Avens Publishing Group
J Clin Investigat Dermatol
May 2023 Volume 11, Issue 1

Mycosis Fungoides Presenting After Dupilumab Therapy: Case Report and Systematic Review

Keywords: Atopic dermatitis; Cutaneous T cell Lymphoma; Cytokine; Mycosis Fungoides; Cutaneous T cell Lymphoma; IL-13, IL-4; IL-13Rα1 and IL-13Rα2

Abstract

Introduction: Several reports have been made associating dupilumab therapy for atopic dermatitis (AD) with the development of mycosis fungoides (MF) and other cutaneous T cell lymphomas (CTCL)

Methods: A new case report and systematic review were conducted to identify reports of MF/CTCL after minimum 6 weeks of dupilumab therapy between January 2021 and March 2023.

Results: 28 patients from 18 publications (including our case) were identified, averaging 17.4 years of AD duration with 18.5 weeks of dupilumab therapy prior to MF/CTCL diagnosis. MF/CTCL presented as 6 stage I, 4 stage II, 3 stage III, 4 stage IV, 3 Sezary syndrome, 6 large cell transformation, 2 peripheral T cell lymphoma (PTCL) and 1 with coexisting Hodgkin's lymphoma. There were 13 females, 15 males, and included 2 African-Americans, 4 Asians, and 22 Caucasians. 11 patients had initial improvement on dupilumab.

Conclusion: Clinical unmasking of MF/CTCL or de novo lymphomagenesis as the mechanism in these patients is unknown. Increased IL-13 and/or inhibition of reactive T cells through IL-4/IL-13 blockade are possible mechanisms of action. Awareness of this phenomenon during AD treatment and close follow-up and biopsy of non-responders or those who develop new morphologies is important.

Open Access **Case Report**

Journal of Clinical & Investigative Dermatology

Visconti M[1], Teklehaimanot F[2], Tan V[2] and Fivenson D[1,3]*

[1]*Department of Dermatology, St Joseph Mercy Hospital Ann Arbor, Ypsilanti, Michigan*
[2]*Michigan State School of Osteopathic Medicine, East Lansing, Michigan*
[3]*Fivenson Dermatology, 3200 W Liberty Rd, Suite C5, Ann Arbor, Michigan*

***Address for Correspondence**
Fivenson D, Fivenson Dermatology, 3200 W Liberty Rd, Suite C5, Ann Arbor, Michigan 48103; USA; Phone: 734-222-9630; E-mail: dfivenson@fivensondermatology.com

Submission: 24 March, 2023
Accepted: 04 April, 2023
Published: 02 May, 2023

Introduction

Mycosis Fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL) [1,2]. The disease is characterized by patches, plaques, and tumors that can be intensely pruritic and present in various sizes, shapes, and colors [2]. The cutaneous findings of MF can mimic other common cutaneous diseases such as atopic dermatitis, psoriasis, and parapsoriasis, making diagnosis challenging, and often requiring serial biopsies [3].

While the etiology of MF remains unknown, various hypotheses have been proposed which include genetic, environmental, infectious, and autoimmune involvement [4,5]. Recently, there have been several reports of MF diagnosed after the initiation of dupilumab therapy for atopic dermatitis (AD) or other eczematous conditions [6-23]. In this report, we present another case of AD developing stage IIB MF in the ensuing months after starting dupilumab and a systematic review of all published cases of this association, as well as the hypotheses for how this transition may occur.

Methods

A systematic English language literature review using PubMed and Google Scholar between January 2021 and March 2023, with key words of (mycosis fungoides and dupilumab, cutaneous T cell lymphoma and dupilumab, as well as descriptors of transformation, progression and misdiagnosis) was conducted to identify reports of the diagnosis of MF/CTCL in association with dupilumab treatment. All relevant reports had full text review by the senior author. Inclusion criteria included patients who were diagnosed with MF/CTCL following treatment with dupilumab, any preexisting dermatosis was included. Exclusion criteria included reports without histologic confirmation of MF/CTCL and those with diagnosis after less than 3 doses (6 weeks of standard initial therapy) of dupilumab therapy. This was done to exclude cases that could have been benign dermatoses that were temporarily given dupilumab while diagnostic workup for MF/CTCL was ongoing, as biologic transformation seems unlikely in such a short time frame. Preexisting MF/CTCL reports that were exposed to dupilumab were also excluded.

Data extracted included age, sex, AD duration, initial clinical and histologic features, prior therapies, duration of dupilumab treatment, MF/CTCL clinical presentation, MF histology, immunophenotyping, TCR gene rearrangement, TNMB staging, and subsequent therapy.

Results

Case 1: A 77-year-old male with a 10-year history of AD, presented to our clinic with worsening pruritus on the upper trunk and buttocks. Skin biopsies previously had shown spongiotic dermatitis with eosinophilic infiltrates. Prior treatments had included narrow-band ultraviolet light phototherapy (NBUVB), high-potency topical steroids (TS), and 17 weeks of dupilumab. Examination revealed extensive annular, atrophic, erythematous, scaling, patches and plaques which the patient noted had thickened since starting dupilumab. Repeat skin biopsy revealed an acanthotic epidermis with an atypical epidermotropic infiltrate of hyperchromatic-lymphocytes. Immunophenotyping showed a predominant T cell infiltrate that was CD2+, CD4+, CD1a-, CD3-, CD5-, CD8-, CD7-. T cell receptor (TCR) gamma and beta gene rearrangements were positive. Peripheral blood immunophenotyping, TCR, and PET scan revealed no systemic involvement. The patient discontinued dupilumab and started psoralen plus ultraviolet A photochemotherapy (PUVA) treatments twice weekly. Improvement in disease extent and lesion thickness was noted within 8 weeks and after 30 treatments the patient was almost clear.

ISSN: 2373-1044

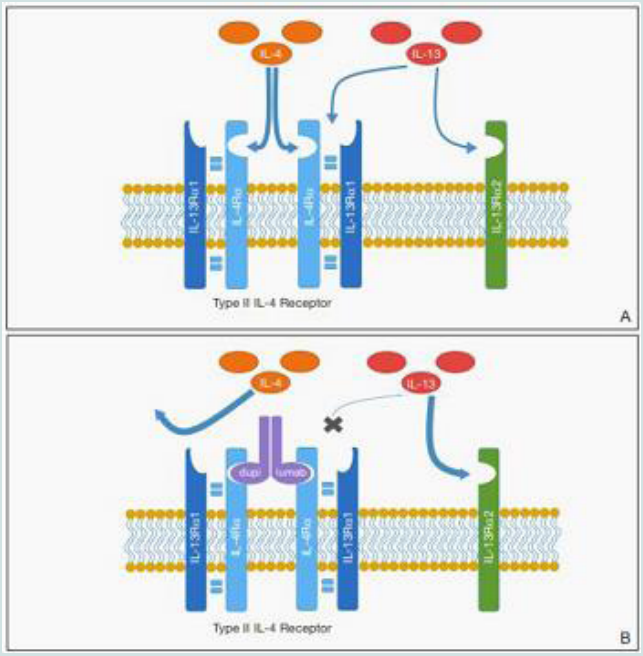

Figure 1: Proposed mechanism for promotion of cutaneous T-cell lymphoma (CTCL) by dupilumab. A, IL-4 and IL-13 bind to the type II IL-4 receptor (IL-4R). IL-13 also may bind at a distinct IL-13 receptor α2 (IL-13Rα2) site. B, Following blockade of the type II IL-4R, reduced binding at IL-4R may result in increased free IL-13 available for binding at the IL-13Rα2 site, which may have a role in promoting CTCL proliferation. Reprinted with permission from Hollins LC, et al, from Cutis.2020 August; 106: E8-E11. ©2020, Frontline Medical Communications Inc.

Patient demographics, clinical and histology before dupilumab therapy

19 studies were included, totaling 28 patients included in our series. 9 patients excluded after review of the publications due to insufficient length of dupilumab exposure (n=3) or its use reported in preexisting MF/CTCL subjects in the study (n=6)

The demographics of the patients included in this study are summarized in table 1. There were 15 males and 13 females. There were 22 Caucasian, 2 African American and 4 Asians with an age range of 27-77 years and a mean of 55 years. Duration of disease ranged from 1 to 58 years, mean= 17.4. Patients starting dupilumab therapy had a history of AD or presumed AD although several did not report skin biopsy findings pretreatment (table 1), with associated diseases including IgE mediated disorders (asthma, allergic rhinitis, idiopathic eosinophilia, and conjunctivitis) (n=5), and single cases each, allergic contact dermatitis, maxillary sinus carcinoma, oropharyngeal cancer, and ichthyosis vulgaris.

Clinical presentation and distribution of the skin eruption was widespread with reports of extensive disease (>70% body surface area-BSA) or exfoliative erythroderma prior to starting dupilumab in 18/23 cases that described disease extent prior to dupilumab therapy. Pruritus was dominant in most cases with morphologies described including prototypical AD (lichenified and excoriated flexural patches and plaques), urticarial, palmoplantar dermatitis, ichthyosiform xerosis, blepharitis and conjunctivitis.

Post-dupilumab clinical and histologic findings

Clinical and histologic features that changed after dupilumab treatment are also summarized in table 1. The mean duration of therapy was 18.5 weeks prior to MF/CTCL diagnosis. There were 2 reports of complete clearing and 8 of partial improvement of symptoms while on dupilumab. But eventual worsening and associated with the progression of lesions occurred in all reports. Some describe the development of secondary lesions including thicker plaques, nodules, erosions, exfoliative erythroderma, and ulcerating tumors.

The majority of patients had CD3+, CD4+, CD7-, CD8- atypical infiltrates with increased CD4:CD8 ratio with one case of CD8+ MF. Including the case above, there were 28 cases of MF/CTCL with staging including: 6 stage I, 4 stage II, 3 stage III, 4 stage IV, 3 Sezary syndrome, 6 large cell lymphoma (LCL) transformation, 2 PTCL and 1 with coexisting Hodgkin's lymphoma. TCR was positive in 6/14 and not reported in 14 cases.

Discussion

In 2017, Dupilumab became FDA approved to treat adults with moderate/severe AD [25]. Dupilumab is a monoclonal IgG4 antibody that blocks the IL4 receptor alpha chain in the shared IL-4/IL-13 receptor, leading to a decrease in TH2 cell cytokine-mediated signal transduction [26-28]. Common side effects include injection site reactions, headache, myalgia and blepharoconjunctivitis [28,29]. In this review, we have summarized a total of 28 cases (including 1 new case from the senior author's practice) that have a temporal association with the development of MF/CTCL, a mean time of 18.5 weeks on dupilumab therapy. Park et al and Schaefer et al have recently reviewed MF/CTCL in association with dupilumab or other biologic therapies [30,31], but these series did not apply stringent criteria of at least 6 weeks of dupilumab exposure as we have to underscore meaningful exposure to this agent in association with the evolution of MF/CTCL.

Heymann's commentary highlighted new reports of dupilumab in prurigo nodularis and bullous pemphigoid that appeared in the same journal issue as that of Espinosa et al [32], who reported 3 cases of AD developing MF while on dupilumab as well as 3 cases of MF who received it as adjuvant therapy for itching [12]. No adverse events were reported in the studies involving PN or BP, although the patients with AD who eventually were diagnosed with CTCL had worsening symptoms after various initial periods of improvement. In the same issue, the editor summarized several cases of MF after dupilumab treatment and commented on the role of IL-13 excess in lymphomas and the complex interplay of TH1/TH2 cell responses in the microenvironments of these diseases by paraphrasing the adage 'if it's dry, wet it and if it's wet, dry it' as not being the same as 'if it is upregulated, downregulate it' [33].

MF is a malignancy of TH2 T cells, and it is unclear how inhibition of the IL4/IL13 receptor might facilitate the proliferation of these cells. It is possible that blocking IL-4/IL-13 signaling on normal/reactive lymphocytes allows pre-existing small numbers of transformed T cells to proliferate. This is analogous to prior reports of progressive MF/CTCL in response to other immunosuppressive regimens, including classical chemotherapy and calcineurin inhibitors [34].

ISSN: 2373-1044

Table 1a: Mycosis Fungoides presenting after dupilumab therapy- Patient demographics and initial treatment

Author (manuscript reference number)	Age	Sex	Associated Medical History	AD duration (years)	Initial PE	Labs/Biopsy Prior to Dupilumab	Treatment Prior to Dupilumab	Dupilumab duration (weeks)	Dupilumab Response
Ayasse et al. (6)	40	F	Childhood AD, Eosinophilic asthma, chronic eosinophilia	4	Annular, erythematous to hyperpigmented patches and plaques, face, upper chest, LE, hands and feet, 80% BSA	Eosinophilic spongiosis	MTX, TS, TT	56	partial improvement in first 4 months
Chiba et al. (7)	58	M**	Childhood AD, Maxillary sinus carcinoma, allergic rhinitis, conjunctivitis, asthma	10	Faint erythematous, poikiloderma, patches, papules and nodules on face and trunk	Elevated TARC, IgE and LDH	TS	6	none
Lazaridou et al. (8)	37	F	none	19	Arcuate, finely, scaly erythematous patches, plaques 70% BSA	Thickened epidermis with parakeratosis, spongiosis, mononuclear infiltrate of superficial dermis	PUVA, TT, TS, MTX, cyclosporin	8	none
Miyashiro et al. (9)	51	F	none	1	pruritic eruption of hands, UE, LE and trunk	Spongiotic dermatitis, eosinophilia, mild exocytosis of lymphocytes	TS, SS, AZA	16	Mild relief of pruritis, spreading of plaques and new tumors.
Newsom et al. (10)	48	F	Presumed AD	6	Exfoliate erythroderma on LE, back, hands, face and scalp.	Spongiotic dermatitis	TS, MTX, NBUVB	20	none
	55	M	AD, oropharyngeal cancer with radiation to base of tongue	5	Excoriated patches on neck, trunk, inguinal folds and retroauricular region	Acanthosis, papillomatosis of epidermis, think parakeratotic stratum corneum and spongiotic dermatitis	TS, NBUVB	24	none
Russomanno et al. (11)	43	M*	Childhood AD, ichthyosis vulgaris, recrurrent hospitalizations as child	40	Lichenified, hyperpigmented plaques, flexural and intertriginous sparing, ichthyosiform scaling, alopecia, and lymphadenopathy	spongiotic dermatitis w/ eosinophils, elevated IgE, peripheral eosinophilia	TS, intramuscular triamcinolone.	8	Initial significant pruritus improvement, mild dermatitis improvement..
Sokumbi et al. (15)	66	F	Chronic dermatitis	6	Pruritus, papulosquamous patches and erythema of face, scalp, chest, back, UE	focal folliculotropism, vessel ectasia, wiry collagen, lymphocyte tagging; second biopsy urticarial reaction	TS, SS, oral antihistamines, NBUVB, dapsone, gabapentin, adalimumab, MMF, interferon	6	NR
	65	F	Chronic AD, idiopathic eosinophilia	4	Pruritus and exfoliative dermatitis of scalp, face, trunk, UE, LE	spongiotic and perivascular dermatitis with eosinophils	TS, SS, NBUVB, hydroxyurea	10	NR
	74	M	Chronic dermatitis	6	Pruritus, erythroderma, scaling of scalp, trunk, UE, LE, fissures of feet,	lymphocyte tagging, spongiosis, epidermotropism, vessel ectasia, wiry collagen	TS, SS, apremilast, topical pimecrolimus,	96	NR
	73	M*	Chronic dermatitis	5	Patchy alopecia, pruritus, erythroderma, poikiloderma of trunk, scalp, face, UE, LE	Epidermotropism, spongiosis, psoriasiform dermatitis, wiry collagen	TS, SS, MTX, cyclosporin, mycophenolate mofetil, AZA, omalizumab, antihistamines	56	NR
	44	F	AD	9	Erythroderma, scaling and ulceration of scalp, face, neck, trunk, UE, LE	none	TS, MTX	48	NR
	27	M	AD, allergic contact dermatitis	7	Skin pain and burning, pruritus, erythematous, scaling patches of head, face, neck, trunk, UE, LE	none	TS, SS, cyclosporin	56	NR

ISSN: 2373-1044

Espinosa et al. (12)	72	M	Presumed AD	--	not reported	not reported	TS, MTX	16	slight improvement, then progressive disease
	59	F	Presumed AD	--	not reported	not reported	TS, TT, gabapentin	108	90% improvement
	40	F	Presumed AD	--	not reported	not reported	Pantoprazole, Montelukast, Mirabegron	60	slight improvement
Poyner et al. (14)	60	M	Childhood AD	58	scaly facial patches	not reported	TS, SS	9	slight improvement
Hollins et al. (13)	52	M	AD vs psoriasis	--	indurated, scaly plaques on UE and LE	psoriasiform dermatitis	TS, multiple biologics, SS	12	partial improvement then progressive disease
	60	F	AD vs psoriasis	3	erythematous, pruritic dermatitis	spongiotic, eczematous dermatitis	TS, NBUVB, guselkumab	6	none
Tran et al. (16)	64	M	AD	5	exfoliative erythroderma	atypical lymphoid infiltrate, epidermal hyperplasia and lymphocyte and neutrophil exocytosis	TS, NBUVB	10	none
Du-Thanh et al. (17)	50	F	AD	50	erythematous scaling patches, 80% BSA	spongiotic dermatitis	TS, MTX, cyclosporin,	20	complete clearance
Umemoto et al. (18)	48	F**	AD since infancy	48	exfoliative erythroderma of scalp, trunk and buttocks, 80% BSA	none	not reported	8	no response
Ahatov et al. (20)	62	F	AD	50	erythematous, pruritic, and occasionally associated with crusts	nonspecific	not reported	72	partial improvement
Nakazaki et al. (19)	47	M**	AD	45	not reported	not reported	not reported	52	not reported
Park et al. (22)	72	M	AD	2	diffuse pruritic eruption	not reported	TS, TT, topical antifungals	9	progressive disease
Saad et al. (23)	55	M	AD	21	diffuse lichenified and excoriated patches and plaques	not reported	not reported	24	complete clearance
Amagai et al. (24)	38	M**	AD	3	erythematous plaques and disseminated papules	elevated IgE, TARC and IL-2R levels	TS, NBUVB, SS	52	NR
Authors' case	77	M	AD	10	lichenified, scaling patches and plaques	Spongiotic dermatitis with eosinophilic infiltrate	TS, NBUVB, SS	17	progressive thickening of plaques, increased spread of eruption

Abbreviations: MF- mycosis fungoides, CTCL- cutaneous T cell lymphoma, UE- upper extremities, LE- lower extremities, TS- topical steroids, SS- systemic steroids,, TT- topical tacrolimus, NBUVB- narrow band ultraviolet B, PUVA- psoralen plus ultraviolet A, TCR- T cell receptor gene rearrangement, AZA- azathioprine, MTX- methotrexate, ALK- anaplastic lymphoma kinase, TIA-1- T cell intracellular antigen 1, PTCL- peripheral T cell lymphoma, MMF- mycophenolate mofetil, BSA- body surface area, NR- not reported. *= African american, **Asian

Table 1b: Mycosis Fungoides presenting after dupilumab therapy- Mycosis fungoides presentation and treatment

Author (manuscript reference number)	MF Clinical Presentation	MF Histopathology, Immunophenotyping and TCR gene rearrangement	MFStage	MF Treatment
Ayasse et al. (6)	progressive disease with erosions on lower extremities; nodules on chest, neck, and face; facial plaques with follicular spicules	1.Focal parakeratosis, spongiosis with vesiculation, exocytosis of lymphocytes, dense superficial perivascular lymphohistiocytic infiltrate w/ occasional eosinophils. No TCR done 2.Epidermotropism of atypical hyperchromatic lymphocytes, spongiosis with vesiculation, atypical hyperchromic lymphocytes in dermis, large cell transformation. CD3+, CD7-, CD30+, CD4+, folliculotropic, few CD8+ T cells, few CD20+ B cells.	MF Stage IIB folliculotropic with large cell transformation	NR
Chiba et al. (7)	progressive disease, more prominent lesions	Band-like atypical lymphocytic infiltrate. Atypical epidermotropic lymphocytes without spongiosis in epidermis, Pautrier's microabcess. CD3+, CD4+, TCR+; further elevation of TARC, IgE and LDH	MF- no staging reported	TS, NBUVB
Lazaridou et al. (8)	intense pruritus, skin plaques, palmoplantar keratosis	Atypical dermal infiltrate -CD3+ CD4+, CD7-, PD1+, CD30- T cells, Blood CD4/CD8 ratio 22:1. Same phenotype in blood and skin.	Sezary Syndrome	gemcitabine, brentuximab,
Miyashiro et al. (9)	multiple patches, plaques and ulcerated tumors	1.Spongiotic, psoriasiform dermatitis, exocytosis of few lymphocytes, dermal eosinophils. 2.Atypical lymphohistiocytic lichenoid dermal infiltrate- CD4+ CD7- T cells; CD4/CD8 ratio =6.9 TCR+ skin, TCR- blood, Normal flow cytometry, no Sezary cells	MF- tumor stage	Acitretin, PUVA
Newsom et al. (10)	progressive exfoliative erythroderma	Infiltrate of atypical lymphocytes lining epidermis: atypical CD3+, CD4+, CD5+, CD7-, CD8-, CD20-, CD30- T cells	MF Stage IB	NR

ISSN: 2373-1044

	widespread hyperpigmented and hypopigmented patches	Atypical lymphocytes in epidermis, papillary dermal fibrosis, pigment incontinence. Atypical CD3+, CD5+, decreased CD7, rare CD30+, CD20- T cells; increased CD4:CD8 ratio.	MF Stage IB	NR
Russomanno et al. (11)	increased dermatitis and lymphadenopathy, 10-15 pound weight loss	Atypical lymphoid infiltrates. MF with large cell transformation, 40% CD30+ .	MF Stage IVA2 with large cell transformation; T2bN3M0B1b	brentuximab monotherapy + pralatrexate
Sokumbi et al. (15)	NR	Epidermotropism, Pautrier microabscesses, folliculotropic. atypical CD3+, CD5+, CD7- T cells, CD4/CD8 ratio >20:1; TCR-	MF Stage IIA, T2aN2M0B0	NR
	NR	No epidermotropism, lichenoid and eosinophilic infiltrate, wiry collage; atypical CD3+, CD5+, CD7- T cells, CD4/CD8 ratio >20:1; TCR-	MF Stage IB, T2aN0M0B0	NR
	NR	Atypical lymphocyte tagging, epidermotropism, vessel ectasia, wiry collagen; atypical CD3+, CD5+, CD7+ T cells; CD4/CD8 ratio =10:1; TCR-	MF Stage III, T4N0M0B0	NR
	NR	Lymphocyte tagging, epidermotropism, spongiosis, wiry collagen, atypical folliculotropic; CD3+, CD5+, CD7- T cells, CD4/CD8 ratio >20:1; TCR-	MF Stage III, T4N0M0B0	NR
	NR	Lymphocyte tagging, epidermotropism, Pautrier microabscesses, psoriasiform with neutrophils and eosinophils and lymphocytes, wiry collagen; atypical CD3+, CD5+ T cells, CD4/CD8 ratio =5:1; TCR-.	MF Stage IV, T4N3M0B0	NR
	NR	Parakeratosis, spongiosis, lymphocyte tagging, epidermotropism, lymphocyte atypia, wiry collagen, focal lichenoid; atypical CD3+, CD5+, CD7+ T cells, CD4/CD8 ratio =20:1; TCR not done	MF Stage IB, T2aN0M0B0	NR
Espinosa et al. (12)	thick plaques and papules on face	NR	MF Stage IB	TS, NBUVB
	enlarging facial plaques, fatigue, weight loss	NR	MF Stage IA	dupilumab continued
	erythroderma, blepharoconjunctivitis, worsening pruritus	NR	MF Stage IIIA	SS, TS, NBUVB, MTX
Poyner et al. (14)	enlarging facial plaques, new nodules on neck, arms, legs and back, ulcerated nodules in groin, lymphadenopathy	Prominent dermal infiltrate of atypical CD3+, CD30+, CD4-, CD8-, ALK-, TIA-1- T cells; TCR-; blood negative except for CD4/CD8 ratio =6.8	MF Stage IVA with large cell transformation	NR
Hollins et al. (13)	NR	MF - no details reported	MF- no staging reported	NR
	NR	MF - no details reported	MF- no staging reported	NR
Tran et al. (16)	Increased exfoliative erythroderma to 95% BSA, burning, pruritus and diffuse lymphadenopathy	MF in skin, no details reported; Sezary Syndrome with blood immunophenotyping of CD4/8 ratio = 43:1, CD4+,CD7-, CD26-; TCR+	Sezary Syndrome	bexarotene, photophoresis
Du-Thanh et al. (17)	new onset painful, ulcerated nodule of breast	Atypical CD2+, CD3+, CD4+, CD5-,CD8-, CD30+. TIA-1+, Granzyme B+ T cells; CT scan with multiple areas of lymph node involvement	CD30+ Anaplastic large cell lymphoma	Chemotherapy, brentuximab, autologous stem cell transplant
Umemoto et al. (18)	exfoliative erythroderma, thick scaling, lymphadenopathy	Acanthosis, exocytosis, atypical CD4+ T cells, Pautrier's microabscesses; blood CD4/CD8 ratio= 3.6; TCR+.	Sezary syndrome T4N2M0B2, Stage IVA1	TS, NBUVB, vorinostat
Ahatov et al. (20)	generalized rash with widespread polycyclic erosions and ulcers	Atypical CD3+. CD4-, CD8-, CD5-, CD7-, CD30-, CD45+, CD56-, Granzyme B+, Perforin +, TIA-1- T cells with cerebriform nuclear contour and hyperchromatic nuclei; TCR indeterminant	PTCL-cytotoxic T cell lymphoma	Died of sepsis before therapy
Nakazaki et al. (19)	bulky right axillary and chest wall mass; scaly, hyperpigmented, erythematous patches on UE and LE	Atypical CD3+, CD4+, CD5-, CD7-, CD20-, CD8 and Granzyme B partially + T cells; TCR+; lymph node - nodular sclerosis type Hodgkin lymphoma with Hodgkin and Reed-Sternberg cells CD15+, CD30+, MUM-1+, PD-L1+, CD3-, CD5-, CD7-, CD45-, TIA-1-, Granzyme B-.	Hodgkins lymphoma and PTCL	Brentuximab, vedotin, doxorubicin, vinblastine and dacarbazine
Park et al. (22)	erythematous scaling plaques on trunk and proximal UE and LE	Interface dermatitis with atypical CD3+, CD8+, CD5+, CD2/CD7 partial loss, TCR-	CD8+ MF Stage IIa	TS, NBUVB, bexarotene, ECPP
Saad et al. (23)	erythematous ulcerating nodules on palms	atypical dermal and epidermotropic infiltrate CD3+, CD4+, CD7-, CD30+, granzyme B+, ALK-, TCR+	MF and anaplastic large cell lymphoma	radiation therapy, dupilumab continued with complete response
Amagai et al. (24)	dome-shaped crusted papules and nodules	dense dermal infiltrate of CD2+, CD4+, CD30+, CD3-, CD5-, CD7-, CD8-, ALK-	CD30+, ALK- anaplastic large cell lymphoma	TS, brentuximab
Authors' case	annular, annular, atrophic, erythematous and scaling, patches and plaques	Atypical epidermotropic infiltrate of hyperchromatic T cells CD2+, CD4+, CD1a-, CD3-, CD5-, CD8-, CD7-; TCR+; blood immunophenotyping, TCR- and PET scan revealed no systemic involvement.	MF Stage IIb	PUVA

Abbreviations: MF- mycosis fungoides, CTCL- cutaneous T cell lymphoma, UE- upper extremities, LE- lower extremities, TS- topical steroids, SS- systemic steroids,, TT- topical tacrolimus, NBUVB- narrow band ultraviolet B, PUVA- psoralen plus ultraviolet A, TCR- T cell receptor gene rearrangement, AZA- azathioprine, MTX- methotrexate, ALK- anaplastic lymphoma kinase, TIA-1- T cell intracellular antigen 1, PTCL- peripheral T cell lymphoma, MMF- mycophenolate mofetil, BSA- body surface area, NR- not reported. *= African american, **Asian

ISSN: 2373-1044

It is not possible to tell if any/all these patients had preexisting MF/CTCL or whether this was de novo transformation into a malignancy. Due to the relatively short time frame for MF diagnosis, we review here (median time after dupilumab therapy was 8 months) and the overall rarity of this presentation compared to the extensive use of dupilumab in AD, we suspect that atypical T cells were already existing in many of these patients' skin prior to dupilumab therapy. Proliferative T cell neoplasia may have been thus allowed to progress, much the same as how the gradual diminution of host immunity with the advancing stage of CTCL has been classically described to promote progressive disease over time [35]. Additional hypotheses include the upregulation of IL-13Rα2, a decoy receptor involved in atopic dermatitis but not blocked by dupilumab [36]. IL-13Rα2 binding by the excess IL-13 could have autocrine effects in the microenvironment that may further stimulate the growth of the malignant cells as proposed by Wadele et al [37] and Geskin et al [38] and previously proposed in the figure published by Hollis et al [13]. Another possible mechanism is that malignant T cells may no longer bind dupilumab with the same efficacy of normal T cells [37-39].

Conclusion

All these mechanisms remain unproven but have a permissive effect of dupilumab in mycosis fungoides evolution. Dupilumab has been a very effective new agent in our armamentarium and these cases are best seen as a cautionary tale that clinicians pay attention to the patient's history and presenting symptoms when initiating this therapy and have a low threshold for biopsy of any lesions that are not classic. Atypical/poor responders should be closely followed up and repeat biopsies considered detecting any unmasked cases of CTCL as early in therapy as possible.

References

1. Larocca C, Kupper T (2019) Mycosis Fungoides and Sézary Syndrome. Hematol Oncol Clin North Am 33: 103-120.
2. Cerroni L (2018) Mycosis Fungoides-Clinical and Histopathologic Features, Differential Diagnosis, and Treatment. Semin Cutan Med Surg 37: 2-10.
3. Hodak E, Amitay-Laish I (2019). Mycosis Fungoides: A Great Imitator. Clin Dermatol 37: 255-267.
4. Slodownik D, Moshe S, Sprecher E, Goldberg I (2017) Occupational Mycosis Fungoides - A Case Series. Int J Dermatol 56: 733-737.
5. Fujii K (2018) New Therapies and Immunological Findings in Cutaneous T-Cell Lymphoma. Front Oncol 8: 198.
6. Ayasse M, Nelson K, Glass F, Silverberg JI (2020) Mycosis Fungoides Unmasked by Dupilumab Treatment in a Patient with a History of Atopic Dermatitis. Dermatitis 32: e88-e89.
7. Chiba T, Nagai T, Osada SI, Manabe M (2019) Diagnosis of Mycosis Fungoides Following Administration of Dupilumab for Misdiagnosed Atopic Dermatitis. Acta Derm Venereol 99: 818-819.
8. Lazaridou I, Ram-Wolff C, Bouaziz JD, Bégon E, Battistella M, et al. (2020) Dupilumab Treatment in Two Patients with Cutaneous T-cell Lymphomas. Acta DermVenereol 100: adv00271.
9. Miyashiro D, Vivarelli AG, Gonçalves F, Cury-Martins J, Sanches JA (2020) Progression of mycosis fungoides after treatment with dupilumab: A case report. Dermatol Ther 33: e13880.
10. Newsom M, Hrin ML, Hamid RN, Strowd LC, Ahn C, et al. (2021) Two cases of mycosis fungoides diagnosed after treatment non-response to dupilumab. Dermatol Online J 7: 13030/qt1133121d.
11. Russomanno K, Carver DeKlotz CM (2020) Acceleration of cutaneous T-cell lymphoma following dupilumab administration. J Dermatol Case Rep 8: 83-85.
12. Espinosa ML, Nguyen MT, Aguirre AS, Martinez-Escala ME, Kim J, et al. (2020) Progression of cutaneous T-cell lymphoma after dupilumab: Case review of 7 patients. J Am Acad Dermatol 83: 197-199.
13. Hollins LC, Wirth P, Fulchiero GJ Jr, Foulke GT (2020) Long-standing dermatitis treated with dupilumab with subsequent progression to cutaneous T-cell lymphoma. Cutis 106: E8-E11.
14. Poyner EFM, Bacon CM, Osborne W, Frew JA, Weatherhead SC (2022) Dupilumab unmasking cutaneous T-cell lymphoma: report of a fatal case. Clin Exp Dermatol 47: 974-976.
15. Sokumbi O, Shamim H, Davis MDP, Wetter DA, Newman CC, et al. (2021) Evolution of Dupilumab-Associated Cutaneous Atypical Lymphoid Infiltrates. Am J Dermatopathol 43: 714-720.
16. Tran J, Morris L, Vu A, Duvic M (2020) Development of Sézary syndrome following the administration of dupilumab. Dermatol Online J 26: 13030/qt1m67z8sb.
17. Du-Thanh A, Gustave V, Dereure O (2021) Lethal anaplastic large-cell lymphoma occurring in a patient treated with dupilumab. J Dermatol Case Rep 18: 4-7.
18. Umemoto N, Demitsu T, Otaki K, Matsumoto T, Takazawa M, et al. (2020) Dupilumab therapy in Sézary syndrome misdiagnosed as atopic dermatitis: A case report. J Dermatol 47: e356-e357.
19. Nakazaki K, Yoshida M, Masamoto Y, Shinozaki-Ushiku A, Ikemura M, et al. (2022) Discordant lymphomas of classic Hodgkin lymphoma and peripheral T-cell lymphoma following dupilumab treatment for atopic dermatitis. Int J Hematol 116: 446-452.
20. Ahatov R, Good AJ, Joo M, Tipton S, Goodwin B, et al. (2022) A rare case of aggressive cytotoxic T-cell lymphoma in a patient on dupilumab. J Dermatol Case Rep 24:112-114.
21. Hashimoto M, Miyagaki T, Komaki R, Takeuchi S, Kadono T (2022) Development of Nodular Lesions after Dupilumab Therapy in Erythrodermic Mycosis Fungoides with Interleukin-13 Receptor alpha2 Expression. Acta DermVenereol 102: adv00766.
22. Park A, Wong L, Lang A, Kraus C, Anderson N, et al. (2022) Dupilumab-Associated Mycosis Fungoides with a CD8+ Immunophenotype. Dermatopathol 9: 385-391.
23. Saad S, Ram-Wolff C, De Masson A, Jachiet M, Battistella M, et al. (2022) CD30-positive anaplastic large-cell lymphoma associated with mycosis fungoides after treatment with dupilumab. Eur J Dermatol 32: 536-537.
24. Amagai M, Ozawa M, Amagai R, Ohuchi K, Muto Y, et al. (2022) Nodal anaplastic large cell lymphoma with lymphomatoid papulosis following treatment of initially presumed atopic dermatitis with dupilumab: A case report. Dermatol Ther 35: e15290.
25. Seegräber M, Srour J, Walter A, Knop M, Wollenberg A (2018) Dupilumab for treatment of atopic dermatitis. Expert Rev Clin Pharmacol 11: 467-474.
26. Harb H, Chatila TA (2019) Mechanisms of Dupilumab. Clin Exp Allergy 50: 5-14.
27. Thibodeaux Q, Smith MP, Ly K, Beck K, Liao W, Bhutani T (2019) A review of dupilumab in the treatment of atopic diseases. Hum Vaccin Immunother 15: 2129-2139.
28. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, et al. (2016) SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med 375: 2335-2348.
29. Ou Z, Chen C, Chen A, Yang Y, Zhou W (2017) Adverse events of Dupilumab in adults with moderate-to-severe atopic dermatitis: A meta-analysis. Int Immunopharmacol 54: 303-310.
30. Park A, Wong L, Lang A, Kraus C, Anderson N, Elsensohn A (2022) Cutaneous T-cell lymphoma following dupilumab use: a systematic review. Int J Dermatol 62: 1-15.
31. Schaefer L, Comfere N, Sokumbi O (2023) Development of Cutaneous T-Cell

ISSN: 2373-1044

Lymphoma Following Biologic Treatment: A Systematic Review. Am J Clin Dermatol 24: 153-164.

32. Heymann WR (2020) Dupilumab cuts both ways. J Am Acad Dermatol 83: 35-36.

33. Elston, Dirk M (2020) Dupilumab and Cutaneous T-Cell Lymphoma. JAmAcad Dermatol 83: 33-34.

34. Pomerantz RG, Campbell LS, Jukic DM, Geskin LJ (2010) Posttransplant cutaneous T-cell lymphoma: case reports and review of the association of calcineurin inhibitor use with posttransplant lymphoproliferative disease risk. Arch Dermatol 146: 513-516.

35. Larocca C, Kupper T (2019) Mycosis Fungoides and Sézary Syndrome: An Update. Hematol Oncol Clin North Am 33: 103-120.

36. Furue M, Ulzii D, Nakahara T, Tsuji G, Furue K, et al. (2020) Implications of IL-13RA2 in Atopic Skin Inflammation. Allergol Int 69: 412-416.

37. Wäldele K, Schneider G, Ruckes T, Grassmann R (2004) Interleukin-13 overexpression by tax transactivation: a potential autocrine stimulus in human T-cell leukemia virus-infected lymphocytes. J Virol 78: 6081-6090.

38. Geskin L, Viragova s, Stolz D, Fuschetti P (2015) Interleukin-13 is overexpressed in cutaneous T-cell lymphoma cells and regulates their proliferation. Blood 125: 2798-2805.

39. Joshi TP, Duvic M (2023) Unmasking a masquerader: mycosis fungoides unveiled after dupilumab treatment, J Am Acad Dermatol S0190-9622(23)00327-4.