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Article type : Case Report

Clinical and histopathological characterization of paradoxical head and neck erythema in atopic dermatitis patients treated with dupilumab: a case series.

Short Title: Erythema in a specific head-neck distribution during dupilumab treatment

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Funding: none

Conflict of interest disclosures

LEM de Wijs: *none*, NT Nguyen: *none*, ACM Kunkeler: *none*, TEC Nijsten: *none*, J Damman: *none*, DJ Hijnen: *investigator for AbbVie, LEO pharma, MedImmune/Astrazeneca, Novartis, Sanofi/Regeneron; consultancies for Regeneron/Sanofi, LEO pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen, Pfizer*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BJD.18730](#)

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Word count: 1066

Table count: 1

Figure count: 4

What's already known about this topic?

- Dupilumab has shown to be an efficacious and effective treatment for atopic dermatitis with an acceptable safety profile.
- The most frequently observed side effects in atopic dermatitis patients treated with dupilumab are conjunctivitis, herpes infections, and injection-site reactions.

What does this study add?

- For the first time, we report on atopic dermatitis patients treated with dupilumab who developed a paradoxical, mainly asymptomatic erythema in a head and neck distribution.
- Histological examination of skin biopsies revealed a psoriasiform reaction pattern suggestive of a drug-induced skin reaction.

Summary

Dupilumab is the first biologic registered for the treatment of atopic dermatitis (AD). We report on 7 AD patients presenting with a paradoxical head-neck erythema which appeared 10 to 39 weeks after start of dupilumab treatment. Patients presented with a relatively sharp demarcated, patchy erythema in the head and neck area that showed no or less scaling compared to their usual eczema. Only 1 patient experienced symptoms of itch and burning, although this was notably different from his pre-existent facial AD. Except for a notable “red face”, eczema on other body parts had greatly improved in 6 out of 7 patients with a mean NRS treatment satisfaction of 9/10 at time of biopsy. Treatment of the erythema with topical and systemic drugs was unsuccessful. Despite the presence of this erythema, none of our patients discontinued dupilumab treatment.

Lesional skin biopsies showed an increased number of ectatic capillaries, and a perivascular lymphohistiocytic infiltration in all patients. In addition, epidermal hyperplasia with elongation of the rete ridges was observed in 4 patients, resembling a psoriasiform dermatitis. Additional immunohistochemical stainings revealed increased numbers of plasma cells, histiocytes and T-lymphocytes. Interestingly, spongiosis was largely absent in all biopsies.

We report on AD patients treated with dupilumab developing a paradoxical erythema in a head-neck distribution. Both clinically and histopathologically we found a heterogeneous response, which was most suggestive of a drug-induced skin reaction.

Key words

Atopic dermatitis, dupilumab, erythema, side effect

Abbreviations

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; H&E, Hematoxylin & Eosin; NRS, Numeric Rating Scale; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; Th, T-helper

Dupilumab is the first biologic registered for treatment of moderate-to-severe atopic dermatitis (AD). By binding to the IL-4 receptor alpha chain, dupilumab blocks IL-4 and IL-13 signaling, thereby modulating the T-helper (Th)2-mediated inflammation in AD.¹ In clinical trials, conjunctivitis, herpes infections, and injection-site reactions were found to be the most frequently observed side effects.¹ Currently, only one case of paradoxical, refractory erythema in a head-neck distribution developed during dupilumab treatment is reported.²

Here, we describe a series of 7 AD patients who were treated with dupilumab and developed a paradoxical erythema in a head-neck distribution, differing from their usual AD lesions. Until now, we did not systematically check for this erythema in our dupilumab treated AD patients (n>150). However, we increasingly seem to observe this phenomenon. We recorded medical history, patient- and physician reported outcome measures, clinical symptoms and obtained lesional skin biopsies for histological examination.

Patient characteristics are summarized in Table 1. The erythema appeared after at least 10 weeks of dupilumab treatment and patients were treated with dupilumab for 12-71 weeks at time of biopsy. Concomitant treatment included topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) but no systemic immunosuppressants. There were no relevant (non-atopic, dermatologic) comorbidities and patients did not use any other systemic drugs. Prior to dupilumab treatment, 6 out of 7 patients suffered from erythematous lesions in the head and neck area, associated with symptoms of itching and burning in 5 of these patients. Patients noted that the signs and symptoms of the paradoxical erythema were different from their regular eczema. Strikingly, 6/7 patients did not report any symptoms of itch and burning in the head and neck area during dupilumab treatment.

During dupilumab treatment, patients presented with a relatively sharp demarcated, patchy erythema in the head and neck area that showed less or no scaling compared to their usual eczema (Figure 1a-b). Follicular accentuation was absent. Only 1 patient who presented with scaling lesions experienced symptoms of itch and burning, although notably different from the pre-existent symptoms. Treatment of the erythema with topical and systemic drugs, including potent TCS, TCI, emollients, antifungal medication, antibiotics, antihistamines and oral corticosteroids was unsuccessful (Table 1). Although the lesions did not respond to treatment all patients continued dupilumab treatment.

All patients experienced a clinically relevant reduction of the total Eczema Area and Severity Index (EASI) score (Table S2; see supporting information). However, in all 7 patients, disease severity scores increased again after 10-39 weeks of treatment. In the same period, all patients gradually developed an erythema specifically in the head and neck region which was reflected by a disproportional increase of the head-neck EASI subscore (Table S2). Despite the development of this erythema, the mean NRS treatment satisfaction rated by patients at time of biopsy was still 9 on a 10-point scale.

Histopathologic examination of lesional skin biopsies (n=7) included H&E (Hematoxylin & Eosin) (Figure 1c-d) and immunohistochemical stainings for CD3, CD20, CD68, CD138 and CD117 (Table S1). Histopathology showed epidermal hyperplasia with bulbous elongated rete ridges, increased numbers of ectatic capillaries in the papillary dermis and a moderate perivascular lymphocytic inflammation reminiscent of a psoriasiform dermatitis in 4 patients (Figure 1c-d, Table S1). Biopsies from the other 3 patients also showed increased ectatic capillaries and perivascular lymphocytic exocytosis, but no epidermal hyperplasia. Overall, a small number of eosinophils was found, and neutrophils and melanophages were largely absent. We found normal numbers of mast cells (CD117), T-cells (CD3) and histiocytes (CD68). There were variable numbers of plasma cells (CD138), but B-cells (CD20) were largely absent. Surprisingly, spongiosis was largely absent in all biopsies.

Discussion

We describe a paradoxical erythema in a head-neck distribution that developed in AD patients during dupilumab treatment. Histopathology showed a psoriasiform hyperplasia in 4 out of 7 patients, with ectatic capillaries in 6 out of 7 patients. Interestingly, spongiosis was absent in 5 out of 7 patients. Although, the histological findings could represent an atypical manifestation of chronic AD, the clinical manifestation with a sharply demarcated, patchy erythema, and absence of itch was not typical for AD.³ Although these patients were very satisfied with their overall treatment result, it has been shown that involvement of the face or neck are associated with higher patient-perceived importance of almost or complete skin clearance.⁴

The histopathology of acute AD lesions is characterized by spongiosis and perivascular lymphocytic and eosinophilic infiltrates.³ Subacute and chronic lesions show acanthosis, sometimes in a psoriasiform pattern, hyper- and parakeratosis, fibrosis, spongiosis, dense infiltrates of mononuclear cells, eosinophils and increased mast cells.³ Interestingly, we found that most of these histopathological hallmarks of AD were

missing in the biopsies. Spongiosis as well as mononuclear, mast cell and eosinophilic infiltrates were mostly absent, confirming our clinical observation that these are not typical AD lesions.

AD has been hypothesized to be a biphasic T-cell driven disease, with a predominance of Th2 cytokines in the acute phase and increased expression of Th1/Th17/Th22 cytokines in the chronic phase.⁵

As dupilumab targets IL-4RA, it blocks the key signaling pathways for Th2 T-cell differentiation.¹ Blocking the Th2 pathway could hypothetically result in a shift towards a more Th1/Th17/Th22 dominated response, resulting in the psoriasiform reaction pattern that we observed.⁶ Fowler et al. (2019), recently reported the development of psoriatic lesions during dupilumab treatment in 2 patients,⁷ but in contrast to our findings, they describe typical psoriasis lesions that were not located in the head-neck region.

Because we only found this paradoxical erythema in a typical head and neck distribution, we also considered allergic contact dermatitis (ACD), *Malassezia furfur* associated head and neck dermatitis, Demodex associated rosacea like dermatosis, and a drug-induced photosensitivity reaction. Patch testing for allergic contact dermatitis (ACD) was performed in three patients during dupilumab treatment but only one patient showed positive patch tests to lanolin and cocamidopropyl betaine. However, avoidance of the allergens did not improve this erythema and the histopathological findings were not suggestive of ACD.⁸ It has been suggested that (co)sensitization to human and/or fungal (including *Malassezia* spp.) enzyme superoxide dismutase might play an important role in the pathogenesis of atopic dermatitis and associated head and neck dermatitis.^{9,10} In murine models it was recently shown that *Malassezia* induces Th17 driven inflammation.¹¹ In AD patients treated with dupilumab, IL-4R blockade might facilitate a Th17 dominated response. However, in these mouse models, *Malassezia* also triggered massive infiltration of neutrophils and monocytes in the skin, which we did not find in the biopsies of our patients. Increased Th17 cytokine expression could also be in favour of Demodex colonization, which is associated with rosacea.¹² However, the clinical presentation in our patients was not typical for rosacea. In addition, histological features of rosacea were absent.¹³ The distribution of the lesions in our patients was also suggestive of a drug induced photosensitivity reaction, but none of our patients was using a known photosensitive drug and remarked influence of UV-radiation on the erythema was denied.¹⁴ Furthermore, the most common histological pattern found in drug induced photosensitivity reactions is a vacuolar interface dermatitis,¹⁵ which was not seen in our patients.

We speculate that this paradoxical head-neck erythema is a dupilumab-induced skin reaction. From personal communication with other AD experts we know that others have also observed this phenomenon. This emphasizes the importance of daily practice registries to gain better insights in the incidences of this phenomenon. Also, further research is needed to elucidate the underlying pathophysiological process.

Acknowledgments

None

References

- 1 Beck LA, Thaçi D, Hamilton JD *et al.* Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis. *New England Journal of Medicine* 2014; **371**: 130-9.
- 2 Albader SS, Alharbi AA, Alenezi RF *et al.* Dupilumab side effect in a patient with atopic dermatitis: a case report study. *Biologics* 2019; **13**: 79-82.

- 3 Weidinger S, Beck LA, Bieber T *et al.* Atopic dermatitis. *Nat Rev Dis Primers* 2018; **4**: 1.
- 4 Egeberg A, Thyssen JP. Factors associated with patient-reported importance of skin clearance among
adults with psoriasis and atopic dermatitis. *J Am Acad Dermatol* 2019.
- 5 Gittler JK, Shemer A, Suarez-Farinas M *et al.* Progressive activation of T(H)2/T(H)22 cytokines and
selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*
2012; **130**: 1344-54.
- 6 Greb JE, Goldminz AM, Elder JT *et al.* Psoriasis. *Nat Rev Dis Primers* 2016; **2**: 16082.
- 7 Fowler E, Silverberg JI, Fox JD *et al.* Presentation of Psoriasiform Dermatitis After Initiation of
Treatment With Dupilumab for Atopic Dermatitis. *Dermatitis* 2019.
- 8 So JK, Hamstra A, Calame A *et al.* Another Great Imitator: Allergic Contact Dermatitis Differential
Diagnosis, Clues to Diagnosis, Histopathology, and Treatment. *Current Treatment Options in Allergy*
2015; **2**: 333-48.
- 9 Sugita T, Boekhout T, Velegraki A *et al.* Epidemiology of Malassezia-Related Skin Diseases. In:
Malassezia and the Skin: Science and Clinical Practice (Boekhout T, Mayser P, Guého-Kellermann E *et*
al., eds). Berlin, Heidelberg: Springer Berlin Heidelberg. 2010; 65-119.
- 10 Schmid-Grendelmeier P, Fluckiger S, Disch R *et al.* IgE-mediated and T cell-mediated autoimmunity
against manganese superoxide dismutase in atopic dermatitis. *J Allergy Clin Immunol* 2005; **115**:
1068-75.
- 11 Sparber F, De Gregorio C, Steckholzer S *et al.* The Skin Commensal Yeast Malassezia Triggers a Type 17
Response that Coordinates Anti-fungal Immunity and Exacerbates Skin Inflammation. *Cell Host*
Microbe 2019; **25**: 389-403 e6.
- 12 Thyssen JP. Could conjunctivitis in patients with atopic dermatitis treated with dupilumab be caused
by colonization with Demodex and increased interleukin-17 levels? *Br J Dermatol* 2018; **178**: 1220.
- 13 Cribier B. Rosacea under the microscope: characteristic histological findings. *J Eur Acad Dermatol*
Venereol 2013; **27**: 1336-43.
- 14 Kim WB, Shelley AJ, Novice K *et al.* Drug-induced phototoxicity: A systematic review. *J Am Acad*
Dermatol 2018; **79**: 1069-75.
- 15 Weyers W, Metze D. Histopathology of drug eruptions - general criteria, common patterns, and
differential diagnosis. *Dermatol Pract Concept* 2011; **1**: 33-47.

Figure Legends

Figure 1a-d.

Clinical pictures (a,b) of paradoxical erythema in a head-neck distribution with corresponding histological H&E staining (c, d) of lesional biopsies

(a) Patient 1: 28 year old male patient showing a relatively sharp demarcated, minimally scaling, patchy erythema of the face and neck (scalp not affected) which was associated with burning and itching, but notably different from his usual eczema. (b) Patient 2: 29 year old female patient showing a minimally scaling, patchy erythema of the face and neck (scalp not affected) which was asymptomatic. (c,d) Histological examination of lesional skin biopsies of subjects 1 (c) and 2 (d), both obtained from the neck, revealed psoriasiform epidermal hyperplasia with bulbous elongated rete ridges (*), increased numbers of ectatic capillaries in the papillary dermis (→) and a moderate perivascular lymphocytic infiltrate (▲). Interestingly, spongiosis was largely absent in all biopsies.

Tables

Table 1. Patient and clinical characteristics (n=7)

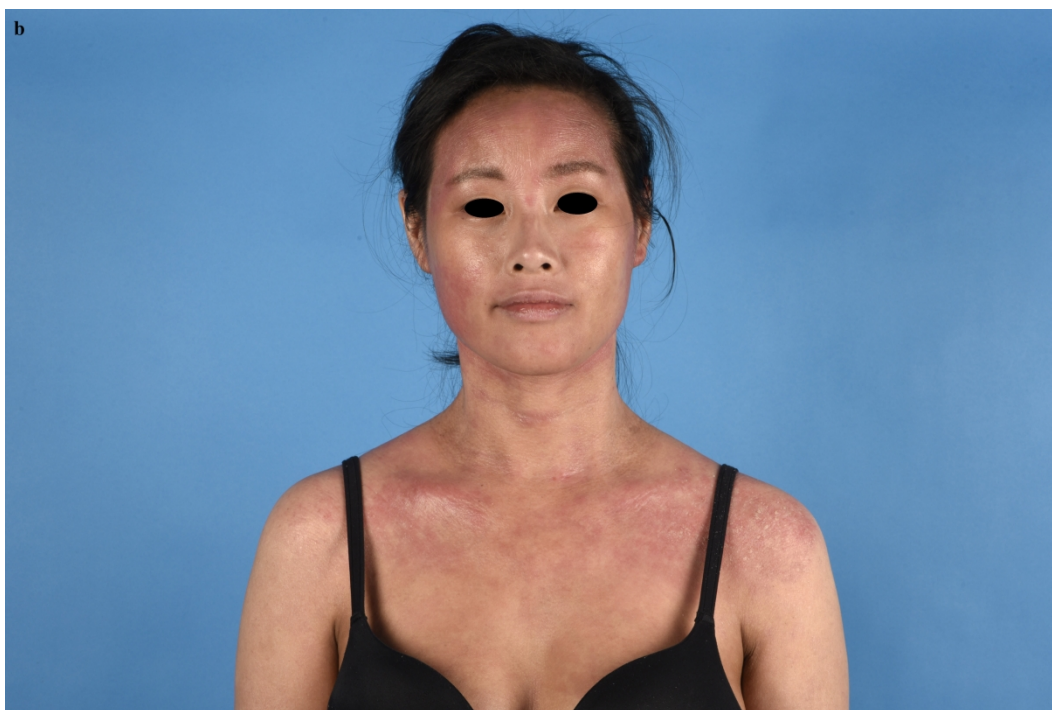
	Patient						
	1	2	3	4	5	6	7
Patient characteristics							
Sex	M	F	M	M	M	M	M
Age (years)	28	29	26	19	58	35	46
Disease duration (years)	16	29	26	19	52	35	46
Fitzpatrick skin type	2	3	2	2	3	2	2
Asthma/Allergic rhinoconjunctivitis)	+ / +	+ / +	- / +	+ / +	- / +	+ / +	+ / +
Allergic Contact Dermatitis ¹	+	-	-	+	N.A.	N.A.	-
Occupation, hobbies	Office job	Office job	Biologic crop control, soccer	Student	Warehouse worker	PE teacher, tennis coach	Salesman
Previous systemic immunosuppressants	CsA, MMF, AZA, MTX, APR, UST, prednisone	CsA, prednisone	CsA, prednisone	CsA, AZA, prednisone	CsA, MTX, prednisone	CsA, MTX, prednisone	CsA, MTX, prednisone
Clinical characteristics							
Onset of erythema (weeks of dupilumab treatment)	39	28	16-29	16-28	10-22	20	11
Treatment duration at time of biopsy (weeks)	49	53	42	51	22	71	12
Signs & symptoms before dupilumab (+/-)							
Erythema	+	+	+	+	-	+	+
Scaling	+	+	+	+	-	+	+
Itch	+	-	+	+	-	+	+
Burning sensation	+	-	+	+	-	+	+
Signs & symptoms of paradoxical erythema (+/-)							
Erythema	+	+	+	+	+	+	+
Scaling	+	+/-	-	-	-	-	-
Itch	+ ²	-	-	-	-	-	-
Burning sensation	+ ²	+/-	-	-	-	-	-

Influence of (+/-)							
UV	-	-	+	-	-	-	-
Alcohol	-	N.A.	-	-	-	-	-
Smoking	-	N.A.	N.A.	N.A.	N.A.	-	-
Re-testing Allergic Contact Dermatitis ³	N.A.	-	-	N.A.	N.A.	+	N.A.
Topicals prescriptions ^{4,5}	Class 3-4 TCS, TCI, emollients, ivermectine	Class 3-4 TCS, emollients	Class 3-4 TCS, emollients, fusidic acid	Class 3-4 TCS, emollients	Class 3-4 TCS, emollients	Class 3 TCS, TCI, emollients	Class 5 TCS
Systemic prescriptions ⁴	prednisone	prednisone	antifungals antibiotics antihistamine	antihistamine	none	none	none

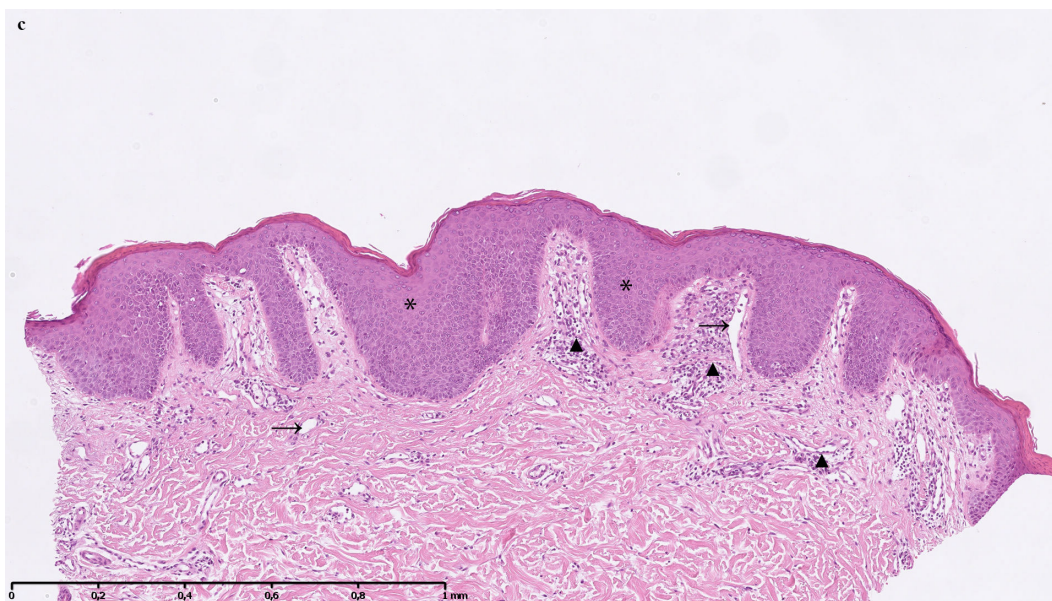
CsA, cyclosporine A; MMF, mycophenolate mofetil; AZA, azathioprine; MTX, methotrexate; APR, apremilast; UST, ustekinumab; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; N.A., not applicable ¹ Epicutaneous patch-proven allergic contact dermatitis, tested prior to dupilumab treatment; ² symptoms were notably different from pre-existing situation; ³ Epicutaneous patch-proven allergic contact dermatitis, (re)tested after onset of erythema; ⁴ Prescribed for head-neck erythema; ⁵ WHO classification for topical corticosteroids.



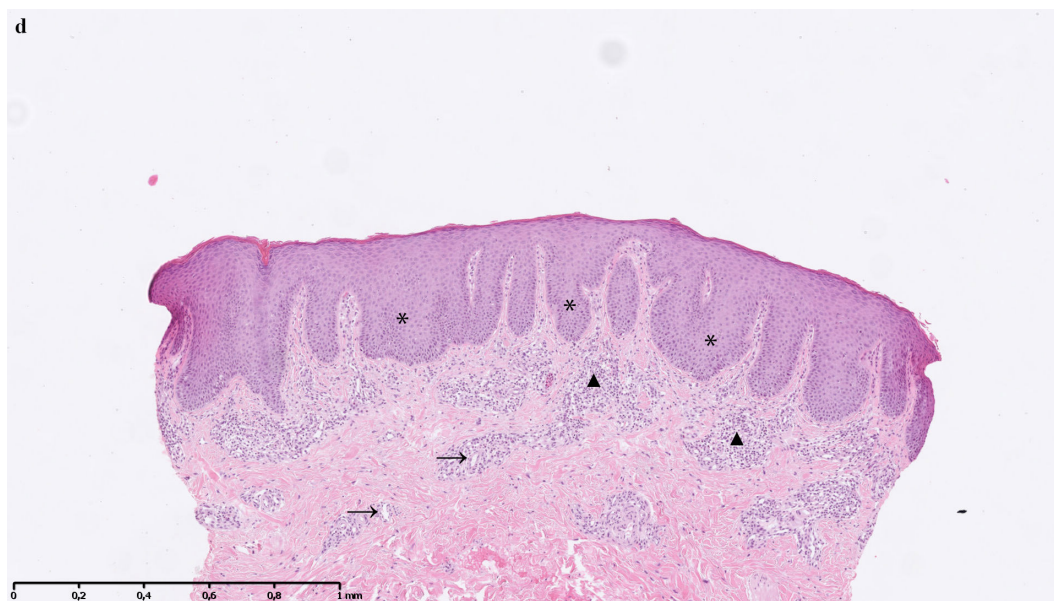
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Supporting information

Table S1. Histopathological findings in lesional skin biopsies (n=7)

	Patient						
	1	2	3	4	5	6	7
Histopathological findings							
Epidermal							
Psoriasiform hyperplasia	yes	yes	yes	no	no	no	yes
Serum	yes	no	yes	no	no	no	no
Spongiosis	yes (minimal)	no	yes	no	no	no	no
Parakeratosis	yes	no	yes	no	no	no	no
Basal vacuolisation	no	no	yes	no	no	no	yes
Lymphocytic exocytosis	scant	scant	scant	scant	scant	scant	scant
Apoptosis	no	no	no	no	no	no	no
Dermal							
Total infiltrate	moderate	moderate	moderate	moderate	scant	moderate	moderate
Level	superficial	mid-ret	deep	superficial	superficial	superficial	superficial
Perivascular	yes	yes	yes	yes	yes	yes	yes
Interstitial	no	no	no	no	no	no	no
Perifollicular	no	no	yes	yes	yes	yes	no
T-lymphocytes (CD3)	moderate	moderate	moderate	moderate	moderate	moderate	moderate
B-lymphocytes (CD20)	absent	scant	scant	absent	absent	absent	scant
Histiocytes (CD68)	moderate	moderate	moderate	moderate	moderate	moderate	moderate
Plasmacells (CD138)	scant	scant	moderate (and deep)	absent	absent	moderate	moderate
Eosinophils	scant	scant	absent	scant	scant	scant	scant
Neutrophils	scant	moderate	absent	scant	absent	absent	absent
Mast cells (CD117)	normal	normal	normal	normal	normal	normal	normal
Melanophages	absent	absent	absent	scant	scant	scant	scant
Vessels							
Number	increased	increased	increased	normal	increased	normal	increased
Ectatic	yes	yes	yes	yes	yes	no	yes
Other		pustule in follicle					

Table S2. Disease severity (sub)scores at baseline and during dupilumab treatment

Patient	EASI score at t=0		EASI score at t=1		EASI score at t=2		Proportion of head and neck region in total change EASI after t=2 ¹
	EASI	Head and neck subscore	EASI	Head and neck subscore	EASI	Head and neck subscore	
1	10.4	2.0	0.1 ↓↓	0.1 ↓↓	7.1 ↑↑↑	5.4 ↑↑↑	76%
2	34.8	2.4	3.2 ↓↓	0.8 ↓↓	7.6 ↑↑↑	2.4 ↑↑↑	36%
3	19.9	5.4	5.5 ↓↓	2.1 ↓↓	12.0 ↑↑↑	4.0 ↑↑	29%
4	12.3	1.2	9.3 ↓	0.3 ↓↓	11.5 ↑	2.0 ↑↑↑	77%
5	25.2	1.2	N.A.	N.A.	4.7 (N.A.)	1.5 (N.A.)	N.A.
6	18.3	1.5	5.1 ↓↓	0.9 ↓	10.2 ↑↑	2.8 ↑↑↑	37%
7	27.8	3.2	4.5 ↓↓	0.9 ↓↓	3.2 ↓	1.8 ↑↑	N.A.

EASI, Eczema Area and Severity Index; N.A., not available

↕: increase/decrease of <50% (compared to last measurement)

↕↕: increase/decrease of 50-100% (compared to last measurement)

↕↕↕: increase/decrease of >100% (compared to last measurement)

t=0: baseline, before start of dupilumab treatment

t=1: the last clinical assessment before onset of the paradoxical head-neck erythema

t=2: the first clinical assessment after onset of the paradoxical head-neck erythema

¹The head and neck area accounts for 20% of the total EASI score. This means that if the total eczema would have worsened proportionally, the proportion of the EASI score in the total change would have been 20%.