

# A Practical Approach to Recalcitrant Face and Neck Dermatitis in Atopic Dermatitis

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**Face and neck dermatitis in the atopic dermatitis patient is a diagnostically challenging entity with broad differential diagnoses. Recent case reports reporting face and neck dermatitis in patients on dupilumab therapy have added further complexity to diagnosis and management. Herein, we discuss a broad diagnostic algorithm and practical management strategy for recalcitrant face and neck dermatitis in the atopic patient with an emphasis on face and neck dermatitis associated with dupilumab therapy. Our aim is to raise awareness about the probable entity of drug-associated face and neck dermatitis and share a practical management strategy that may also be applied broadly to atopic dermatitis patients presenting with face and neck dermatitis.**

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease affecting approximately 20% of children and 10% of adults worldwide.<sup>1</sup> The pathophysiology of AD is multifactorial and includes immune dysregulation, skin barrier defects, alterations in cutaneous microbiome, and abnormal neurosensory transmission.<sup>2</sup> Skin barrier restoration with emollients and immunomodulation with topical corticosteroids (TCSs) is the first-line approach in most treatment algorithms.<sup>3</sup> Approximately 10% of patients have more severe or treatment-resistant AD that may require the addition of systemic therapies.<sup>4</sup>

Although AD can affect almost anywhere on the skin, facial and neck involvement is particularly distressing and carries with it additional therapeutic challenges.<sup>5</sup> Long-term TCS use carries risk of facial skin atrophy and TCS withdrawal. Occlusive therapies are impractical

and often poorly tolerated on the head and neck area, as they are greasy and cosmetically unpleasant and may cause occlusive folliculitis.<sup>6</sup> Classically, step-up therapy has included oral corticosteroids, as well as off-label agents including cyclosporine, methotrexate, and mycophenolate mofetil; however, these medications are broadly immunosuppressive and have significant systemic adverse effects.<sup>4</sup>

In March 2017, the Food and Drug Administration approved a targeted systemic therapy for adults with moderate to severe AD. Dupilumab is a human monoclonal antibody that inhibits the interleukin 4 (IL-4) receptor  $\alpha$  subunit leading to blockade of IL-4 and IL-13 signaling, important drivers of T-helper 2 (T<sub>H</sub>2)-type inflammation.<sup>7</sup> Several trials have shown that dupilumab significantly improves skin lesion severity, symptoms, and health-related quality-of-life scores in patients with moderate to severe AD previously uncontrolled with topical agents.<sup>8</sup> Importantly, dupilumab has been shown to treat AD effectively everywhere on the body, including the head and neck area.<sup>6</sup>

However, an emerging adverse effect was recently brought to light by Dalia and Johnson, who reported the case of a 26-year-old female patient who developed fine, scaling, edematous, pink to red plaques on the face and anterolateral neck after 6 months on dupilumab treatment. The patient did not have any other dupilumab-associated adverse effects, including conjunctivitis.<sup>9</sup>

Additional reports of dupilumab-associated face and neck dermatitis have surfaced since this initial report<sup>10–15</sup> under the names “new regional dermatosis”<sup>14</sup> and “dupilumab facial redness.”<sup>15</sup> This condition seems to be distinct in that it starts after initiation of dupilumab therapy and is refractory to TCSs. Herein, we will refer to it as drug-associated face and neck dermatitis (DAFND). The addition of this new nosologic entity adds yet more complexity to the diagnostic and therapeutic challenges inherent in head and neck dermatitis. Herein, we will review some of the key clinical considerations in the setting of AD, including patients on dupilumab.

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The presentations of DAFND seem highly variable. For example, Yamane et al<sup>12</sup> described 2 cases of new-onset, periocular dermatitis associated with dupilumab. The first case presented 1 week after a loading dose of dupilumab (corresponding to peak drug serum concentration) with a severe, bilateral periocular dermatitis; the second case presented after 5 months of continuous treatment, with milder periocular dermatitis. In both patients, periocular dermatitis was new (ie, the patients had no history of periocular AD or periocular allergic contact dermatitis [ACD]) and resolved 10 to 12 weeks after drug discontinuation, which is consistent with drug clearance rates.<sup>12</sup> Although both patients in this case report also developed concomitant conjunctivitis, it does not seem that all cases of DAFND present in the context of dupilumab-associated conjunctivitis.<sup>9–13</sup> A recent retrospective analysis of 42 adult patients (mean age, 38.4 years) with AD on dupilumab who developed face and neck dermatitis found a mean onset of 65.4 days (range, 5–365 days) from dupilumab initiation; 42% had concomitant adverse ocular events, and, to add to the complexity, a recent phase 3 trial of adults with AD treated with dupilumab found that by week 16, patients receiving dupilumab had improvements in AD across all anatomic sites, including the face and neck.<sup>6</sup>

Various etiopathogenic mechanisms for DAFND have been proposed. In several of the reports, ACD has been suspected because of dupilumab-associated suppression of the T<sub>H</sub>2 axis leading to sensitization toward T<sub>H</sub>1-biased haptens and subsequent contact hypersensitivity.<sup>10,12,16</sup> Dysregulations in T-helper cells may arise due to “a modulation of TH cell signaling via IL-4 receptor  $\alpha$  blockade, unmasking an ACD or an activation of the T<sub>H</sub>17 pathway, leading to a proliferation of *Malassezia* fungus, which is predominantly localized in the sebaceous head/neck area.”<sup>6</sup> Finally, the development of antidrug antibodies has been seen with other biologic therapies.<sup>16</sup>

Herein, we discuss a comprehensive differential diagnosis and management algorithm for head and neck dermatitis in the atopic patient with an emphasis on patients on dupilumab. We discuss the emerging entity of DAFND as a diagnosis of exclusion and present potential treatment strategies.

## DIFFERENTIAL DIAGNOSIS FOR FACE AND NECK DERMATITIS IN AD

The differential diagnosis for face and neck dermatitis in AD is broad and includes ACD, rosacea/steroid-induced rosacea (SIR), periorificial dermatitis (POD), demodicosis, topical steroid withdrawal, *Malassezia* head and neck dermatitis, and seborrheic dermatitis (Table 1). Less likely dermatoses include acne vulgaris, steroid acne, impetigo, irritant contact dermatitis, airborne contact dermatitis, and tinea faciei, but these conditions must be considered in certain subsets of patients and contexts. Our goals are to review common facial dermatoses and to provide diagnostic and management guidance.

### (Facial) Allergic Contact Dermatitis

Allergic contact dermatitis is a type 4 delayed-hypersensitivity reaction with an increased incidence in AD patients. In 100 pediatric

patients with AD, 30% will have reactivity to at least 1 patch test allergen, and 17% have a contact allergy relevant to their cutaneous symptoms.<sup>17</sup> This increased susceptibility to ACD in atopic patients is due to impaired epidermal barrier integrity, frequent use of topical agents that may contain sensitizers, and shared immune pathogenesis.<sup>18,19</sup> In dupilumab patients specifically, ACD has been suggested to occur because of a drug-related sensitization to type 1 helper cell-biased haptens.<sup>10</sup> It is important to note that an ACD comorbidity does not seem to negatively impact dupilumab's efficacy in treating the patient's underlying AD. A recent retrospective study of 31 patients with comorbid AD/ACD and 33 controls with AD found no differences in the efficacy of dupilumab therapy using the investigator's global assessment scoring system, body surface area measurement, and pruritus.<sup>20</sup>

Given the frequent comorbidity of ACD and AD, diagnosis of ACD in atopic patients can be especially challenging. Allergic contact dermatitis presents acutely as crusted or weeping papulovesicular lesions on an erythematous base and may be more eczematous or lichenified in subacute or chronic cases; however, the appearance of a facial dermatitis in AD can be distorted by underlying disease activity, chronic steroid use, or comorbidities. In patients on dupilumab, ACD should be considered if there is partial therapeutic response to dupilumab and/or if there is clinical improvement of the patient's typical AD symptoms, but there remains a persistent, localized dermatitis.<sup>18</sup> Suresh and Murase<sup>11</sup> reported 3 cases of severe AD treated with dupilumab in which patch testing unmasked an underlying ACD. This series suggests that patients can be reliably patch tested while on dupilumab, with prior positive tests acting as controls. Patch testing could be considered for dupilumab candidates with a history of head and neck dermatitis before initiation of therapy to help identify underlying ACD.<sup>11</sup> Patients with residual head and neck dermatitis on dupilumab may also benefit from expanded patch testing.

It is important to note that any patient with eyelid dermatitis should also raise concern for ACD. In a retrospective study of 203 patients who presented with persistent or recurrent eyelid dermatitis (with or without extra-eyelid involvement), ACD was found to be the diagnosis in 74%.<sup>21</sup> In the subset of AD patients with eyelid dermatitis, 70% (16/23) were diagnosed with ACD after extensive workup. In facial dermatitis with eyelid involvement or predominance, patch testing and allergen avoidance are recommended.

Finally, there remains the question: “Can we kill two birds with one stone?”; that is, in patients with AD and concomitant ACD, can dupilumab reliably treat *both* conditions? Initially, isolated case reports suggested an improvement of ACD with off-label dupilumab use.<sup>22</sup> A case series of 15 AD patients with patch-positive ACD reported improvement in disease severity and symptoms with dupilumab; however, it is unclear whether this response was due to improvements in AD, ACD, or both.<sup>23</sup> Most recently, however, a retrospective study of 13 AD patients with ACD found variable and unreliable impact of dupilumab on patch testing results and ACD lesions.<sup>18</sup> Ultimately, the jury is still out, and although we wait for larger, randomized controlled trials, off-label use of dupilumab for ACD should not replace allergen avoidance, as patients may still be susceptible to allergic

**TABLE 1. Differential Diagnosis of Facial Dermatitis in AD**

|                                        | Clinical Features                                                                                                                                                                                                             | Diagnosis                                                                                                                                                           |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ACD                                    | <ul style="list-style-type: none"> <li>• Intensely pruritic</li> <li>• Eyelid involvement or</li> <li>• Localized, refractory dermatitis despite lesion clearance in other body surface areas (partial responders)</li> </ul> | • Patch testing vs expanded patch testing                                                                                                                           |
| POD                                    | <ul style="list-style-type: none"> <li>• Erythematous monomorphic papules, often asymptomatic</li> <li>• No open or closed comedones</li> <li>• TCS use is a risk factor</li> </ul>                                           | • Clinical                                                                                                                                                          |
| Rosacea/SIR                            | <ul style="list-style-type: none"> <li>• &lt;1% perioral, most appear in centrofacial or malar distribution</li> <li>• Papules, erythema, edema</li> </ul>                                                                    | • Clinical                                                                                                                                                          |
| <i>Demodex</i>                         | <ul style="list-style-type: none"> <li>• Perinasal, periocular papules, pustulous follicular ostia</li> </ul>                                                                                                                 | • <i>Demodex</i> scrape test                                                                                                                                        |
| TSW                                    | <ul style="list-style-type: none"> <li>• Burning sensation, blushing, erythema, heat intolerance</li> <li>• Prolonged or inappropriate TCS use</li> <li>• Women &gt; men</li> </ul>                                           | • Clinical                                                                                                                                                          |
| <i>Malassezia</i> head/neck dermatitis | <ul style="list-style-type: none"> <li>• Postpubertal onset</li> <li>• Lesions on head and neck most severe</li> <li>• Nonresponsive to standard AD regimen</li> </ul>                                                        | <ul style="list-style-type: none"> <li>• Response to antifungals is confirmatory</li> <li>• IgE levels, skin prick, and patch testing generally positive</li> </ul> |
| DAFND                                  | <ul style="list-style-type: none"> <li>• Patient on dupilumab</li> <li>• Unilateral</li> <li>• Neck involvement</li> </ul>                                                                                                    | <ul style="list-style-type: none"> <li>• Clinical</li> <li>• Diagnosis of exclusion</li> </ul>                                                                      |

TSW, topical steroid withdrawal.

reactions upon exposure. Patch test results should be interpreted with caution given the unclear impact of dupilumab on their results.

## Rosacea/SIR

Steroid-induced rosacea is a condition associated with prolonged and improper use of midpotency to high-potency TCSs. The pathogenesis is poorly understood but is thought to be due to vasomotor instability.<sup>24</sup> Clinical appearance mimics classical rosacea, which presents on the forehead, nose, and cheeks with erythematous, monomorphic papules or pustules on a background of edema and erythema.<sup>24</sup> In a study of 110 patients with SIR, 44% had diffuse involvement, 36% had isolated malar, 18% had perinasal, and more than 1% had perioral involvement.<sup>25</sup> The term “red face syndrome” has been used to describe the scaling and flushing of severe SIR. Permanent cutaneous atrophy and telangiectasias are long-term sequelae of uncontrolled, late-stage SIR.<sup>24</sup> Given that SIR is clinically indistinguishable from classic rosacea, a thorough history is crucial for establishing the diagnosis.

Treatment of SIR involves prompt discontinuation of TCS. Topical calcineurin inhibitors are the mainstay of treatment for mild cases. A regimen of oral antibiotics plus topical calcineurin inhibitors is recommended for severe cases. A retrospective study of 200 patients treated for SIR reported that oral tetracyclines or oral macrolides plus a topical calcineurin inhibitor were effective in

achieving disease resolution in both mild and severe cases.<sup>24</sup> Patients with mild symptoms were given topical tacrolimus for 4 to 6 weeks and were reported to be symptom-free within 4 weeks. Those with severe symptoms achieved symptom resolution by 2 to 3 months on a regimen of oral doxycycline (100 mg) twice daily for 4 to 6 weeks plus topical tacrolimus 0.03% ointment twice daily or oral azithromycin (500 mg) in a weekly pulse therapy format (3 tablets/wk) for 4 to 6 weeks. Emollients, calamine, and oral vitamin C and E seemed beneficial for atrophy and telangiectasia, but the number of patients treated and strength of these beneficial effects are poorly described.<sup>24</sup> Topical adapalene and azelaic acid have shown promise in treating facial dermatitis, but current evidence is largely anecdotal and requires randomized controlled trials to support efficacy in SIR.<sup>26</sup> A case of recalcitrant SIR was reportedly treated with 0.03% tacrolimus and 595-nm pulsed-dye laser.<sup>27</sup>

## Periorificial Dermatitis

Periorificial dermatitis is a chronic condition of unknown etiology that presents with multiple skin-colored to erythematous follicular papules around the mouth, eyes, or nose. Perioral POD spares the vermilion border and does not present with comedones.<sup>28</sup> Although the perioral region is most commonly affected, POD can also manifest in periocular and paranasal regions, giving rise to the name “periorificial dermatitis.” Although POD is most commonly

seen in females, men and children are also susceptible.<sup>28</sup> In a study of children and adolescents, 70% of patients had perioral involvement, 43% paranasal, 25% periocular, and 1% perivulvar. Only 64% of children had well-defined POD; the remainder also had lesions extending to the cheeks, chin, and forehead.<sup>29</sup>

Two clinical variants of POD exist: classical and granulomatous. Granulomatous POD is more common in children and African Americans.<sup>30</sup> Extrafacial manifestations in the genital region, trunk, and extremities are rare but have been reported, particularly in granulomatous POD.<sup>30</sup> Periorificial dermatitis lesions are typically asymptomatic; however, 1 study found that 4% to 19% of their subjects reported associated tenderness, burning, or pruritus, which is not insignificant.<sup>29,31</sup> Risk factors for POD include female sex, history of AD or asthma, and recent topical or inhaled corticosteroid use.<sup>31,32</sup>

Given that corticosteroid use often precedes POD and is a risk factor for its development, TCS withdrawal and SIR must be considered and ruled out. The diagnosis of POD is clinical. In adults, the classical treatment is oral tetracyclines.<sup>33,34</sup> A common dosing regimen is oral doxycycline 100 mg twice daily.<sup>28</sup> Duration of treatment is determined by patient response and usually lasts 4 to 8 weeks. Patients should always be counseled about potential adverse effects including gastrointestinal upset, diarrhea, and phototoxicity.

In pediatric patients younger than 8 years who may not be candidates for oral tetracyclines because of concerns for potential tooth staining, oral azithromycin in conjunction with topical metronidazole gel (0.75%) or sodium sulfacetamide lotion is recommended.<sup>31,35</sup> Of note, recent trials of short courses of doxycycline in children report no tooth staining or enamel hypoplasia, and it is possible that guidelines for doxycycline use in pediatric populations may shift in the coming years.<sup>36</sup> Azelaic acid 20% cream was trialed in 10 pediatric patients with steroid-induced POD and led to complete resolution of skin lesions after 4 to 8 weeks (mean, 5.4 weeks) in all patients. Adverse effects were minimal, and there were no recurrences at 8-month follow-up.<sup>37,38</sup>

### Demodex/Demodicosis

Demodicosis is caused by overproliferation of commensal *Demodex folliculorum* and/or *brevis*, parasitic arthropods, which colonize hair follicles and sebaceous glands.<sup>39</sup> Demodicosis may present in various clinical forms: pityriasis folliculorum (thought to be early-stage demodicosis), rosacea-like demodicosis, follicular eczematids, *Demodex* folliculitis, demodectic prurigo, isolated inflammatory papules, demodectic postinflammatory pigmentation, and ocular demodicosis.<sup>40</sup> Increased *Demodex* mite density has also been implicated in both papulopustular and erythematotelangiectatic rosacea.<sup>6</sup> It is theorized that death of *Demodex* mites results in toxin release that stimulates IL-17 signaling.<sup>41</sup> To date, no large randomized controlled trials have demonstrated an association between AD and *Demodex* mite colonization/density. However, it is important to note that *Demodex* mites have a predilection for high-pH and low-moisture skin, which is commonly seen in atopic patients.<sup>41,42</sup>

Importantly, a meta-analysis of 2706 patients on dupilumab for moderate to severe AD found a decreased incidence of bacterial skin

infections and eczema herpeticum,<sup>43</sup> suggesting that an infectious etiology should be less likely in patients with DAFND dermatitis. However, demodicosis is more akin to a parasitic infestation and likely managed by T<sub>H</sub>2-type immunity rather than the T<sub>H</sub>1- and T<sub>H</sub>21-type responses that target bacteria. This is supported by an emerging study, which showed that *Demodex* mites rapidly colonize mice with impaired T<sub>H</sub>2 responses in vivo.<sup>41</sup> Given this evidence, it is not unreasonable to postulate that *Demodex* would thrive in the relatively T<sub>H</sub>2-compromised milieu of dupilumab patients.<sup>41</sup> *Demodex* colonization has also been proposed as a contributor to dupilumab-associated conjunctivitis. Thyssen<sup>41</sup> proposed that the T<sub>H</sub>2-poor environment could theoretically lead to a rise in *Demodex* mite density eventuating in increased periocular and ocular inflammation. Further study is needed to elucidate the role of *Demodex* in AD patients and dupilumab-associated adverse events.

In patients with periocular and perinasal papules suggestive of demodicosis, diagnosis can be confirmed by skin scraping and microscopic evaluation. Evidence for the treatment of demodicosis remains sparse and is largely based on case reports. Ivermectin, an acaricidal agent, is the treatment of choice for canine and human demodicosis<sup>44</sup> and is now available as a topical preparation approved for the treatment of rosacea.<sup>45</sup> Other antiparasitic agents such as permethrin, benzyl benzoate, crotamiton, or lindane are approved for the treatment of scabies, and although they are likely able to reduce *Demodex* numbers, high-quality evidence in humans is lacking.<sup>46</sup> Systemic tetracycline or macrolide antibiotics have anti-inflammatory and potentially some acaricidal effects.<sup>47</sup>

### Topical Steroid Withdrawal

Topical corticosteroids are a cornerstone of treatment for AD patients. Topical corticosteroid withdrawal (TCW) is an adverse event of TCS use that presents several days to weeks after discontinuation of midpotency to high-potency TCS. Although an acute rebound of underlying AD often occurs after TCS discontinuation, TCW seems to be a much more significant and prolonged state. Typically, TCW presents in middle-aged females as a confluent erythema, edema, and/or pustulosis on the face and/or genital regions.<sup>48</sup> A meta-analysis of 34 studies found that 81% of TCW patients were female, 99.3% had lesions on the face or genitals, 92.3% had erythema on examination, and 65.5% reported burning or stinging as a primary symptom.<sup>48</sup>

The pathogenesis of TCW is incompletely understood, but it is theorized that chronic TCS application suppresses nitric oxide production and/or release from mast cells, leading to decreased release of nitric oxide from endothelial cells. Upon TCS discontinuation, nitric oxide release and production are disinhibited, resulting in inappropriate and exaggerated vasodilatation and inflammation.<sup>49,50</sup> Lavker and Schechter<sup>51</sup> found that nitric oxide dysregulation in TCW is reversible, and nitric oxide production and secretion return to baseline within 3 months.

Classical symptoms of TCW include burning/stinging, erythema, pruritus, facial “hot flashes,” and exacerbation with heat and/or sun

exposure.<sup>48</sup> On presentation, 2 morphologic subtypes exist: papulopustular and erythematodematous. The papulopustular variant presents with erythematous papules, pustules, and nodules, but less significant pain and burning symptoms. The erythematodematous presentation involves erythema, edema, and severe flushing and burning.<sup>49</sup> Diagnosis is clinical, and laboratory testing is not helpful in guiding management.

When suspecting TCW, the first step in treatment is to discontinue TCS use. A recent systematic review suggests that TCW stems from TCS overuse. Thus, counseling patients about this disease entity, timing of symptom resolution (up to 3 months), and the significance of TCS avoidance should be a priority.<sup>48</sup> Symptom control may be attempted with nonsteroidal therapies such as cool compresses, cooling pillows, and mineral water.<sup>5,52</sup> Topical calcineurin inhibitors and cyclosporine may also be considered.<sup>49</sup>

Interestingly, a retrospective case series of 5 patients with moderate to severe AD found that dupilumab therapy may serve a role in treating comorbid TCW; thus, it may be especially beneficial to continue dupilumab in these cases.<sup>49</sup> Some clinicians may opt to start a

systematic corticosteroid taper to prevent flares; however, there are no existing clinical trials that support this practice at this time.<sup>49</sup>

### ***Malassezia* Head/Neck Dermatitis Versus Seborrheic Dermatitis**

*Malassezia* is a commensal, lipophilic yeast that resides in the healthy skin microbiome. In healthy, nonatopic skin, *Malassezia* is thought to selectively induce IL-17 production, which prevents fungal overgrowth on the skin via disruption of the IL-17/IL-23 axis.<sup>53</sup> Recently, Sparber et al<sup>53</sup> developed a murine epicutaneous infection model mimicking AD skin and found that *Malassezia* species dramatically aggravate cutaneous inflammation through potentiation of the IL-17 and IL-23 pathways. When compared with healthy controls, AD patients also demonstrate an expansion of *Malassezia*-specific CCR6<sup>+</sup> T<sub>H</sub>17 memory T cells, which contribute to sensitization. Immunoglobulin E (IgE)-mediated sensitization to *Malassezia* is also a known component of the head and neck subtype of AD.<sup>54</sup> A study of 589 AD patients found that 100% of those with head and neck

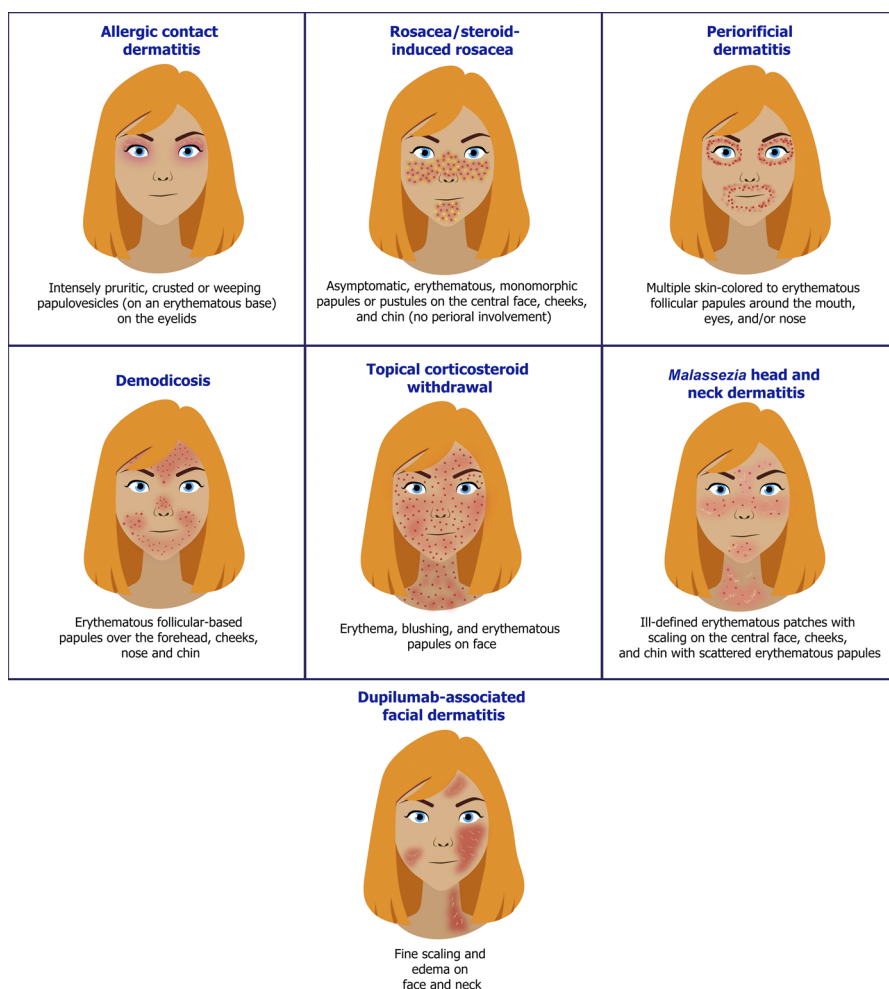


**Figure 1.** Selected face and neck dermatoses.

AD had increased *Malassezia*-specific IgE, compared with only 13% of patients with AD but no head and neck involvement.<sup>55</sup> Immunoglobulin E levels may also correlate with head and neck AD clinical severity.<sup>55–58</sup> Select patients may also develop a type 1 hypersensitivity reaction to *Malassezia* yeast protein, which is present in sweat. If this is suspected, patients should be counseled to be mindful about removing sweat after physical activity; antihistamines may be considered in severe cases and administered 1 hour before sweat-inducing activities.<sup>59</sup>

At present, head and neck dermatitis is considered a subtype of AD that is driven by a hypersensitivity to *Malassezia* yeast.<sup>60</sup> It is noteworthy that the pathogenesis of head and neck dermatitis is distinct from other *Malassezia*-driven diseases (such as tinea versicolor), which occur because of yeast overgrowth rather than

hypersensitivity.<sup>60</sup> *Malassezia restricta* is the predominant species in children with AD, whereas both *M. restricta* and *Malassezia globosa* are present in adults postpuberty.<sup>61</sup> The classic presentation is a patient with known AD who presents during or shortly after puberty with severe dermatitis on the forehead, eyelids, and/or neck. Lesions are new and in addition to preexisting AD lesions, for example, those on the extremities.

Several diagnostic clues can point to *Malassezia* involvement. First, patients with the *Malassezia* subtype of AD have more severe disease in the head and neck regions than in other AD-affected areas of the body (eg, flexor surfaces). Second, the head and neck lesions will often be refractory to conventional anti-inflammatory treatment modalities, for example, emollients, TCS, and calcineurin inhibitors.<sup>58</sup> It is important to note that *Malassezia* head and neck

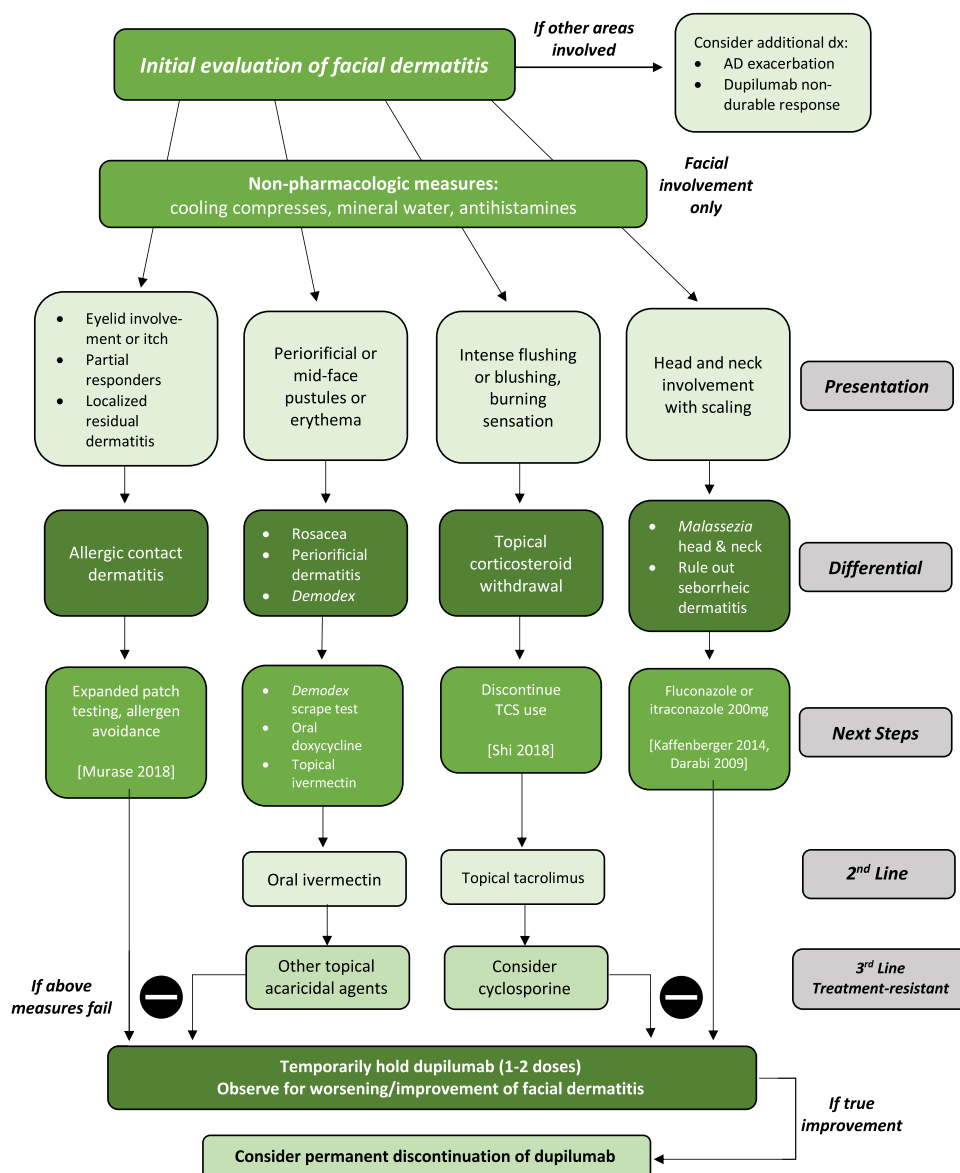


**Figure 2.** Management of head and neck dermatitis in AD patients on dupilumab.

dermatitis may appear clinically similar to seborrheic dermatitis. However, patients with seborrheic dermatitis do not have immunoreactivity to *Malassezia* on IgE testing, atopy patch testing, or skin-prick testing.<sup>62</sup>

Diagnosis of *Malassezia* is unreliable on scrape or culture tests outside a research setting; thus, diagnosis is based on clinical findings.<sup>58</sup> In patients with suspected *Malassezia* head and neck dermatitis, empiric treatment includes oral antifungals, such as itraconazole or fluconazole. In a retrospective study of oral azole antifungal agents, 17 of 24 patients with patch test–negative head and neck predominant AD responded to a 2-month course of itraconazole 200 mg daily or fluconazole 200 mg daily.<sup>60</sup> The only reported adverse effects were mild liver function test elevation in one patient and headaches in another patient that resolved upon discontinuation of azole therapy.<sup>60</sup>

Of note, recent case reports have brought to light that dupilumab therapy is associated with psoriasis flare-ups and/or psoriasiform eruptions.<sup>63–66</sup> These accounts suggest that DAFND may actually be a form of atypical facial seborrheic dermatitis and would thus be amenable to a trial of oral antifungals. In nonresponders, patch testing for ACD would be the next step.

### Drug-Associated Face and Neck Dermatitis

To date, at least 20 cases of DAFND on dupilumab have been reported in the scientific literature. Although its nosology remains unclear, the clinical presentations often include a generally eczematous morphology with fine scaling and some degree of edema on the face with variable neck involvement.<sup>9–13</sup> Until more data are available, it may be best to consider DAFND as a diagnosis of exclusion only after completing a thorough workup for other common facial dermatoses. In these cases, the decision to discontinue dupilumab should be made on an individual basis, weighing the risks and benefits of continued treatment with the patient.

The clinical appearance of each of the above face and neck dermatoses is presented in Figure 1. The management strategy for face and neck dermatitis in AD patients on dupilumab is depicted in Figure 2.

### CONCLUSIONS

Causes of face and neck dermatitis in AD patients are numerous and require clinical vigilance, astute history taking, and careful physical examination for accurate diagnosis. Assessment of face and neck dermatitis should include consideration of ACD, POD, rosacea or SIR, *Demodex* overproliferation, TCS withdrawal, and *Malassezia* head and neck dermatitis. Diagnostic testing may include potassium hydroxide or *Demodex* scrape testing for fungal or parasitic infection and patch testing (including expanded patch) in suspected ACD. These entities may arise regardless of dupilumab treatment status and require thoughtful and thorough assessment. Drug-associated face and neck dermatitis is an emerging entity associated with dupilumab that is gaining attention as additional cases come to light in the medical literature. Although reported clinical presentations are somewhat variable, they generally involve an eczematous dermatitis with fine scaling. Once a thorough workup for other

potential causes of head and neck dermatitis has been considered, DAFND may be considered as a diagnosis of exclusion. Potential treatment options include TCS, topical calcineurin inhibitors, and regular moisturization. Dupilumab discontinuation may be considered in cases of severe and treatment-refractory head and neck dermatitis. Practitioners should be aware of the potential for DAFND as an adverse effect of dupilumab therapy that may be addressed in medication counseling. As our understanding of the pathogenesis of DAFND evolves, we hope to be able to better identify at-risk patients and counsel accordingly.

### KEY POINTS

- Face and neck dermatitis in the atopic dermatitis patient has a broad differential.
- Case reports of recalcitrant face and neck dermatitis in atopic dermatitis patients on dupilumab are surfacing.
- Drug-associated face and neck dermatitis is a new diagnosis associated with dupilumab use that must be considered in the appropriate clinical setting.
- We present a management algorithm for face and neck dermatitis in the atopic patient with an emphasis on dupilumab.

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