**Demodex-induced follicular mucinosis of the head and neck mimicking folliculotropic mycosis fungoides**

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**INTRODUCTION**

Follicular mucinosis (FM) is a cutaneous disorder arising from the pilosebaceous unit that is most strongly associated with folliculotropic mycosis fungoides (FMF), an aggressive form of mycosis fungoides (MF). Demodicidosis is a cutaneous infection caused by *Demodex*, an ectoparasitic mite that permanently resides in or near the pilosebaceous unit of mammalian hair follicles. Demodicidosis can have a variety of presentations including rosacea-like demodicidosis, pityriasis folliculorum, and demodicidosis gravis.1 Here we describe 4 cases of FM associated with underlying *Demodex* infestation in the absence of malignancy.

**CASE PRESENTATION 1**

A 43-year-old man with psoriasis was referred to Columbia University Irving Medical Center (CUIMC) for assessment of a facial rash of 4 years’ duration (Table I). Individual papules cyclically developed, crusted, and regressed. He reported exposure to dust at home and denied use of over-the-counter or prescription medications.

Physical examination found many firm, erythematous papules on a background of mild diffuse erythema. Crusting papules were observed on the forehead, bridge of the nose, cheek, and temples. Biopsies of papules on the right temple and zygomatic arch showed necrosis and mixed inflammatory cell infiltrates (lymphocytes, histiocytes, eosinophils) within and surrounding the hair follicle (Fig 1). Adjacent follicles showed spongiosis within the infundibula in association with abundant mucin. These findings were consistent with a diagnosis of FM (Fig 1). The papule on the right temple also showed clonal T-cell receptor (TCR) gene rearrangements. Oil preparation and microscopic examination of a neighboring papule showed live *Demodex*.

Given suspicion that FM might be secondary to *Demodex*, he was treated with oral and topical ivermectin. After 4 weeks of treatment, the patient noted significant improvement of his rash, although scattered erythematous papules persisted. Microscopic examination of the forehead papules showed few dead *Demodex* but no live mites. He repeated another dose of oral and topical ivermectin with lifelong prophylactic treatment.

**CASE PRESENTATION 2**

A 48-year-old woman with systemic lupus erythematosus on hydroxychloroquine presented to CUIMC for evaluation of itchy red bumps on the face for 6 months. One week prior she noted a similar rash on the arms and forearms. She completed a month-long course of clobetasol and fluocinonide for presumed dermatitis without...
improvement. Subsequent biopsy of the affected papule on the left lateral cheek found dense spongionotic folliculitis and perifolliculitis with folliculotropic large and atypical lymphocytes and a deep perivascular and perifollicular mixed inflammatory infiltrate (lymphocytes, histiocytes, eosinophils). The lymphocytes present within the follicular epithelium were associated with a slightly increased amount of mucin, and one follicle had necrosis and neutrophils, consistent with a diagnosis of FM. Gene rearrangement studies were negative for a TCR clonal population.

On physical examination, scattered erythematous papules and pustules covered the entire face and posterior aspects of the arms. Skin scraping and microscopic examination did not find Demodex mites. Because of high clinical suspicion for infection despite negative skin scraping, the patient was treated empirically with ivermectin. One month later, she had near-complete resolution of the lesions. She has remained on maintenance topical therapy for 2 years without additional symptoms.

**CASE PRESENTATION 3**

A 21-year-old woman presented to CUIMC with a 3-year history of asymptomatic bumps on the cheeks, initially diagnosed as rosacea (Fig 2). Numerous topical therapies failed, and lesions continued to develop. She had not been treated with antiparasitic agents. Prior biopsy of an affected lesion by an outside dermatologist found minute vellus-type hairs surrounded and permeated by lymphocytic infiltrates with accumulation of dermal mucin within the outer root sheath epithelium, consistent with a diagnosis of FM. No significant nuclear contour irregularity of lymphocytes was appreciated. Gene rearrangement studies were negative for a TCR clonal population. Treatment with hydroxychloroquine and minocycline for 2 years was associated with minimal improvement. Repeat skin biopsy result was again consistent with that of FM. Immunohistochemistry findings were similar to those of MF. The infiltrate was composed of CD5+ T cells without CD20+ B cells (CD4:CD8 ratio of 5:1, modest reduction in CD7 within intrafollicular lymphocytes; ~40% reduction compared with CD3), preserved CD5 expression, and rare cells positive for CD30 (Fig 3). These biopsies were performed prior to presentation to CUIMC.

On initial presentation to CUIMC, physical examination found numerous 1- to 2-mm follicular flesh-colored to red papules, pustules, and excoriations on the cheeks. Oil preparation and microscopic examination of lesions found numerous Demodex mites. She additionally tested positive for dust mite allergy. The patient was treated with oral and topical ivermectin. At 1-week follow-up there was a significant decrease in the number of erythematous papules. After completion of the month-long course of oral and topical ivermectin, the papules completely resolved, and she has been on maintenance therapy with daily topical ivermectin for 2 years.

**CASE PRESENTATION 4**

A 38-year-old man was referred to the Rabin Medical Center Belinson Hospital in Israel for evaluation of a forehead lesion present since 2014. Initially, the lesion presented as a flat erythematous plaque with occasional pustule formation and was thought to be an unusual presentation of rosacea. Various treatments had no response, although antiparasitic treatments had not been used.

Over the year prior to referral, the lesion became increasingly infiltrated. A biopsy result was interpreted as FMF with clonality based on polymerase chain reaction for TCR. On presentation, he had a wide, infiltrated, slightly edematous plaque with follicular opening accentuation on the forehead covered by scattered follicular pustules. Oil preparation and microscopic examination found numerous Demodex confined to the lesion. Repeat biopsy found a perifollicular lymphohistiocytic infiltrate with some folliculotropism without mucin deposits. Significant nuclear atypia was not seen. The vellous follicular units showed spongiosis with numerous Demodex mites and some neutrophils. Immunohistochemistry showed a CD4/CD8 ratio of 2:1 and low CD7 expression.

Given these findings, facial demodicidosis mimicking FMF clinically and pathologically was the diagnosis. Oral metronidazole, 500 mg daily for 2 weeks, followed by topical ivermectin 1% and oral isotretinoin, 20 mg twice weekly, were prescribed. Follow-up examination 4 months later found partial regression, and he is continually following up.

**DISCUSSION**

The differential diagnosis of FM includes FMF and idiopathic (primary) FM. FMF, which describes the well-known association of FM with MF, does not respond to treatment with ivermectin and is an aggressive form of MF with a 5-year survival rate of 41%. Idiopathic FM in young adults may have an acneiform presentation characterized by erythematous to skin-colored papules on the head and neck. Acneiform FM has a benign course with disease duration of months to years. Recognizing the indolent nature of this form of FM should prevent overdiagnosis of MF.
Table I. Patient characteristics, histopathology, skin scraping results, and treatments

| Patient | Gender/age | Past medical history, medications | Histopathology | Skin scraping | Treatment |
|---------|------------|----------------------------------|----------------|--------------|-----------|
| 1       | M/43       | Psoriasis, anxiety on escitalopram | Right temple: Necrotizing folliculitis and perifolliculitis with FM. Positive TCR γ and β clonal populations. Right zygomatic arch: Necrotizing folliculitis and perifolliculitis with FM. Negative TCR γ and β PCR was negative for clonal populations. | Live *Demodex* at initial visit. Dead *Demodex* at 1-month follow-up | Ivermectin oral and topical cream with significant improvement. Advised to consider lifelong prophylactic treatment. |
| 2       | F/48       | Systemic lupus erythematosus on hydroxychloroquine | Left lateral cheek: Dense spongiotic folliculitis and perifolliculitis with folliculotropic lymphocytes suggestive of FM. TCR γ and β PCR was negative for clonal populations. | No evidence of *Demodex* mites. | Ivermectin oral and topical cream with near-complete resolution. She has remained on maintenance therapy (5% permethrin cream daily). |
| 3       | F/21       | None                              | Right side of face: Minute vellus hairs are surrounded and permeated by lymphocytic infiltrates with accumulations of dermal mucin within the outer root sheath epithelium. No significant nuclear contour irregularity of lymphocytes is appreciated. TCR γ and β was negative for clonal populations. | Numerous *Demodex* mites present on microscopic examination. | Ivermectin oral and topical cream with complete resolution. She has been followed up for 3 years with no recurrence and is on daily topical ivermectin maintenance therapy. |
| 4       | M/38       | None                              | Forehead: The vellous follicular units show spongiosis with numerous *Demodex* mites and some neutrophils. The adjacent dermis shows a mixed infiltrate with adnexal exocytosis. The dermis shows a variable mostly perivascular lymphohistiocytic infiltrate. Significant nuclear atypia was not noted. Alcian blue was negative for follicular or dermal deposits of acide mucopolysaccharides. Immunohistochemistry showed infiltrate composed primarily of CD3 cells with a CD4/CD8 ratio of 2:1 and low CD7 expression. | Numerous *Demodex* mites on microscopy and biopsy. | Oral metronidazole, 500-mg daily for 2 weeks, followed by topical ivermectin 1% and oral isotretinoin, 20 mg with partial regression of the lesion. |

*PCR*, Polymerase chain reaction.
Fig 1. Top panel shows necrosis and accompanying mixed inflammatory cell infiltrate within hair follicle, peripheral mucin deposition, and lymphocyte exocytosis. (Hematoxylin-eosin stain; original magnifications, left, \( \times 100 \); right, \( \times 200 \).) Bottom panel shows a colloidal iron stain highlighting mucin deposition in blue (left) and live Demodex mite seen on oil preparation microscopy (right).

Fig 2. Clinical images before and after 3 years of treatment with ivermectin in case 3.
FM arising within the context of *Demodex* infestation has been reported in a handful of cases. Some cases of idiopathic FM have resolved completely with 2 weeks of mite-targeted therapy. In the cases described here, the concomitant presence of *Demodex* and FM, which responded to ivermectin, supports the diagnosis of FM triggered by an immune response to *Demodex*. Apart from the difference in treatment response, FMF and idiopathic FM triggered by *Demodex* are difficult to differentiate. Histologically, FMF and idiopathic FM both show mucin deposition within the hair follicles and perifollicular lymphohistiocytic infiltrate. Monoclonality in T-cell infiltrates can be seen in both diseases as well as other benign inflammatory dermatoses.

The pathogenesis of demodicidosis is controversial but likely arises secondary to immune system dysregulation. Primary skin conditions may create a pro-inflammatory environment that promotes increased proliferation of the *Demodex* mites, or the mites themselves may cause the cutaneous manifestations. In support of the first hypothesis, characteristic features of rosacea including increased vascularization and elevated temperatures may lead to growth of the organisms. Yet, it has also been proposed that mites may be the causative agent of the cutaneous processes through mechanical blockade, secretion of digestive enzymes that directly damage hair follicles, or induction of an antigenic response that creates an inflammation cascade. Additionally, a bacterium, *Bacillus oleronius*, has been isolated from *Demodex*. Release of *Bacillus* proteins leads to increased neutrophil signaling, activation, chemotaxis, and pro-inflammatory cytokine release, possibly contributing to the development of FM (Fig 4).

While *Demodex* infestation is fairly common with a prevalence ranging from 23% to 100% in healthy
adults, most are asymptomatic carriers. Clinical presentation appears dependent on a combination of extrinsic and intrinsic factors. One contributing factor is immunosuppression. A primary underlying T-cell immunodeficiency may be a predisposing factor for demodicidosis, or secondary immunosuppression induced by corticosteroids may serve as trigger for clinical manifestations.

The patients presented were not immunocompromised, which is uncharacteristic of demodicidosis. Other factors, including a hypersensitivity reaction, increased density of *Demodex*, or genetic predisposition may have contributed to these presentations. Two showed clonal TCR populations mimicking lymphoproliferative disorders, possibly caused by robust immune responses. Higher densities of mites correlate with increased perifollicular inflammation and clinical manifestations of disease. These cases support the hypothesis that a subset of idiopathic FM arises secondary to an aberrant immune response to

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**Fig 4.** Schematic of FM development after *Demodex* infestation. Environmental factors such as dust and immunosuppression can predispose patients for *Demodex* infestation. *Demodex* mites reside in or near the pilosebaceous unit of mammalian hair follicles. *Bacillus oleronius* are found on the surface of *Demodex* mites. Proteins from *Bacillus oleronius* lead to induction of the innate immune response. Exposure of neutrophils to proteins from *Bacillus oleronius* leads to neutrophil chemotaxis, degranulation, and production of pro-inflammatory cytokines (interleukin-6, and interleukin-1β). The aberrant immune response leads to destruction of hair follicles and development of FM, which presents clinically as papules or plaques on the skin, mimicking MF.
Demodex. Given the typically robust response of Demodex to treatment with ivermectin, identification of this subset of patients would potentially provide significant clinical benefit.

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