

RESEARCH LETTER

Diagnosis of mycosis fungoides or Sézary syndrome after dupilumab use: A systematic review

To the Editor: Reports of patients developing mycosis fungoides (MF) or Sézary Syndrome (SS) Supplementary Refs s1-s11, available via Mendeley at <https://data.mendeley.com/datasets/nn8xj6zgst> while on dupilumab suggest the drug may cause or unmask MF/SS. To explore whether dupilumab promotes malignant transformation, unmasks MF/SS, or whether patients with MF/SS are misdiagnosed with atopic dermatitis (AD), we performed a systematic review of published data on patients with MF/SS previously treated with dupilumab for presumed AD to identify common patient and disease characteristics. The search strategy is provided in (Supplementary Materials, available via Mendeley at <https://data.mendeley.com/datasets/nn8xj6zgst>).

We identified reports of patients with AD treated with dupilumab who subsequently developed pathology-confirmed MF/SS (Fig 1). Using Naranjo analysis, we evaluated likelihood of dupilumab-associated MF/SS.¹

Twenty-three cases from 11 sites (Table I, Supplementary References, available via Mendeley at <https://data.mendeley.com/datasets/nn8xj6zgst>) diagnosed with MF/SS post-dupilumab for presumed AD were included [median (range) age 58 (27-74); adult AD onset, $n = 19$ (82.60%)]. AD onset was mostly in adulthood in 19 (82.61%) vs 4 (17.39%) in childhood. Pre-dupilumab biopsies performed in 13 (56.52%) cases were not diagnostic of MF/SS, but five had atypical features for AD (epidermotropism, folliculotropism, lichenoid inflammation). Among cases with pre-/post-dupilumab biopsies, increased lymphoid infiltrates and epidermotropism were observed over time. None reported tissue T-cell

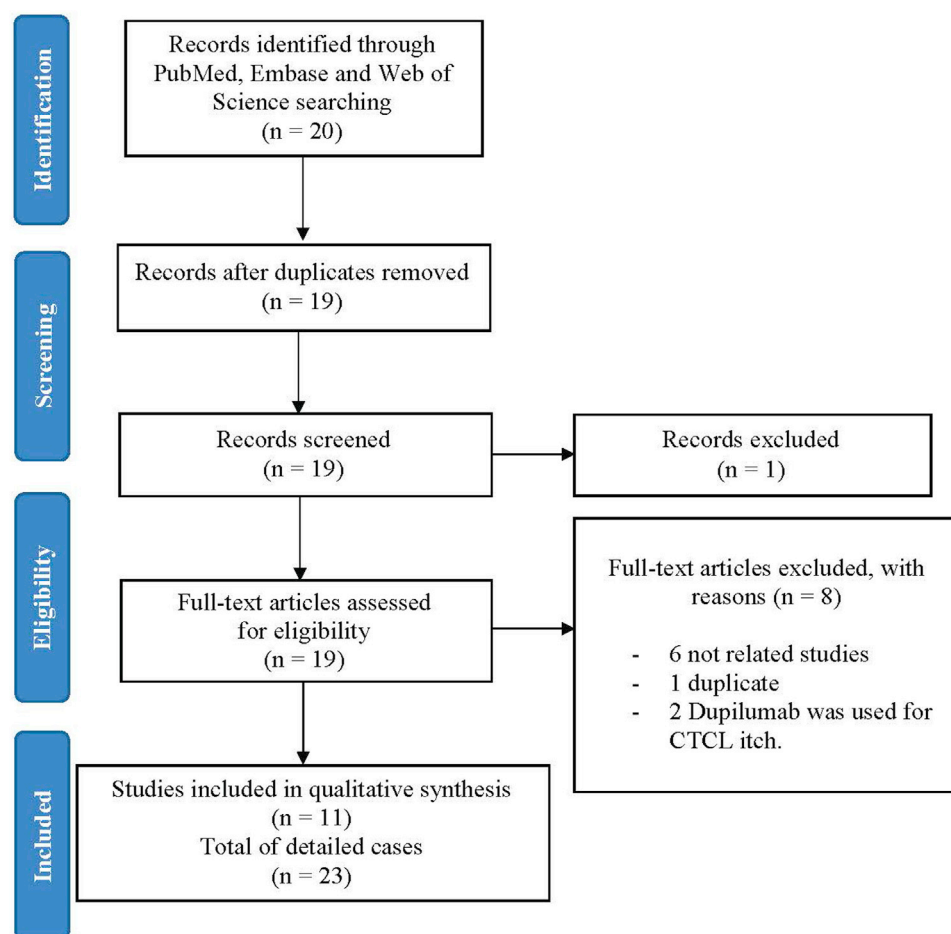


Fig 1. Study flowchart as per the preferred reporting items for systematic reviews and meta-analyses criteria.

Table I. Patient's demographics and characteristics

Case	Age	Sex	AD duration	Physical exam findings (pre-dupilumab)	Pre-dupilumab biopsy	Dupilumab initiation to MF/SS diagnosis (mo)	MF/SS type/stage at time of diagnosis	MF/SS overall outcome	Naranjo score*
1	58	M	Childhood	Erythematous lesions on the face, papules, and nodules on the back. Poikiloderma lesions	ND	1	MF/NR	NR	3
2	40	F	Childhood	NR	Eosinophilic spongiosis	13	MF/IIB	NR	3
3	64	M	3-27 mo	NR	ND	8	MF/IIIA	NR	4
4	72	M	3-27 mo	NR	ND	4	MF/IB	NR	4
5	59	F	3-27 mo	NR	ND	27	MF/IA	NR	4
6	40	F	3-27	NR	ND	15	MF/IVA	NR	4
7	61	M	10 y	NR	Nonspecific eczematous dermatitis	1	MF/NR	NR	3
8	52	M	NR	Indurated, red, scaly plaques on the legs and arms.	Eczematous process	3	MF/NR	NR	3
9	60	F	3 y	Diffuse, pruritic, and erythematous dermatitis and one isolated plaque	Eczematous dermatitis	2	MF/NR	NR	3
10	37	F	19 y	Finely scaly erythematous patches affecting 70% of the body surface area	Thickened epidermis with parakeratosis, discrete spongiosis, mononuclear infiltrate of superficial dermis, consistent with eczema	2	SS	PR	4
11	51	F	1 y	Pruritic cutaneous lesions on the hands, trunk, upper and lower limbs. No lymphadenopathy	Spongiotic dermatitis, eosinophilia, and mild exocytosis of lymphocytes	8	MF/at least IIB	PR	3
12	64	M	5 y	Erythroderma. Lymphadenopathy	ND	4	SS	NR	3
13	48	F	Childhood	Erythroderma	ND	2	Sezary/IVA1	NR	3
14	48	F	6 y	Exfoliate erythroderma	Spongiotic dermatitis	5	MF/IB	NR	3
15	55	M	5 y	NR	ND	6	MF/IB	NR	3

16	43	M	Childhood	Diffuse ill-defined, lichenified, and hyperpigmented plaques with sparing of the flexural and intertriginous surfaces as well as the genitalia. Ichthyosiform scaling and diffuse thinning of the hair on the scalp and eyebrows. Painful fissures on his hands and feet. Palpable lymphadenopathy.	Spongiotic dermatitis with eosinophils without evidence of cutaneous T cell lymphoma	2	MF/IVA2	Stable	4
17	66	F	6 y	NR	Focal folliculotropism, vessel ectasia, wiry collagen, lymphocyte tagging with perivascular lymphohistiocytic inflammation	1.2	MF/IIA	NR	3
18	65	F	4 y	NR	Spongiosis with perivascular lymphohistiocytic infiltrates, eosinophils, and focal lichenoid dermatitis.	2	MF/IB	NR	3
19	74	M	6 y	NR	Mild epidermotropism, lymphocyte tagging, spongiosis, vessel ectasia, wiry collagen, and mild perivascular lymphohistiocytic inflammation with eosinophils	24	MF/III	NR	3

Continued

Table I. Cont'd

Case	Age	Sex	AD duration	Physical exam findings (pre-dupilumab)	Pre-dupilumab biopsy	Dupilumab initiation to MF/SS diagnosis (mo)	MF/SS type/stage at time of diagnosis	MF/SS overall outcome	Naranjo score*
20	73	M	5 y	NR	Mild epidermotropism, spongiosis, psoriasiform, wiry collagen, mild perivascular lymphohistiocytic inflammation	14	MF/III	NR	3
21	74	M	4 y	NR	Mild epidermotropism, lymphocyte tagging, spongiotic, psoriasiform, wiry collagen, lymphohistiocytic inflammation with focal lichenoid dermatitis	1	MF/IIA	NR	3
22	44	F	9 y	NR	ND	12	MF/IV	NR	3
23	27	M	7 y	NR	ND	14	MF/IB	NR	3

AD, Atopic dermatitis; MF, mycosis fungoides; ND, not done; NR, not reported; PR, partial response; SS, Sezary syndrome.

*Naranjo score: total: -4 to +13; the reaction is definite: ≥ 9 , probable: 5-8, possible: 1-4, and doubtful: ≤ 0 .

clonality assessment pre-dupilumab; 4 of 10 (40%) reported positive clonality post-dupilumab. Most ($n = 20$) were diagnosed with MF (87%), followed by SS in $n = 3$ (13%). Mean time (SD) between dupilumab initiation to biopsy-proven cutaneous T cell lymphoma was $7.5 \pm (7.4)$ months. Eleven had advanced disease (Stage IIB-IV) at diagnosis. Personal/family atopic history, a major criterion for clinical AD diagnosis,² existed in only 4 of 23 cases. Several cases had features that are not typical of AD including indurated plaques, nodules, poikiloderma, and sparing of flexural sites. Three (13.04%) had pre-dupilumab erythroderma; only 1 had peripheral blood flow cytometry prior to dupilumab. Seven dupilumab patients initially improved with 2 months median duration.

This analysis found a possible association of MF/SS, post-dupilumab initiation by Naranjo analysis (Table 1). The strongest cases supporting a possible association between dupilumab use and the development of MF/SS are 2 cases with a long-standing diagnosis of AD since childhood and pre-dupilumab biopsy showing features consistent with AD. Of those with adult-onset AD ($n = 19$), only 5 cases had clinical presentations and pre-dupilumab biopsies consistent with AD, also suggesting that dupilumab is associated with MF/SS development or can unmask subclinical MF/SS, as MF/SS can be difficult to diagnose in early stages. In 14 cases, it is unclear whether dupilumab unmasked MF/SS or whether cases were initially misdiagnosed as several had atypical clinical and histologic features for AD or lacked pathologic and laboratory studies to exclude a diagnosis of MF/SS prior to dupilumab.

Dupilumab has been associated with rapid disease progression in MF/SS.² Therefore, it is critical to have a low threshold to evaluate for MF/SS prior to initiation of dupilumab in presumed cases of AD, especially in those with new adult-onset severe AD lacking personal atopic history. MF/SS diagnosis requires clinicopathologic correlation, including immunohistochemistry and molecular studies.^{3,4} Peripheral blood flow cytometry is essential in erythrodermic cases.³ In addition, multiple skin biopsies may be needed to establish the diagnosis of MF/SS.³ While histology and molecular studies may not be diagnostic in all cases of early MF, a diagnosis of MF/SS will certainly be missed if no diagnostic evaluation is undertaken. Additionally close clinical follow-up is warranted. Worsening pruritus or new rash in atypical areas despite initial improvement on dupilumab, or no improvement, should be re-evaluated for MF/SS.

The limitations include retrospective nature of analyses and inclusion of published case reports,

which are subject to reporting bias. Larger cohort studies, including the use of high throughput T cell receptor sequencing and long-term follow up studies to assess whether dupilumab is associated with the development of MF/SS in AD or a reflection of the challenging nature of making a diagnosis of MF/SS and the prognosis of MF/SS post-dupilumab are needed.

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Conflicts of interest

None disclosed.

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