenesis of demodicosis and encourage basic research on the biology of *Demodex* mites.

Definition and diagnosis

Human demodicosis is a skin disease of the pilosebaceous units associated with human *Demodex* mites that involves predominantly the face and head.[3] Two clinical variants, primary and secondary, can be observed. Primary demodicosis can be defined when the following diagnostic criteria are met: (i) absence of pre-existing or concurrent inflammatory dermatoses, such as acne, rosacea or perioral dermatitis; (ii) abnormal increase in mite colonization, which should be identified from the active lesions at the time of examination; and (iii) remission of the disease only after adequate treatment with topical or systemic acaricides/arachnicides,[3,6] but not with antibiotics possessing anti-inflammatory effects, such as tetracycline or doxycycline, or macrolides (erythromycin/azithromycin/clarithromycin). A count of more than 5 mites per cm^2 identified from lesions by way of 'standardized skin surface biopsy' is currently accepted as abnormal, although this figure is based on very limited studies.[7] Moreover, considering that the method of sampling and quantification varies in most case reports and that control groups are often lacking, it is unclear whether this threshold of mite density can be applied to characterize a diseased state in different age groups and different sexes.[8] It is also unknown whether *Demodex* mites captured by 'standardized skin surface biopsy' from their sequestration in the deep follicular canal are of clinical relevance in the initiation of inflammation. Preliminary studies using new diagnostic techniques such as dematoscopy,[9] confocal laser scanning microscopy[10] or high-definition optical coherence tomography show promising results;[11] however, the precision, validity and clinical practicability of these methods remain to be determined. An integration of imaging studies and fluorescein staining may provide a fast and exact solution for the detection and (semi)quantification of mites in daily clinical practice.[12]

Skin lesions associated with an abnormal increase of *Demodex* mites in patients with other known skin or systemic diseases can be classified as secondary demodicosis. It occurs most commonly in significantly immunosuppressed patients, such as those with leukaemia and HIV infection,[13–16] as well as those being treated with immunosuppressants including topical glucocorticoids or topical calcineurin inhibitors.[17,18] Although the relationship is less straightforward, other conditions associated with secondary demodicosis include certain inflammatory dermatoses,[19–22] treatment with epidermal growth factor receptor inhibitors,[23,24] skin tumours,[25–27] chronic renal failure[28] and ultraviolet phototherapy (Table 1).[29] The primary role of *Demodex* mites in the pathogenesis of rosacea remains debatable, considering that none of the available data show a direct positive causal relationship.[19,30] The hypothesis that primary demodicosis is caused by *D. folliculorum* and secondary demodicosis by *D. brevis* has not yet been proven and differs considerably from our concept of classification.[31]

Clinical manifestations of primary demodicosis

Primary human demodicosis is clinically characterized by (i) late onset, usually after age 40 years and especially in the elderly population; (ii) facial involvement, typically affecting periorificial areas (perioral, periorbital or periauricular); (iii) usually asymmetric distribution, grouped in an irregular shape with satellite lesions within one affected area; (iv) being follicle bound; and (v) being asymptomatic or mildly pruritic. The affected patients usually lack classical manifestations of rosacea, such as erythema, transient flushing or telangiectasias.[32] In contrast, secondary demodicosis can occur early in life and show a more diffuse facial distribution or truncal involvement with more extensive inflammation. Past history and features of the underlying diseases, such as perioral dermatitis or rosacea, are usually obvious.

Terminology of demodicosis

The current terminology to describe human demodicosis is unspecific and confusing, and may include pityriasis folliculorum,[30,33] rosacea-like (rosaceiform) dermatitis,[16,17] demodectic rosacea,[34] *Demodex* facial dermatitis,[35] granulomatous rosacea-like dermatitis,[33] perioral/periorbital dermatitis-like demodicosis,[3,33] facial demodicosis,[36] pityriasis folliculitis,[37] scalp folliculitis,[38,39] favus-like scalp demodicidosis,[40] *Demodex* abscess[41] and facial abscess-like conglomerates.[42] We propose the following classification to describe primary demodicosis (Table 2).

Table 1 Examples of skin diseases or situations associated with secondary demodicosis

Skin diseases	Entities
Inflammatory dermatoses	Perioral dermatitis[19]
	Papulopustular rosacea[20]
	Seborrhoeic dermatitis[21]
	Steroid dermatitis[22]
Treatment-associated diseases	Epidermal growth factor receptor inhibitors[24]
	Phototherapy[29]
Tumours	Melanocytic naevi[25]
	Eyelid basal cell carcinoma[26]
	Mycosis fungoides[27]
Systemic diseases	Chronic renal failure[28]

Table 2 Primary human demodicosis: proposed classification and nomenclature

Current terminology and description	Proposed nomenclature	Definition and clinical manifestations
Pityriasis folliculorum	Spinulate demodicosis	Discrete fine, whitish, partly yellowish, spiky, changes involving sebaceous hair follicles, with or without faint erythema and little inflammation
Rosacea-like (rosaceiform) demodicosis, perioral/periorbital/periauricular dermatitis-like demodicosis	Papulopustular demodicosis, perioral demodicosis, periorbital demodicosis, periauricular demodicosis	Papulopustules involving mostly the face, in patients without (primary form) or with pre-existing inflammatory dermatoses such as rosacea or perioral dermatitis (secondary form). The inflammatory stages show predilection for perioral, periorbital and periauricular regions
Demodex abscess/facial abscess-like conglomerates	Nodulocystic/conglobate demodicosis	Intense immune reaction with massive follicular and perifollicular inflammatory infiltrates caused by *Demodex* proliferation, pus accumulation and suppurative succulent changes

Spinulate demodicosis, currently known as pityriasis folliculorum, describes discrete, fine, whitish, partly yellowish, spiky changes involving mainly facial sebaceous hair follicles, which are isolated but grouped, with or without faint erythema and little inflammation (Fig. 1). It is likely caused by the caudal portion of the mites (opisthosoma of *Demodex*).

Demodex folliculitis, meaning inflammation of the follicle due to *Demodex* mites, can be morphologically divided into the following patterns: papulopustular (Figs 2,3), nodulocystic (Fig. 4) and conglobate, which depicts abscess-like lesions.

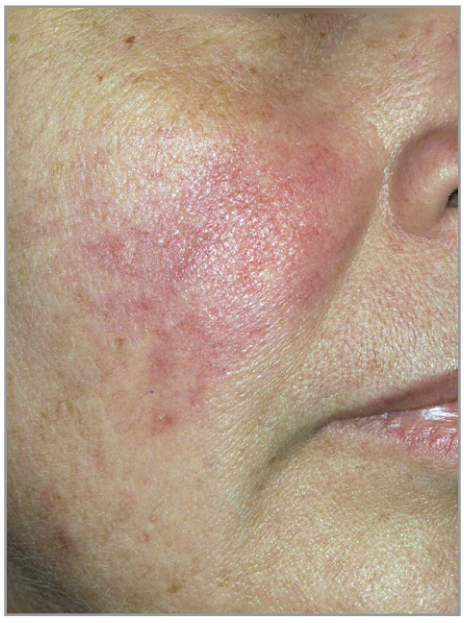

Fig 1. Spinulate demodicosis. Primary human demodicosis depicting discrete, fine, whitish, partly yellowish, keratotic, spiky scaly changes involving sebaceous hair follicles in the background of faint erythema.

Perioral demodicosis is a primary demodicosis and should be differentiated from perioral dermatitis with a secondary increase in *Demodex* mites. The use of 'perioral dermatitis-like demodicosis' is confusing and superfluous. According to the morphological pattern and localization, it may be termed 'papulopustular perioral demodicosis' or 'papulopustular periorbital demodicosis'. Demodicosis of the scalp (demodicosis capitis) occurs more commonly on the balding scalp of elderly men,[38,39] who rarely develop bacterial folliculitis (personal observation). Crusted demodicosis with thick yellow crusts is associated with chronic long-standing inflammation caused by *Demodex* mites (Fig. 5).

Ocular demodicosis may include blepharitis or chalazia due to *Demodex* and, less commonly, conjunctivitis due to *Demodex*.[43,44]

Auricular demodicosis involves the external ear canal or tympanic membrane (myringitis due to *Demodex*).[45]

Pathogenesis

The pathogenesis of human demodicosis remains largely obscure. The initial stage of spinulate demodicosis and its transition from a noninflammatory to an inflammatory state is a critical point. When and how *Demodex* mites initiate the inflammation cascade is paradigmatic to the understanding of host–parasite immunological interactions. It is unclear whether cystic or crusted demodicosis is caused more by an overshooting host immune response or by a huge amount of *Demodex* mites as observed in the crusted scabies. The identification of cathelicidin LL-37 in inflammatory dermatoses and the differential expression of various cytokines/proteins involved in inflammasome activation shed light on the interaction between skin innate immunity and microbial homoeostasis.[46,47] Recent observations regarding human scabies infection may help us to understand better how mites can evade immune surveillance

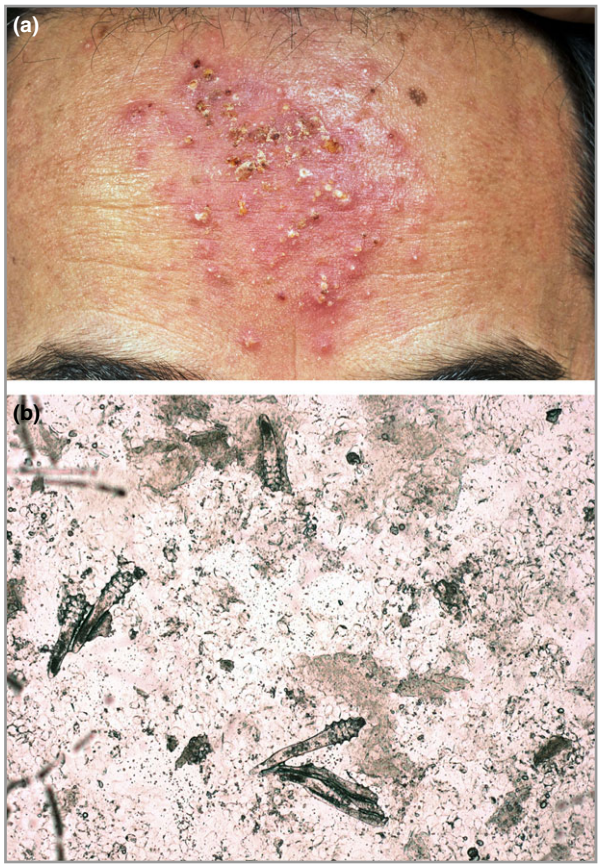

Fig 2. Papulopustular demodicosis. (a) Primary human demodicosis characterized by a typical protracting course involving the forehead of a 46-year-old man with agminated follicle-bound lesions in an irregular shape. (b) Microscopic examination of skin scrapings revealed more than 5 mites per cm^2.

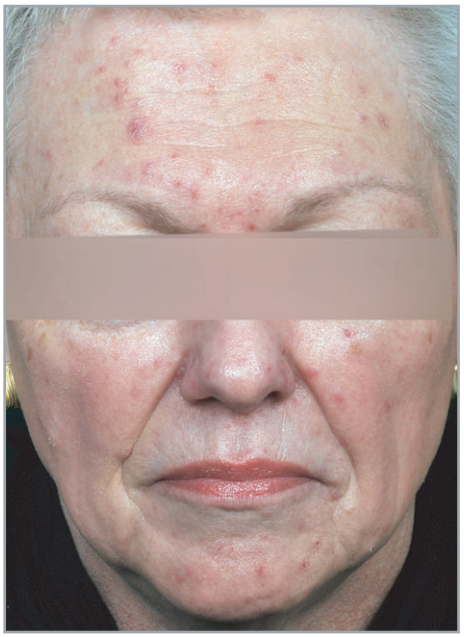

Fig 3. Papulopustular demodicosis. Primary human demodicosis displaying disseminate involvement of the face of a 64-year-old woman with mild keratotic inflammatory papules of different sizes in an asymmetric distribution.

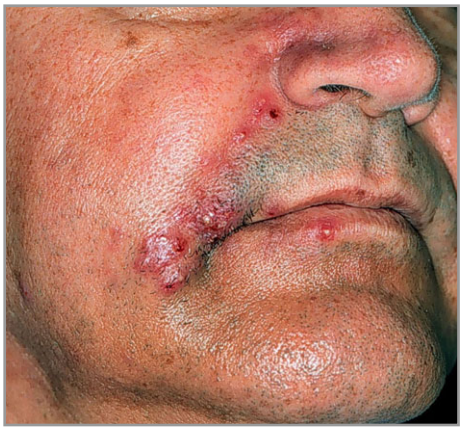

Fig 4. Nodulocystic demodicosis. Primary human demodicosis with intense inflammatory reaction including pus and suppurative succulent changes.

or suppress the immune responses.[48,49] Firstly, all three pathways of the complement system (classical, lectin and alternative) can be inhibited by 'scabies mite-inactivated serine protease paralogues' and 'serine protease inhibitors' (serpins). Secondly, in a human skin-equivalent model, genes for the expression of interleukin (IL)-1α, IL-1β, granulocyte/macrophage colony-stimulating factor and granulocyte colony-stimulating factor, as well as genes involved in epithelium development and keratinization, are significantly upregulated. Thirdly, crusted scabies show features of a nonprotective T helper (Th)2 polarized response with eosinophilia, extremely high levels of IgE (often 10–100-fold higher than normal) and a predominant CD8+ T-cell infiltrate in the dermis. In ordinary scabies, a protective Th1-oriented immune response in favour of interferon-γ is observed, with a cellular infiltrate dominated by CD4+ T cells in the skin lesions.

The symbiosis between microorganisms and higher eukaryocytes can be divided into three groups: (i) mutualistic (beneficial), (ii) commensal (neutral) and (iii) parasitic (harmful). The recent observation and hypothesis that *Bacillus oleronius*, originally isolated from the hindgut of a termite, may be responsible for the initiation of inflammation in papulopustular rosacea is thought provoking. However, so far the bacterium has been isolated from only one microdissected *Demodex* mite from one patient with papulopustular rosacea.[50] The absence of serum reactivity to *Bacillus* antigens in a significant portion (20%) of patients at the initial stage of rosacea, and the presence of the antibodies in 40% of the controls without visible rosacea, cast doubt on the causative role of these bacteria in the inflammatory process.[51] In another study on chronic blepharitis associated with *Demodex* mites, the detection of *B. oleronius* in eyelash cultures from five of 30 healthy individuals and from only two of 15 patients with moderate

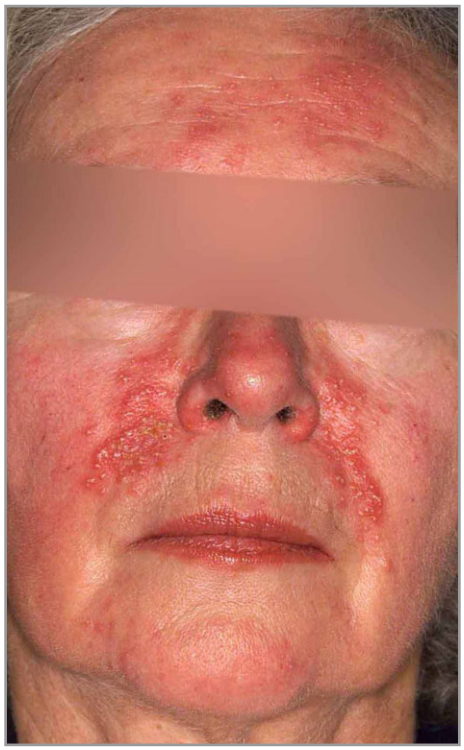

Fig 5. Crusted demodicosis of the face. Primary human demodicosis showing multiple partly confluent papulopustules with thick yellowish crusts.

blepharitis may indicate a low pathogenicity of the strains in the development of chronic inflammation.[52] It remains to be determined whether the *Bacillus* species exist in all dormant *Demodex* mites or only in those that are active, and whether they act as an innocent bystander or a copathogen in the initiation or maintenance of the skin inflammation. In contrast to the results found in filariasis, studies looking for symbiotic pathogens failed to detect *Wolbachia* in *Demodex* mites or *Sarcoptes scabiei*.[53,54] It is unknown whether *S. scabiei* relies on obligatory endosymbionts for survival.[55]

The following are some key factors awaiting answers: (i) the life cycle and behaviour of the human *Demodex* mites, e.g. the male-to-female ratio in the hair follicle, and day vs. night or intrafollicular vs. interfollicular differences; (ii) the increasing prevalence rate with advancing age (permanent residence in 100% of adults); (iii) pathogenesis, relationship and interaction between *D. folliculorum* and *D. brevis* in different body regions and under diseased states; (iv) virulence factors of the mites; (v) correlation between mite densities and clinical disease activity; and (vi) immune reaction, especially the innate immunity of the healthy vs. diseased host.

A recent ophthalmological study indicated that *D. brevis* may play a more important role than *D. folliculorum* in the pathogenesis of chalazia, and recurrence was significantly more common in those with *D. brevis* infestation than those with *D. folliculorum*.[43] Studies of canine demodicosis support the fact that the size of the unique species *Demodex canis* can vary by at least 50% depending on the breed, body site, clinical presentation, skin depth and culture condition.[56] Moreover, genetic factors (breed predisposition) seem to play a crucial role in the pathogenesis of canine juvenile-onset generalized demodicosis.[5] Molecular studies may help to clarify the issue of whether these two human *Demodex* mites are genuinely different subspecies or the same species differing merely in their morphological appearance.

Treatment

Treatment of human demodicosis is so far based on single case reports and is weakly evidence based, due mainly to the following intertwined reasons: (i) lack of ideal *in vitro* or *ex vivo* culture systems on which to test the effectiveness of the drugs and their minimal inhibitory concentrations; (ii) clinical confusion of infestation (primary demodicosis) and inflammatory disease (rosacea with or without secondary demodicosis); and (iii) the dual effects, both anti-inflammatory and antimicrobial, of many agents. Ivermectin is purely acaricidal and has proven to be the treatment of choice for canine and human demodicosis.[57–59] However, the dose of oral ivermectin recommended for the treatment of canine generalized demodicosis is much higher (0·3–0·6 mg kg^{-1} daily for 10–33 weeks) than that used in humans (0·2 mg kg^{-1} single dose).[60] Although topical use of other acaricides, such as permethrin 5%, benzyl benzoate 10–25%, crotamiton 10%, lindane 1% or malathion 0·5%, has been approved for the treatment of scabies,[61] current evidence for the efficacy of these acaricides in the treatment of demodicosis is very limited. The superiority of topical benzyl benzoate 10% in killing *Demodex* mites was demonstrated only in a small number of patients.[6] It is unclear whether treatment of rosacea with systemic low-dose tetracycline or macrolide antibiotics, topical azelaic acid 15–20% or topical metronidazole 0·75–2% is due mainly to anti-inflammatory or also partially acaricidal effects. The hypothesis that the tetracycline drugs can influence the proliferation of *Demodex* mites by targeting the endosymbiotic *B. oleronius* remains to be confirmed.[62] Failure of such treatments is not uncommonly encountered in genuine primary demodicosis.[57–59] The optimal dose of systemic metronidazole in treating demodicosis remains to be determined and should be compared with that of ivermectin. It would be interesting to see whether moxidectin, approved for treatment of generalized canine demodicosis and currently under development for the treatment of human onchocerciasis, can be used topically to treat human demodicosis.[63] Development of arachnicidal resistance has never been discussed, while the method of the repopulation of the *Demodex* mites after arachnicidal killing remains elusive.

In conclusion, human *Demodex* mites are the most prevalent human parasites, enjoying a lifelong symbiotic residence in human beings. The physiological role of human *Demodex* mites in healthy skin remains enigmatic, and the way in which they evade immune surveillance, especially the innate immune system, can be crucial for the understanding of human–parasite interactions. The typical clinical manifestations and specific

therapeutic response to pure acaricides, such as ivermectin, suggest that primary human demodicosis is a disease *sui generis*. Induction of inflammation is the essential step in the pathogenesis. The proliferation of *Demodex* mites, activation of unknown virulence factors and the pathogenic role of endosymbionts in the mites are core issues that warrant intensive investigation. Clinical distinction from other mimicking inflammatory dermatoses, such as papulopustular rosacea or perioral dermatitis, is important. Effective acaricidal drugs and their optimal dosage in killing *Demodex* mites remain to be determined and standardized. Advancement in this field is hampered by the lack of appropriate *in vitro* or *in vivo* models for experimental studies. Recognition of human demodicosis as a primary disease will promote further development of novel therapeutic strategies.

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References

1 Weyers W. Jacob Henle (1809–1885). In: *Pantheon of Dermatology: Outstanding Historical Figures*. (Löser C, Plewig G, Burgdorf WHC, eds), Berlin Heidelberg: Springer, 2013, 472–7.
2 Schaller M. Carl Gustav Theodor Simon (1810–1857). In: *Pantheon of Dermatology: Outstanding Historical Figures*. (Löser C, Plewig G, Burgdorf WHC, eds), Berlin Heidelberg: Springer, 2013, 1039–45.
3 Plewig G, Kligman AM. *Acne and Rosacea*, 3rd edn. Berlin Heidelberg: Springer, 2000.
4 Aylesworth R, Vance JC. *Demodex folliculorum* and *Demodex brevis* in cutaneous biopsies. *J Am Acad Dermatol* 1982; **7**:583–9.
5 Plant JD, Lund EM, Yang M. A case–control study of the risk factors for canine juvenile-onset generalized demodicosis in the U.S.A. *Vet Dermatol* 2011; **22**:95–9.
6 Forton F, Seys B, Marchal JL, Song AM. *Demodex folliculorum* and topical treatment: acaricidal action evaluated by standardized skin surface biopsy. *Br J Dermatol* 1998; **138**:461–6.
7 Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case–control study using standardized skin-surface biopsy. *Br J Dermatol* 1993; **128**:650–9.
8 Kligman AM, Christensen MS. *Demodex folliculorum*: requirements for understanding its role in human skin disease. *J Invest Dermatol* 2011; **131**:8–10.
9 Segal R, Mimouni D, Feuerman H *et al.* Dermoscopy as a diagnostic tool in demodicidosis. *Int J Dermatol* 2010; **49**:1018–23.
10 Longo C, Pellacani G, Ricci C *et al.* *In vivo* detection of *Demodex folliculorum* by means of confocal microscopy. *Br J Dermatol* 2012; **166**:690–2.
11 Maier T, Sattler E, Braun-Falco M *et al.* High-definition optical coherence tomography for the *in vivo* detection of demodex mites. *Dermatology* 2012; **225**:271–6.
12 Kheirkhah A, Blanco G, Casas V, Tseng SC. Fluorescein dye improves microscopic evaluation and counting of *Demodex* in blepharitis with cylindrical dandruff. *Cornea* 2007; **26**:697–700.
13 Benessahraoui M, Paratte F, Plouvier E *et al.* Demodicidosis in a child with xantholeukaemia associated with type 1 neurofibromatosis. *Eur J Dermatol* 2003; **13**:311–12.
14 Damian D, Rogers M. *Demodex* infestation in a child with leukaemia: treatment with ivermectin and permethrin. *Int J Dermatol* 2003; **42**:724–6.
15 Herron MD, O'Reilly MA, Vanderhooft SL. Refractory *Demodex* folliculitis in five children with acute lymphoblastic leukemia. *Pediatr Dermatol* 2005; **22**:407–11.
16 Jansen T, Kastner U, Kreuter A, Altmeyer P. Rosacea-like demodicidosis associated with acquired immunodeficiency syndrome. *Br J Dermatol* 2001; **144**:139–42.
17 Antille C, Saurat JH, Lübbe J. Induction of rosaceiform dermatitis during treatment of facial inflammatory dermatoses with tacrolimus ointment. *Arch Dermatol* 2004; **140**:457–60.
18 Lübbe J, Stucky L, Saurat JH. Rosaceiform dermatitis with follicular *Demodex* after treatment of facial atopic dermatitis with 1% pimecrolimus cream. *Dermatology* 2003; **207**:204–5.
19 Aşkin U, Seçkin D. Comparison of the two techniques for measurement of the density of *Demodex folliculorum*: standardized skin surface biopsy and direct microscopic examination. *Br J Dermatol* 2010; **162**:1124–6.
20 Bonnar E, Eustace P, Powell FC. The *Demodex* mite population in rosacea. *J Am Acad Dermatol* 1993; **28**:443–8.
21 Karincaoglu Y, Tepe B, Kalayci B *et al.* Is *Demodex folliculorum* an aetiological factor in seborrhoeic dermatitis? *Clin Exp Dermatol* 2009; **34**:e516–20.
22 Ljubojeviae S, Basta-Juzbasiae A, Lipozenèiae J. Steroid dermatitis resembling rosacea: aetiopathogenesis and treatment. *J Eur Acad Dermatol Venereol* 2002; **16**:121–6.
23 Patrizi A, Bianchi F, Neri I. Rosaceiform eruption induced by erlotinib. *Dermatol Ther* 2008; **21**(Suppl. 2):S43–5.
24 Gerber PA, Kukova G, Buhren BA, Homey B. Density of *Demodex folliculorum* in patients receiving epidermal growth factor receptor inhibitors. *Dermatology* 2011; **222**:144–7.
25 Serpil S, Ulku K, Cemil C *et al.* Positivity of *Demodex* spp. in biopsy specimens of nevi. *Trop Biomed* 2009; **26**:51–6.
26 Erbagci Z, Erbagci I, Erkiliç S. High incidence of demodicidosis in eyelid basal cell carcinomas. *Int J Dermatol* 2003; **42**:567–71.
27 Nakagawa T, Sasaki M, Fujita K *et al.* *Demodex* folliculitis on the trunk of a patient with mycosis fungoides. *Clin Exp Dermatol* 1996; **21**:148–50.
28 Karincaoglu Y, Esrefoglu Seyhan M, Bayram N *et al.* Incidence of *Demodex folliculorum* in patients with end stage chronic renal failure. *Ren Fail* 2005; **27**:495–9.
29 Kulac M, Ciftci IH, Karaca S, Cetinkaya Z. Clinical importance of *Demodex folliculorum* in patients receiving phototherapy. *Int J Dermatol* 2008; **47**:72–7.
30 Forton FM. Papulopustular rosacea, skin immunity and *Demodex*: pityriasis folliculorum as a missing link. *J Eur Acad Dermatol Venereol* 2012; **26**:19–28.
31 Akilov OE, Butov YS, Mumcuoglu KY. A clinico-pathological approach to the classification of human demodicosis. *J Dtsch Dermatol Ges* 2005; **3**:607–14.
32 Pallotta S, Cianchini G, Martelloni E *et al.* Unilateral demodicidosis. *Eur J Dermatol* 1998; **8**:191–2.
33 Hsu CK, Hsu MM, Lee JY. Demodicosis: a clinicopathological study. *J Am Acad Dermatol* 2009; **60**:453–62.
34 Shelley WB, Shelley ED, Burmeister V. Unilateral demodectic rosacea. *J Am Acad Dermatol* 1989; **20**:915–17.
35 Martinez-Diaz GJ, Clark KM, Vasquez JG, English JC 3rd. Facial erythematous annular plaques: a case of annular *Demodex* facial dermatitis? *J Am Acad Dermatol* 2012; **67**:e268–9.
36 Zomorodian K, Geramishoar M, Saadat F *et al.* Facial demodicosis. *Eur J Dermatol* 2004; **14**:121–2.

37 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**:618–26.

38 Gilaberte Y, Frias MP, Rezusta A, Vera-Alvarez J. Photodynamic therapy with methyl aminolevulinate for resistant scalp folliculitis secondary to *Demodex* infestation. *J Eur Acad Dermatol Venereol* 2009; **23**:718–19.

39 Fernandez-Flores A, Alija A. Scalp folliculitis with *Demodex*: innocent observer or pathogen? *Braz J Infect Dis* 2009; **13**:81–2.

40 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**(2 Suppl.):S19–21.

41 Schaller M, Sander CA, Plewig G. *Demodex* abscesses: clinical and therapeutic challenges. *J Am Acad Dermatol* 2003; **49**(5 Suppl.): S272–4.

42 Aydogan K, Alver O, Tore O, Karadogan SK. Facial abscess-like conglomerates associated with *Demodex* mites. *J Eur Acad Dermatol Venereol* 2006; **20**:1002–4.

43 Liu J, Sheha H, Tseng SC. Pathogenic role of *Demodex* mites in blepharitis. *Curr Opin Allergy Clin Immunol* 2010; **10**:505–10.

44 Liang L, Ding X, Tseng SC. High prevalence of *Demodex brevis* infestation in chalazia. *Am J Ophthalmol* 2014; **157**:342–8.e1.

45 Klemm E, Haroske G, Wollina U. Otitis externa and myringitis due to demodicidosis. *Acta Dermatovenerol Alp Panonica Adriat* 2009; **18**:73–6.

46 Yamasaki K, Di Nardo A, Bardan A *et al.* Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med* 2007; **13**:975–80.

47 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**:906–10.

48 Mounsey KE, McCarthy JS, Walton SF. Scratching the itch: new tools to advance understanding of scabies. *Trends Parasitol* 2013; **29**:35–42.

49 Morgan MS, Arlian LG, Markey MP. *Sarcoptes scabiei* mites modulate gene expression in human skin equivalents. *PLoS ONE* 2013; **8**: e71143.

50 Lacey N, Ní Raghallaigh S, Powell FC. *Demodex* mites – commensals, parasites or mutualistic organisms? *Dermatology* 2011; **222**:128–30.

51 O'Reilly N, Menezes N, Kavanagh K. Positive correlation between serum immunoreactivity to *Demodex*-associated *Bacillus* proteins and erythematotelangiectatic rosacea. *Br J Dermatol* 2012; **167**:1032–6.

52 Szkaradkiewicz A, Chudzicka-Strugała I, Karpiński TM *et al. Bacillus oleronius* and *Demodex* mite infestation in patients with chronic blepharitis. *Clin Microbiol Infect* 2012; **18**:1020–5.

53 Borgo SN, Sattler EC, Hogardt M *et al.* PCR analysis for *Wolbachia* in human and canine *Demodex* mites. *Arch Dermatol Res* 2009; **301**:747–52.

54 Mounsey KE, Holt DC, Fischer K *et al.* Analysis of *Sarcoptes scabiei* finds no evidence of infection with *Wolbachia*. *Int J Parasitol* 2005; **35**:131–5.

55 Holt DC, Fischer K. Novel insights into an old disease: recent developments in scabies mite biology. *Curr Opin Infect Dis* 2013; **26**:110–15.

56 Bourdeau PJ. Variation in size in *Demodex canis*: from the longest to the shortest forms. *Vet Dermatol* 2010; **21**:213.

57 Forstinger C, Kittler H, Binder M. Treatment of rosacea-like demodicidosis with oral ivermectin and topical permethrin cream. *J Am Acad Dermatol* 1999; **41**:775–7.

58 Clyti E, Nacher M, Sainte-Marie D *et al.* Ivermectin treatment of three cases of demodecidosis during human immunodeficiency virus infection. *Int J Dermatol* 2006; **45**:1066–8.

59 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**:149–51.

60 Mueller RS. Treatment protocols for demodicosis: an evidence-based review. *Vet Dermatol* 2004; **15**:75–89.

61 Hay RJ, Steer AC, Engelman D, Walton S. Scabies in the developing world – its prevalence, complications, and management. *Clin Microbiol Infect* 2012; **18**:313–23.

62 Jarmuda S, O'Reilly N, Zaba R *et al.* Potential role of *Demodex* mites and bacteria in the induction of rosacea. *J Med Microbiol* 2012; **61**:1504–10.

63 Mueller RS, Bensignor E, Ferrer L *et al.* Treatment of demodicosis in dogs: 2011 clinical practice guidelines. *Vet Dermatol* 2012; **23**: 86–96, e20–1.