Review paper

Mycosis fungoides unveiled following dupilumab treatment in a patient with a history of atopic dermatitis. Usefulness of HFUS in monitoring skin features. A review with a case report

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Abstract

Dupilumab has revolutionized atopic dermatitis (AD) treatment, but concerns arise about its potential link to cutaneous T-cell lymphomas (CTCL). This review explores CTCL occurrence post-dupilumab therapy in AD and its potential therapeutic effects. A case study of a 76-year-old patient with severe AD treated with dupilumab, developing erythroderma revealing mycosis fungoides (MF), underscores the need to understand associated mechanisms and risk factors for safe dupilumab use. This case also highlights the utility of the high-frequency ultrasound in monitoring cutaneous manifestations in patients with MF.

Key words: non-Hodgkin lymphoma, T-cell lymphoma, T-cell, MF, mycosis fungoides, dupilumab, antibodies, monoclonal, humanized, skin diseases, ultrasonography, skin imaging.

Introduction

Dupilumab is a humanized IgG4 monoclonal antibody that selectively targets interleukin-4 receptor a (IL-4Rα), effectively inhibiting the signalling pathway mediated by interleukin-4 (IL-4) and interleukin-13 (IL-13) [1]. By competitively binding to IL-4Rα, dupilumab hinders the activation of tyrosine kinases involved in transcriptional gene regulation, thereby modulating key processes related to barrier dysfunction and inflammatory responses driven by Th2 cells [2]. The therapeutic potential of dupilumab in atopic dermatitis (AD) was recognized by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2017, making it the first biologic agent approved for the treatment of moderate to severe AD in adults who are unresponsive to topical therapies [1]. Recent case studies have reported several instances of unmasked or progressive cutaneous T-cell lymphomas (CTCL) in association with dupilumab therapy [3].

Here, we report a case study involving a 76-year-old patient with severe AD who developed erythroderma and subsequently revealed to have mycosis fungoides (MF) during treatment with dupilumab. Furthermore, we conducted a literature review with a particular focus on documented cases of AD transforming into CTCL in response to biological therapy.

Case report

A 76-year-old patient presenting with erythroderma and a history of unsuccessful treatments of AD underwent biologic therapy with dupilumab was admitted to the Department of Dermatology for further management and diagnostic assessment. Erythroderma appeared in the 10th week of treatment, prior to the 5th dose of dupilumab. According to the patient's medical history, the initial manifestation of eczema on hands with severe pruritus occurred when the patient was 69. In accordance with the diagnostic criteria for AD by Hanifin and Rajka, the patient was diagnosed then with AD (pruritus, chronic and relapsing course of the disease, family history of atopy in the mother of the patient, xerosis, nonspecific hand eczema, pruritus after sweating).

Despite multiple hospitalizations and various treatments since the age of 69, including phototherapy: nar-

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row-band ultraviolet B (NB-UVB, 311 nm), psoralen and UVA (PUVA) therapy, antihistamines (both first – and second-generation), topical and systemic glucocorticosteroids (prednisone at a maximum dose of 50 mg q.d. or deflazacort 6 mg q.d.), as well as parenteral glucocorticosteroid therapy (hydrocortisone 200 mg q.d.), no significant clinical improvement was achieved. Cyclosporine A (CyA) at a dose of 200 mg q.d. (2.7 mg/kg of body weight) was administered, but was discontinued due to lack of efficacy and increase in arterial blood pressure to 220/130 mm Hg after 2 weeks of treatment. Then subcutaneous methotrexate (MTX) at a dose of 15 mg p.w. was initiated for 6 months at the age of 75.

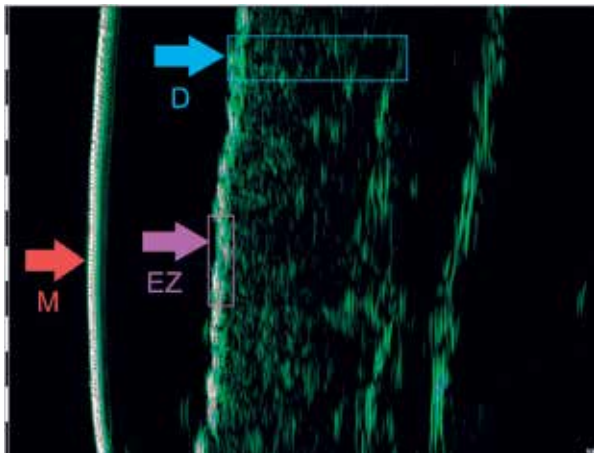
The results of biopsy taken from the lesions on the trunk at the age of 71, were consistent with AD, i.e. significant infiltration of CD4+ T lymphocytes and deposits of collagen in the dermis, along with macrophage infiltration were demonstrated. Immunophenotyping analysis of peripheral blood conducted also at the age of 71 showed no aberrations. Additionally, patch tests and an allergy panel yielded negative results.

During the patient's hospitalization at the age of 74, an immunophenotyping analysis of peripheral blood lymphocytes revealed a predominance of CD4 (+) T lymphocytes (> 95%), with retained expression of CD7 and CD26 antigens. No T-cell receptor mutations were detected. Concurrently, in 2023 ultrasound examination identified abnormal lymph nodes, including supraclavicular lymph nodes (bilateral, up to 1 cm), axillary lymph nodes (bilateral, up to 2.7 cm), and inguinal lymph nodes (bilateral, up to 5.4 cm with clustering). Subsequent histological evaluation of an inguinal lymph node biopsy demonstrated characteristic features of dermatopathic lymphadenitis without evidence of CTCL in the examined nodes.

In the 6th year of observation at the age of 76, due to inadequate response to previous therapeutic approaches including CyA and MTX, the patient was enrolled in a dupilumab drug program due to the diagnosis of chronic, severe AD. MTX was discontinued, and a gradual tapering of deflazacort was initiated, with complete discontinuation achieved in 3 months. However, a week later, the patient presented with significant facial and lower limb oedema, accompanied by erythroderma. This exacerbation occurred during the fifth week of dupilumab biologic therapy. Consequently, the medication was discontinued and the patient was admitted to the department for the management of exacerbated skin symptoms, likely attributed to an outbreak during dupilumab treatment.

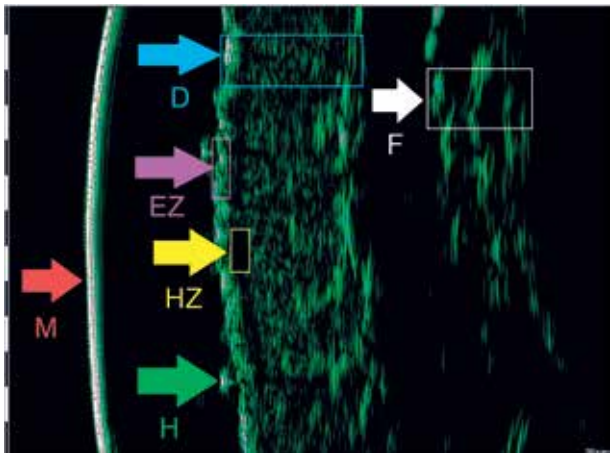
Figure 1. Erythematous-infiltrated cutaneous manifestations situated anteriorly

Figure 2. Erythematous-infiltrated cutaneous manifestations located posteriorly



M – membrane, D – dermis, EZ – entrance zone.

Figure 3. The HFUS (22.5 MHz) picture – the healthy skin



M – membrane, D – dermis, EZ – entrance zone, HZ – hypoechogenic zone, H – hair, F – fascia.

Figure 4. The HFUS (22.5 MHz) picture – the broad band hypoechogenic zone interpreted as infiltration under epidermis

Upon admission, the patient presented with disseminated erythematous and infiltration lesions, generalized xerosis, lichenification with the most pronounced involvement observed on the trunk (Figures 1, 2). Laboratory investigations revealed significant deviations, including leucocytosis (25.7 × 10^3/µl) with lymphocytosis (10.84 × 10^3/µl). A second skin biopsy was obtained for further evaluation of MF from the erythematous plaque in the right subcostal region. The skin biopsy confirmed the diagnosis of MF, i.e. moderately abundant lymphoid infiltration of T cells in the stroma: CD20-, CD3+, CD7+, CD5+/-, CD4>>CD8+, CD30 in single cases, MIB high up to 50%, admixture of histiocytes (CD68), features of epidermotropism with the presence of single abscess-like structures Pautrier-based on histological and immunohistochemical analyses. The patient underwent a consultation with a haematologist. Following immunophenotyping analysis of the blood and exclusion of active cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections, both an aspirational bone marrow biopsy and a trephine biopsy were performed from the right iliac crest. At that time, no infiltration was detected, 3 months later laboratory tests revealed elevated leukocyte and lymphocyte levels, decreased neutrophil and eosinophil levels, and an increased concentration of β2 microglobulin (3.77 mg/l, normal range: 1.09–2.53 mg/l). The activity of lactic acid dehydrogenase was normal (172 U/l). Additionally, the patient underwent high-frequency ultrasound (HFUS) assessment of both unchanged (Figure 3) and skin lesion (Figure 4) which revealed a narrow band max. 0.1 mm hypoechogenic shadow below the entrance zone (EZ). The patient is currently under the care of the haematological outpatient clinic and biological treatment with dupilumab was not resumed.

Discussion

AD represents the predominant chronic inflammatory skin disease which in the most severe expression, can present as erythroderma [4]. According to epidemiological studies, the prevalence of AD in the adult population varies globally, ranging from 3.4% in Israel to 33.7% in Thailand and in the elderly population from 2.1% to 4.9% around the world [5, 6].

Furthermore, secular trends indicate a rise in the prevalence of AD among adults [7].

CTCLs represent a heterogeneous spectrum of infrequent extranodal non-Hodgkin lymphomas (NHL) characterized by malignant monoclonal T-cell proliferations localized within the skin. MF and Sézary syndrome (SS) are prominent subtypes within this classification [8].

MF typically exhibits a protracted clinical evolution, progressing over years through patch, plaque, and tumour stages, eventually involving lymph nodes [9].

Erythrodermic MF is a rare case of MF in which skin lesions merge and advance to erythroderma without blood involvement. SS and erythrodermic MF are recognized as constituents of a more extensive spectrum of erythrodermic cutaneous T-cell lymphoma (e-CTCL) [10].

The incidence of CTCL is 10.2 per million persons, with MF constituting more than half of the diagnosed cases [11]. Nevertheless, a significant meta-analysis has revealed that individuals with AD are at higher risk of developing lymphoma [12].

Furthermore, Mansfield *et al.* [13] reported that the risk of developing NHL escalates in correlation with the severity of eczema.

Table 1. Laboratory and immunological features differentiating atopic dermatitis (AD) from erythrodermic cutaneous T-cell lymphoma (e-CTCL) [14, 15]

Parameter	Atopic dermatitis	Erythrodermic cutaneous T-cell lymphoma
Lactate dehydrogenase (LDH)	+/– ↑	↑
β_2-microglobulin (B2M)	Within normal range	+/– ↑
Soluble interleukin receptor 2 (sIL-2)	+/– ↑	↑
Eosinophilia	+	in the advanced stage
Immunoglobulin E (IgE)	↑	↑ in the advanced stage
Th-2 microenvironment activation	+	in the advanced stage
Antimicrobial peptides (AMPs)	↓	↓
Colonisation of S. aureus	80%	60%

Differentiation between adult-onset AD and e-CTCL is challenging even for experienced clinicians (Table 1) [14, 15].

The differentiation between both diseases is imperative, especially given the common use of CyA in cases of severe AD. Considering the elevated risk of lymphoproliferation associated with therapeutic approaches employing CyA, the use of this medication is contraindicated in the context of CTCL, contrary to previous reports found in the scientific literature [16].

In the literature, there are also several reports highlighting the coexistence of AD with MF [17, 18]. However, it is crucial to acknowledge the potential comorbidity of these conditions in patients as treating AD with dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13, may be associated with the progression of MF and SS.

Influence of dupilumab on the course of CTCL

Dupilumab therapy has been implicated in the unmasking, progression or rarely improvement of CTCL, as reported in recent case studies [19–30] (Table 2).

Appearance of CTCL after dupilumab therapy in AD patients

The majority of existing literature findings suggest the elicitation or manifestation of CTCL in individuals with a prior diagnosis of AD and/or eczema.

Chiba *et al*. [19] reported a case study involving a 58-year-old male patient with a long-standing history of AD since childhood. Due to the severe nature of his AD, treatment with subcutaneous dupilumab with an initial dose of 600 mg *s.c*. followed by subsequent doses of 300 mg *s.c.* every 2 weeks was implemented. The patient's erythematous lesions on the face and trunk showed increased visibility during dupilumab treatment. Histological examination confirmed a diagnosis of MF (Table 2).

A study conducted by Espinosa *et al.* [20] investigated the effects of dupilumab in a cohort of seven patients with AD and CTCL. Among the participants, four patients received dupilumab for clinically presumed AD, while three patients with severe pruritus were administered dupilumab off-label for CTCL. Initial improvement was observed in six out of the seven patients; however, subsequent exacerbation of body surface area involvement, pruritus, lymphadenopathy, and systemic symptoms occurred. Remarkably, all four patients initially diagnosed with AD were eventually confirmed to have CTCL after dupilumab treatment. In the subset of patients with preexisting CTCL, flow cytometry analysis revealed worsened blood involvement, leading to a diagnosis of SS during dupilumab treatment. Finally 2 out of the 3 patients experienced disease progression and succumbed to the illness (Table 2). Next, Miyashiro *et al.* [21] described the case report of a 51-year-old female who presented with 1-year duration of pruritic cutaneous lesions. After the failure of classical forms of pharmacotherapy, dupilumab treatment was prescribed. Following the administration of eight treatment cycles, mild relief in pruritus was observed; however, there was a worsening of the lesions characterized by the spread of plaques and the emergence of tumours. Upon histological examination, the patient received a diagnosis of tumour-stage MF (Table 2).

Moreover, Newsom *et al*. [22] observed 2 patients with primary AD which switched into CTCL. The first patient, a 48-year-old woman, presented with a diffuse pruritic cutaneous eruption that had manifested 6 years earlier and progressively spread from the scalp. A lesional biopsy of the forearm confirmed spongiotic dermatitis. Due to the limited improvement with MTX and PUVA, the patient was initiated on dupilumab. However, after a five-month treatment involving dupilumab and MTX, non-response prompted a second skin biopsy, which revealed the presence of MF. The second patient was a 55-year-old man with a 5-year history of AD, who had no improvement after topical corticosteroids and NB-UVB. Initiation of dupilumab therapy also did not yield any noticeable benefits, resulting in discontinuation of the medication after 6 months. Subsequent biopsy analysis of lesional skin confirmed the diagnosis of MF in stage 1B (Table 2). Next, Russomanno *et al*. [23] presented a case study in-

Table 2. Cutaneous T-cell lymphoma (CTCL) or first diagnosis of atopic dermatitis (AD) cases treated with dupilumab [19–34]

Author	Age	Sex	First diagnosis	Next diagnosis	Response to treatment	Death
Chiba *et al.* case report	58	M	AD	MF	Progression to MF	No
Espinosa *et al.* series of case reports	64	M	AD	CTCL-NOS	Progression of erythroderma	No
	72	M	AD	MF	Progression to MF	No
	59	F	AD	MF and AD	Progression to MF	No
	40	F	AD	MF	Progression to MF	No
	67	M	MF	SS	Progression to MF	Yes
	58	M	MF	SS	Progression to MF	Yes
	77	F	MF	SS	Progression to SS	No
Miyashiro *et al.* case report	51	F	AD	MF	Progression to MF	No
Newsom *et al.* case report	48	F	AD	MF	Progression to MF	No
	55	M	AD	MF	Progression to MF	No
Russomanno *et al.* case report	43	M	AD	MF	Progression to MF	No
Tran *et al.* case report	64	M	AD	SS	Progression to SS	No
	61	M	Eczema	MF	Progression to MF	No
	52	M	Eczema	MF	No clinical improvement	No
Hollins *et al.* series of case reports	60	F	Eczema	MF	No clinical improvement	No
Poyner *et al.* case report	60	M	Eczema	MF	Progression to MF	No
Umemoto *et al.* case report	48	F	AD	SS	Progression to SS	No
Lazaridou *et al.* case reports	37	F	Eczema	SS	Progression to SS	No
Trum *et al.* case report	26	M	MF	MF	No clinical improvement	No
Toker *et al.* case report	65	M	Eczema	MF	Progression to MF	No
Lazaridou *et al.* case report	55	M	MF and AD	MF and AD	Improvement of MF and AD	No
Mollanazar *et al.* case report	68	M	SS and AD	SS and AD	Improvement in SS and AD	No
Talmon *et al.* case report	75	F	CTCL	CTCL	Improvement of CTCL	No
Steck *et al.* case report	74	F	AD	SS	Improvement of SS	No
Qiu *et al.* case report	56	F	MF and AD	MF and AD	Improvement of MF and AD	No

M – male, F – female, AD – atopic dermatitis, CTCL-NOS – cutaneous T-cell lymphoma not otherwise specified, MF – mycosis fungoides, SS – Sézary syndrome.

volving a 43-year-old male who had chronic severe AD since childhood. The patient's condition had worsened significantly over the past year, and the efficacy of corticosteroid injections had diminished, leading to concerns. Pathology reports from recent punch biopsies revealed spongiotic dermatitis with eosinophils, ruling out CTCL. Subsequently, dupilumab at a dose of 600 mg *s.c.*, followed by 300 mg every 2 weeks was prescribed. After 2 months, the patient presented with a significant exacerbation of dermatitis. Repeat punch biopsies were conducted, resulting in the diagnosis of CTCL (Table 2). Tran *et al*. [24] also presented a case study of a male pa-

tient diagnosed with refractory adult-onset AD who was initiated on subcutaneous administration of dupilumab. However, after receiving a loading dose of 600 mg, the patient experienced an extensive erythrodermic rash affecting approximately 95% of the total body surface area. As a result of persistent erythroderma, flow cytometry analysis revealed the presence of SS (Table 2).

A study by Hollins *et al*. [25] described three patients with long-standing eczematous or psoriasiform dermatitis. These patients underwent multiple biopsies to establish the diagnosis of their dermatological conditions. Subsequently, they received off-label treatment with dupilumab. Surprisingly, all three individuals exhibited a marked clinical exacerbation of their skin disease, which prompted further investigation. Histological examination of subsequent biopsy specimens revealed distinctive features consistent with CTCL (Table 2).

Poyner *et al*. [26] also presented a case study involving a 60-year-old male patient who was prescribed dupilumab for the treatment of severe and long-standing atopic eczema. Prior to this, the patient had received MTX and CyA. After 9 weeks of initiating dupilumab, the individual experienced the development of a widespread rash and lymphadenopathy, leading to the discontinuation of dupilumab. Subsequent histological examination confirmed the presence of MF (Table 2). Furthermore, Umemoto *et al*. [27] presented a case report detailing the clinical course of a 48-year-old woman with generalized erythroderma and intense pruritus. Despite receiving three injections of dupilumab subsequent to the AD diagnosis, the therapeutic response for cutaneous symptoms was inadequate. Physical examination revealed severe exfoliative erythroderma accompanied by superficial lymph node enlargement. Histological examination confirmed the diagnosis of SS (Table 2). Lazaridou *et al*. [28] also reported a case involving a 37-year-old woman with a protracted history of pruritic dermatitis initially diagnosed as eczema. Despite multiple treatments, including PUVA, topical tacrolimus, topical corticosteroids, MTX and CyA, the patient showed no improvement leading to the introduction of dupilumab. However, there was no clinical response after 2 months of dupilumab treatment. A subsequent biopsy revealed SS (Table 2). In the study by Trum *et al*. [29], a 26-year-old man with MF despite mogamulizumab and NB-UVB therapy had unsatisfactory results. Dupilumab was then prescribed, resulting in significant pruritus improvement and complete eruption resolution by the seventh injection. Four months later, he tolerated MTX 20 mg s.c. p.w. well with stable disease (Table 2). Toker *et al*. [30] reported a case of a 65-year-old male who initially presented with a 2-month history of pruritus and diffuse symptoms. A biopsy confirmed eczematous dermatitis, leading to the commencement of dupilumab at a dose of 300 mg every 2 weeks. After 6 months and five maintenance doses, the patient developed a new, morphologically distinct rash. Upon comprehensive diagnostic evaluation, MF was identified (Table 2).

Improvement of CTCL after dupilumab therapy

During the literature review, only a limited number of publications, comprising five studies, reported improvement in individuals diagnosed with CTCL following the administration of dupilumab [28, 31–34] (Table 2).

In a study by Lazaridou *et al*. [28] mentioned in the chapter of progression of CTCL due to dupilumab treatment, the second case involved a 55-year-old man whose initial biopsy confirmed AD, but a subsequent biopsy revealed MF. The patient experienced severe pruritus with a Dermatology Life Quality Index (DLQI) score of 22/30, and was treated with dupilumab. This led to improved pruritus and partial remission of MF (Table 2). Moreover, Mollanazar *et al*. [31] reported a comprehensive case study involving a 48-year-old male undergoing multimodal therapeutic interventions for concurrent AD and CTCL. The treatment protocol encompassed bexarotene, interferon α-2b, interferon g-1b, total skin electron beam therapy followed by NB-UVB and extracorporeal photopheresis (ECP). Subsequently, due to the persistence of cutaneous manifestations, dupilumab therapy was initiated. Notably, after 3 months, a favourable outcome was shown (Table 2). A study led by Talmon *et al*. [32] assessed the safety and efficacy of dupilumab as a therapeutic intervention for refractory malignancy-associated pruritus in three subjects. Notably, one of the subjects, a 75-year-old female diagnosed with CTCL, presented with pruritus as a primary manifestation. Despite undergoing multiple lines of treatment, including IFN-α, topical nitrogen mustard, topical corticosteroids, belinostat, gemcitabine, local retinoids, and eventually liposomal doxorubicin, the patient experienced persistent itching. The patient initiated a biweekly regimen of subcutaneous dupilumab, which remains ongoing. Remarkably, a substantial improvement in pruritus was observed after the initial dose and it completely resolved after the third dose (Table 2). In a study led by Steck *et al*. [33], a 74-year-old woman with primary persistent and refractory eczematous dermatitis was finally diagnosed with SS. Despite trying PUVA, topical steroids, ECP, interferon-α-2a and NB-UVB, there was no improvement. Consequently, off-label treatment with dupilumab was initiated (600 mg *s.c*., followed by 300 mg *s.c*. biweekly). After pausing dupilumab between weeks 22 and 29 to assess causality, the patient continued with 300 mg *s.c*. biweekly in conjunction with ECP, currently at 44 weeks post-initiation (Table 2). In the last study by Qiu *et al*. [34], a 56-year-old woman with a 7-year history of AD, concurrent CTCL and mucosa-associated lymphoid tissue (MALT) received dupilumab. Pruritus and the severity of the disease improved significantly after 1 month of treatment. Dupilumab was initiated at a 600 mg loading dose, followed by 300 mg biweekly. After 5 months of dupilumab therapy, remarkable numerical improvement and stability in CTCL recurrence were evident (Table 2).

Conclusions

The observed correlation between dupilumab therapy and the manifestation or progression of CTCL, particularly MF, underscores the necessity for vigilant surveillance. Enhanced comprehension of the underlying pathophysiological mechanisms and identification of predisposing factors warrant dedicated scientific inquiry/study. A multidisciplinary approach remains imperative for the comprehensive management of patients undergoing dupilumab therapy, particularly those with a history of AD. A heightened level of suspicion should be maintained when encountering cases of persistent AD-spectrum that do not respond to standard therapeutic agents. In such instances, a skin biopsy and comprehensive evaluation for an underlying oncologic process should be contemplated.

Moreover, none of the cited authors utilized HFUS. However, we highlight its utility in assessment and recommend performing objective evaluations of CTCL infiltration using HFUS.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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