Development of Sézary syndrome following the administration of dupilumab

Jessica Tran[1,4] BBA, Lisa Morris[2] BS, Alan Vu[3] BS, Madeleine Duvic[4] MD

Affiliations: [1]Baylor College of Medicine, Houston, Texas, USA, [2]University of Missouri-Columbia School of Medicine, Columbia, Missouri, USA, [3]McGovern Medical School, Houston, Texas, USA, [4]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Corresponding Author: Madeleine Duvic MD, Department of Dermatology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard Unit 1452, Houston, TX 77030, USA, Tel: 832-829-0145, Email: mduvic@mdanderson.org

Abstract

Dupilumab is a monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling. It is the first biologic agent to demonstrate efficacy in treating moderate-to-severe refractory atopic dermatitis [1, 2]. Although dupilumab provides promise for the treatment of atopic and allergic conditions, clinicians should take into account its novelty and the potential for unexpected adverse events. We present a patient who developed Sézary syndrome following the initiation of dupilumab.

Keywords: dupilumab, Sézary syndrome, cutaneous T cell lymphoma, erythroderma, atopic dermatitis

Introduction

Dupilumab, a biologic agent approved in March 2017, is a monoclonal antibody developed to target the IL4Rα subunit of IL4 and IL13. Dupilumab is the first biologic agent to demonstrate efficacy in treating moderate to severe refractory atopic dermatitis [1, 2]. We report a patient who experienced erythroderma shortly after the initiation of dupilumab for atopic dermatitis. After further blood testing, he was diagnosed with Sézary syndrome (SS). To our knowledge, this is the first case of SS developing following the administration of dupilumab.

Case Synopsis

A 64-year-old man with a history of refractory adult-onset atopic dermatitis diagnosed in 2014, presented to MD Anderson Cancer Center in September 2019 with a three-month history of erythroderma. Since 2017, he experienced continued progression of atopic dermatitis despite the use of topical corticosteroids and ultraviolet light therapy. In June 2019, the patient was initiated on subcutaneous dupilumab. Two weeks after a 600mg loading dose of dupilumab, he presented with an erythrodermic rash covering 95% of his body surface area. He subsequently received methylprednisolone which resulted in improvement of the erythroderma. However, the erythroderma returned as the corticosteroids were tapered. The patient remained on dupilumab for four subsequent injections during which time he experienced progression of the erythroderma.

A punch biopsy of a left abdominal plaque was performed at this time. Pathology demonstrated psoriasiform epidermal hyperplasia, hypogranulosis, neutrophils within the epidermis, and a superficial perivascular lymphohistiocytic infiltrate. Lymphocytic exocytosis was also present with some small intraepidermal lymphocytes showing convoluted nuclear contours. Despite the presence of atypical lymphocytes, the patient was diagnosed with psoriasis. He was prescribed guselkumab 100mg/mL for one month, cyclosporine 200mg taper for two months, and topical steroids. Despite these treatments, the patient had persistent erythroderma and lymphadenopathy.

In the setting of persistent erythroderma, flow cytometry was performed in September 2019 to rule out SS. Results showed a markedly increased CD4 to CD8 ratio of 43:1. Atypical CD4+ T-lymphocytes were significantly increased in number and demonstrated partial loss of CD7 expression. T-cell receptor (TCR) gene rearrangement studies were also performed, revealing monoclonal TCR-gamma gene

rearrangements and polyclonal TCR-beta gene rearrangements in both the skin and blood. Given these immunophenotypic findings in the setting of erythroderma, the patient was diagnosed with SS.

The patient was subsequently referred to MD Anderson Cancer Center for further workup and management of SS. He presented clinically with mild pruritus, a severe burning sensation, and erythema and exfoliation involving 49% of his total BSA. Physical examination also revealed hyperkeratotic palmar and plantar surfaces, scaling of the bilateral toes, and mild bilateral ectropion. Flow cytometry performed at this time revealed over 7,000 CD4+CD26- Sezary cells/mm3. Given the combination of clinical and laboratory findings, the diagnosis of SS was confirmed.

The patient was initiated on oral bexarotene 300mg and biweekly extracorporeal photopheresis. He also continued to apply topical desoximetasone to the affected areas.

Case Discussion

Dupilumab has proven to be an effective treatment for refractory atopic dermatitis since its approval by the Food and Drug Administration in 2017 [1]. Dupilumab is a human monoclonal IgG antibody that binds to the IL4 receptor, thus inhibiting the actions of IL4 and IL13 [1]. This inhibition of IL4 and IL13 leads to decreased cytokine-induced inflammatory responses, ultimately dampening the Th2 response and minimizing the disease activity of atopic dermatitis [1]. Phase III clinical trials studying the efficacy of dupilumab for atopic dermatitis demonstrated appreciable improvement in refractory atopic dermatitis [1]. In all three clinical trials, response to dupilumab (~37%) was markedly higher than those receiving placebo (~10%), [1]. Although dupilumab has demonstrated efficacy in the treatment of atopic and allergic conditions, unexpected events have been reported following its use, including conjunctivitis and alopecia areata [3, 4]. To our knowledge, this is the first report of a patient diagnosed with SS following the initiation of dupilumab.

Sézary syndrome is associated with a T_H2 response [5]. In SS, both malignant Sezary cells and benign reactionary cells have been shown to have a T_H2 predominance of cytokines such as IL4, IL5, IL10, and IL13 [5]. Dupilumab's effect of inhibiting the T_H2 response suggests that it would combat the progression of SS via a reduction of atypical lymphocytic proliferation. Therefore, the development of SS in the patient in this case is unexpected.

The temporal relationship between the initiation of dupilumab and the onset of erythroderma suggests that dupilumab was a trigger for SS in this patient. Dupilumab has been previously reported to have caused an exacerbation of erythematous lesions in a patient with mycosis fungoides [6]. Chiba et al. (2019) describes a patient who was initially misdiagnosed with atopic dermatitis and prescribed dupilumab injections. However, the use of dupilumab caused a flare of the skin lesions. Owing to the progression of disease, a skin biopsy was performed and confirmed the diagnosis of mycosis fungoides.

Alternatively, our patient may have had mycosis fungoides which was initially misdiagnosed as adult-onset atopic dermatitis. The exacerbation of skin lesions in the patient described by Chiba et al. (2019) and the case described in this report following the use of dupilumab suggests that dupilumab may trigger or promote the development of cutaneous T-cell lymphoma (CTCL) in certain patients.

Sézary syndrome is an uncommon and aggressive primary CTCL characterized by pruritic erythroderma, lymphadenopathy, and atypical circulating lymphocytes. The pathogenesis of SS is only partially understood. Circulating neoplastic T cells in SS have a central memory T-cell phenotype and are capable of circulating between the skin, lymph nodes, and blood [7]. Moreover, certain human leukocyte antigen alleles are associated with CTCL, suggesting that a pathogenic mechanism may involve inappropriate T-cell activation via antigen presentation and subsequent expansion of the aberrant T-cell population [8]. This combined knowledge suggests that the existence of an external trigger or disease-promoting factor

contributes to the development of SS [9]. Multiple infections, medications, and occupational causes have been investigated as triggers or promoters of CTCL, including hydrochlorothiazide diuretics, *Staphylococcus aureus*, *Chlamydia pneumoniae*, dermatophytes, human T-Cell lymphotropic virus type 1, Epstein-Barr virus, and herpes simplex virus [10]. We propose that the dupilumab-induced alteration in cytokines and phenotypic expression of lymphocytes could be an inciting factor for the development or exacerbation of SS in certain patients, as in this case. Further investigation is warranted regarding the inhibition of IL4 and IL13 and the development of SS.

Conclusion

We report, to our knowledge, the first case of SS developing in association with administration of dupilumab. Given the aggressive nature of SS, clinicians should be aware of this association for prompt diagnosis and treatment. Although dupilumab provides promise in the treatment of atopic and allergic conditions, clinicians should take into account its novelty and the potential for unexpected adverse events.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Gooderham MJ, Hong HC-h, Eshtiaghi P, Papp KA. Dupilumab: A review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol*. 2018;78:S28-S36. [PMID: 29471919].
2. Shirley M. Dupilumab: First Global Approval. *Drugs*. 2017;77:1115-21. [PMID: 28547386].
3. Ou Z, Chen C, Chen A, et al. Adverse events of Dupilumab in adults with moderate-to-severe atopic dermatitis: A meta-analysis. *Int Immunopharmacol*. 2018;54:303-10. [PMID: 29182975].
4. Mitchell K, Levitt J. Alopecia areata after dupilumab for atopic dermatitis. *JAAD Case Rep*. 2018;4:143. [PMID: 29387767].
5. Saulite I, Hoetzenecker W, Weidinger S, et al. Sézary syndrome and atopic dermatitis: comparison of immunological aspects and targets. *Biomed Res Int*. 2016;2016:9717530. [PMID: 27294147].
6. Chiba T, Nagai T, Osada SI, Manabe M. Diagnosis of Mycosis Fungoides Following Administration of Dupilumab for Misdiagnosed Atopic Dermatitis. *Acta Derm Venereol*. 2019;99:818-9. [PMID: 31045233].
7. Campbell JJ, Clark RA, Watanabe R, Kupper TS. Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. *Blood*. 2010;116:767-71. [PMID: 20484084].
8. Hodak E, Lapidoth M, Kohn K, et al. Mycosis fungoides: HLA class II associations among Ashkenazi and non-Ashkenazi Jewish patients. *Br J Dermatol*. 2001;145:974-80. [PMID: 11899152].
9. Ghazawi FM, Netchiporouk E, Rahme E, et al. Comprehensive analysis of cutaneous T-cell lymphoma (CTCL) incidence and mortality in Canada reveals changing trends and geographic clustering for this malignancy. *Cancer*. 2017;123:3550-67. [PMID: 28493286].
10. Litvinov IV, Shtreis A, Kobayashi K, et al. Investigating potential exogenous tumor initiating and promoting factors for Cutaneous T-Cell Lymphomas (CTCL), a rare skin malignancy. *Oncoimmunology*. 2016;5:e1175799. [PMID: 27622024].