Dupilumab as a therapy option for treatment refractory mogamulizumab-associated rash

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INTRODUCTION

Mogamulizumab has recently been approved for treatment of relapsed/refractory cutaneous T-cell lymphoma (CTCL) in the United States. While not usually life-threatening, successful treatment of its most common adverse effect (mogamulizumab-associated rash, or 'eruption') has not been reported outside of the use of topical corticosteroids.[1,2] We report a case of treatment refractory mogamulizumab-associated rash that responded positively to dupilumab in a patient with $CD8^+$ poikilodermatous mycosis fungoides.

Abbreviations used:

CTCL:	cutaneous T-cell lymphoma
IL:	interleukin
TCR:	T-cell receptor
Th2:	T lymphocyte helper cell type 2

CASE REPORT

A 26-year-old otherwise healthy Hispanic/African American man presented to the multidisciplinary cutaneous lymphoma clinic for follow up of mycosis fungoides ($CD8^+$, poikilodermatous type) diagnosed in 2015 as stage IB (T2bN0M0B0b). He was referred to our center in 2016 for specialized management. He denied pruritus, and poikilodermatous patches and thin plaques affected 40% of his body surface area (Fig 1), with no palpable lymphadenopathy. Two biopsies (punch, shave) revealed histopathology consistent with $CD8^+$ mycosis fungoides and no evidence of large-cell transformation. Polymerase chain reaction-based molecular analysis of the punch biopsy revealed T-cell receptor (TCR) gene gamma and beta clonality. Flow cytometry and TCR gene rearrangement studies revealed no involvement of the blood compartment. The patient was managed with oral bexarotene, triamcinolone ointment, and mechlorethamine gel, but the patient was lost to follow up until March 2020.

Upon reestablishing care, he stated that his lesions had slowly worsened, with more noticeable exacerbation over the previous 12 months. He confirmed noncompliance shortly after his last visit due to undesirable side effects. In addition to more diffuse poikilodermatous patches and plaques, bilateral scarring alopecia was present on his eyebrows. Flow cytometry was again negative for CTCL involvement.

After discussion of therapy options, the patient elected to start mogamulizumab weekly for the first month and every 2 weeks thereafter plus narrow-band ultraviolet B phototherapy 2-3 times weekly. Mild improvement with visible post-inflammatory hyperpigmentation was noted shortly after the sixth mogamulizumab infusion. After the ninth infusion, an asymptomatic lichenoid eruption was observed on his elbows, arms, and dorsal aspects of the hands bilaterally (Fig 2, *A*). Palmar creases developed painful fissures that required skin adhesive treatment (Fig 2, *B*). Over the following weeks, the eruption became pruritic and progressed to a generalized lichenoid eruption

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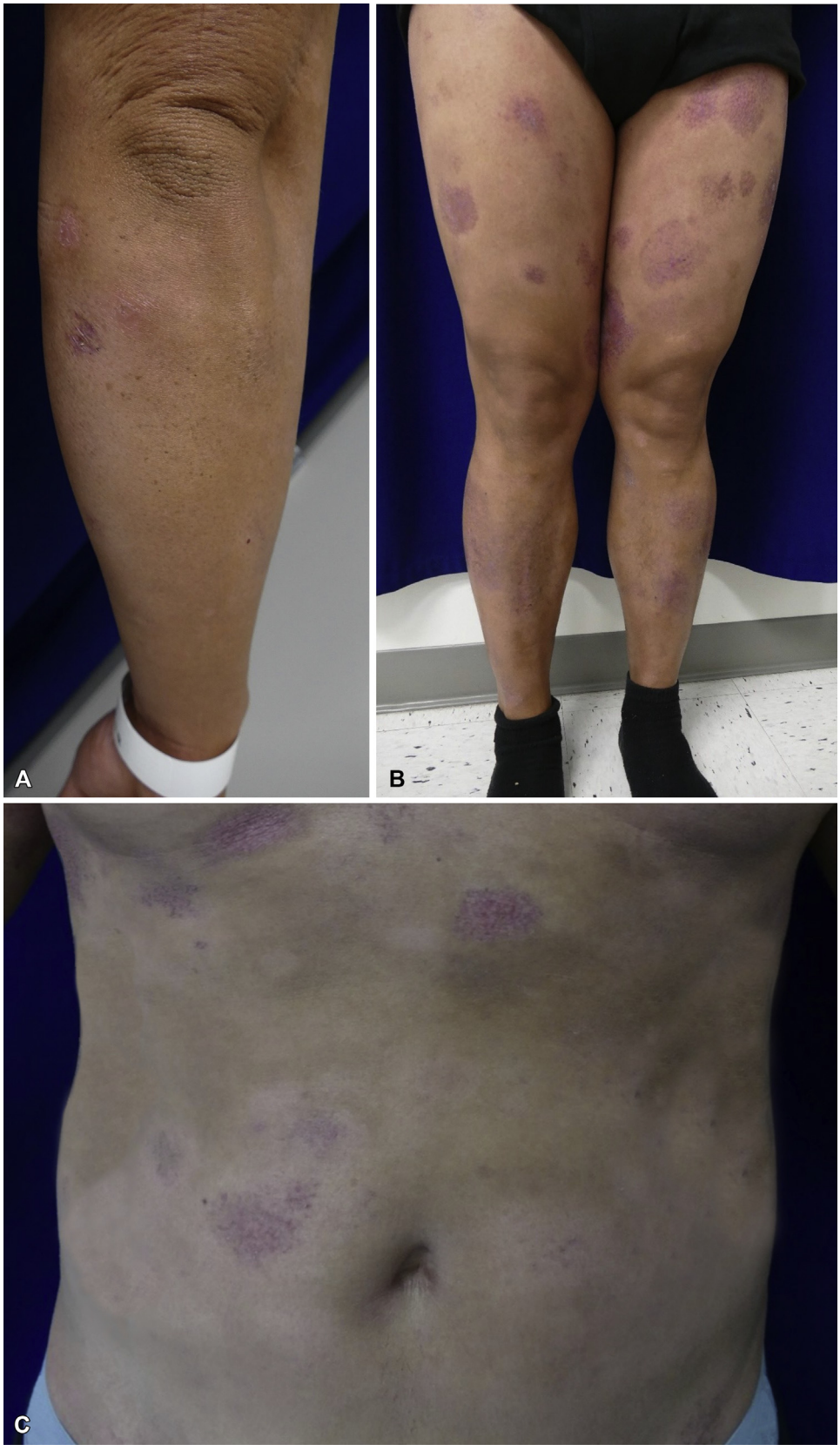

Fig 1. $CD8^{+}$ mycosis fungoides (poikilodermatous type) plaques at mogamulizumab therapy baseline. **A**, right elbow; **B**, anterior aspect of the legs; **C**, abdomen.

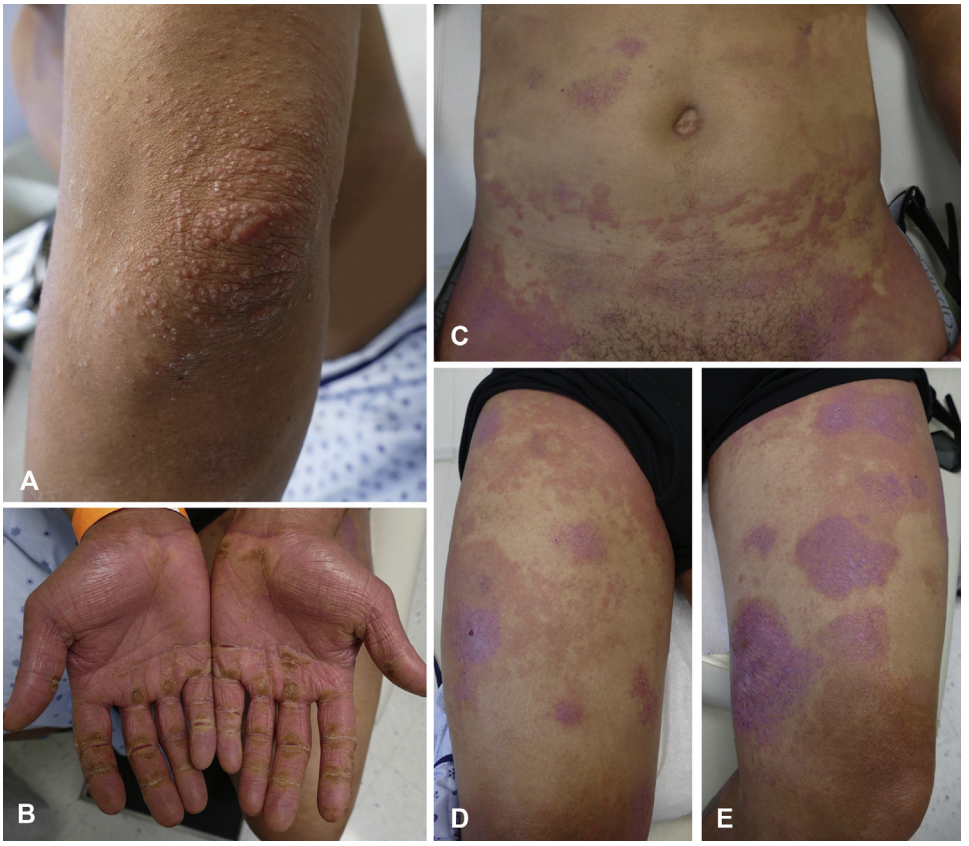

Fig 2. Mogamulizumab-associated rash. **A**, Left elbow, initial eruption presentation of lichenoid erythematous papules. **B**, Hands with painful fissures prior to treatment with skin adhesive, clobetasol cream, and appropriate hand hygiene. **C**, **D**, and **E**, Lower portion of the abdomen and legs, progression of eruption to a bilaterally symmetric violaceous lichenoid eruption often confluent with previous poikilodermatous mycosis fungoides plaques.

with coalescing, bilaterally symmetric violaceous papules and plaques affecting the lower abdomen, inguinal areas, and arms (Fig 2, *C*, *D*, and *E*). Sharply demarcated, bilateral erythematous patches were observed on the distal parts of the forearms.

Mogamulizumab was held after 11 infusions (best response: partial response), and narrow-band ultraviolet B phototherapy was simultaneously discontinued. Low- (4 mg) and high-dose (40 mg) oral methylprednisolone, prednisone, topical clobetasol, and oral antihistamines were tried with minimal improvement of the eruption. Two punch biopsies of the new lesions revealed spongiotic lichenoid dermatitis with eosinophils as well as exocytosis and intermediate-sized lymphocytes (Fig 3). However, repeated flow cytometry and TCR rearrangement studies of both skin biopsies and blood showed no clonal rearrangement, which was most consistent with an eruption rather than recurrent CTCL.

Due to failure of previous eruption-directed therapies, dupilumab was prescribed. The patient began with a 600 mg loading dose, which was followed by 300-mg injections every 2 weeks. By the seventh injection, the patient reported significant improvement in pruritus, followed by complete resolution of the eruption (Fig 4). However, the CTCL component was still present, confirmed by positive TCR rearrangement studies of the remaining lesions. Four months after eruption resolution, the patient is currently tolerating low-dose methotrexate (20 mg) well with stable disease.

DISCUSSION

Dupilumab is a newly approved IgG subclass 4 monoclonal human antibody, which binds to the interleukin (IL) 4-receptor-alpha subunit. It is the first therapy to be approved for the treatment of refractory moderate-severe atopic dermatitis. IL-4 and IL-13 signaling is blocked by the binding of dupilumab to the alpha chain of IL-4-receptor-alpha subunit. T lymphocyte helper cell type 2 (Th2) cells and their stimulatory cytokines, among them IL-4 and

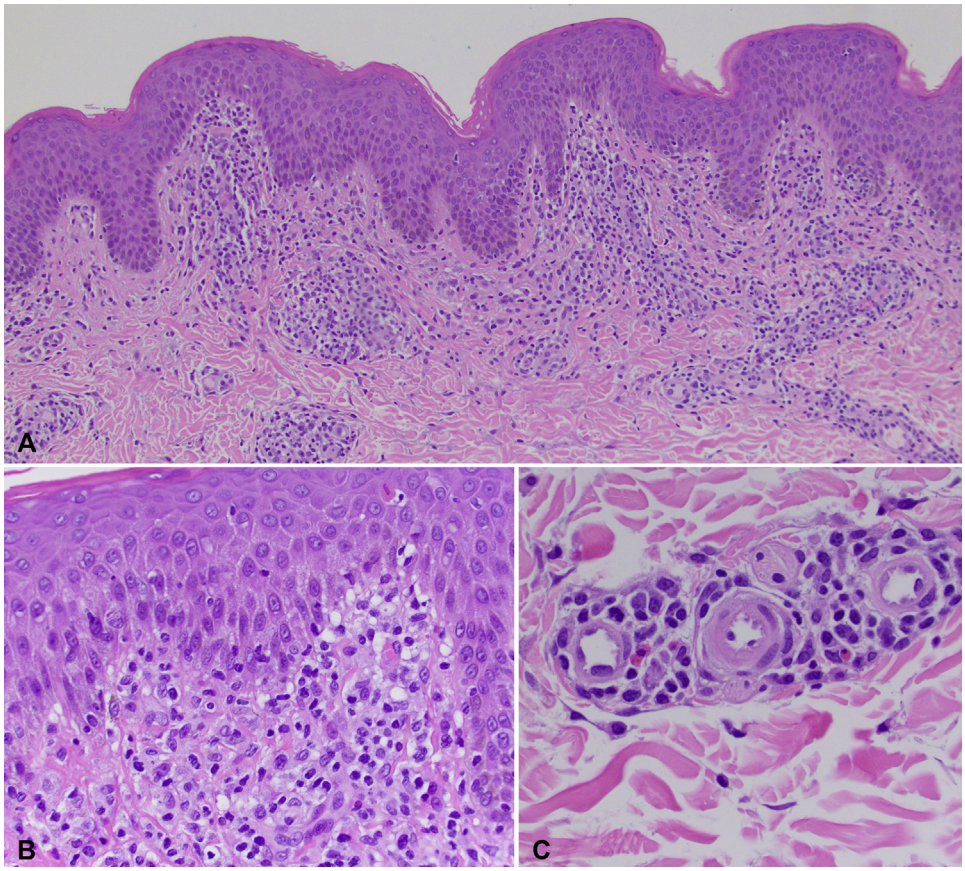

Fig 3. Mogamulizumab-associated rash. **A** and **B**, Histology (**A** and **B**, Hematoxylin-eosin stain; original magnification, **A**, ×40; **B**, ×400). The mildly acanthotic epidermis showed a predominantly spongiotic lichenoid dermatitis, with occasional dermal eosinophils. Focal exocytosis with intermediate-sized lymphocytes with abundant pale cytoplasm may be appreciated, occasionally tagging the dermo-epidermal junction. **C**, Histology revealed a moderate perivascular lymphohistiocytic infiltrate. (Hematoxylin-eosin stain; original magnification: ×100)

IL-13, are implicated in the pathogenesis of atopic conditions as well as several different cancers. It was initially hypothesized that dupilumab could inhibit malignant CTCL cells, as they are typically of the Th2 phenotype.[3] However, a growing body of case reports and series report heterogenous outcomes when giving dupilumab as a CTCL-directed therapy. Some studies report exacerbation or new onset of CTCL associated with dupilumab use[4,5]; yet, others report successful pruritus control[6] or complete responses.[7] Considering these possibilities, we treated our patient with dupilumab, not as a CTCL-directed therapy, but as an eruption-directed therapy. To minimize risk, the patient received a relatively short course of 7 dupilumab injections with simultaneous low-dose methotrexate as the CTCL-directed therapy. To our knowledge, this is the first reported case of the eruption successfully treated with dupilumab.

Although IL-13 has been implicated as a growth or inhibitory factor in different cancers, the role of Th2 stimulatory cytokines in the pathogenesis of CTCL remains to be fully elucidated. In vitro studies have implicated IL-13 as an autocrine messenger in CTCL, acting as a dose-dependent growth factor.[3] IL-13 is also expressed relatively less in earlier stages of CTCL.[3] Therefore, any potential risk of progression due to dupilumab might be minimized in patients with early clinical stage and short exposure as an eruption-directed therapy, such as our patient.

Two clinical morphologies of the eruption were observed in our patient. The sharply demarcated rash on his arms was highly suspicious for a photoaggravated dermatitis secondary to mogamulizumab, which has been reported previously.[8] The progressive lichenoid rash was easier to differentiate clinically from recurrent disease than other morphologies that

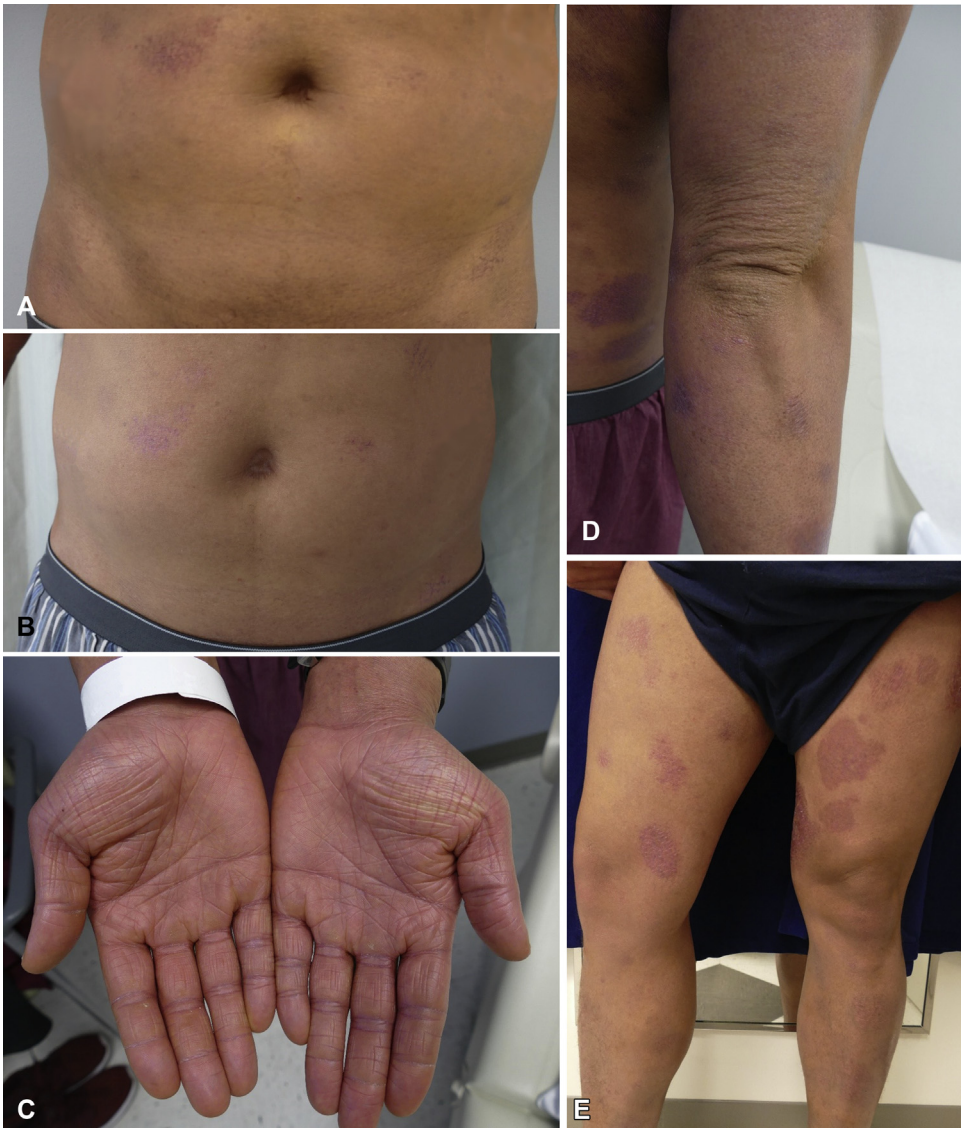

Fig 4. Mogamulizumab-associated rash resolution. **A** and **B**, Hands, healed fissures, and abdomen with absence of lichenoid plaques on the day of the fourth dupilumab injection. **C**, Abdomen, 3 months after **B** showing durable response to dupilumab. (**D** and **E**) Elbow and legs, showing absence of lichenoid papules and plaques.

may mimic CTCL.[9] Further differentiation from recurrent disease was achieved by comparison of histopathology and molecular studies of both skin and blood. In this case, a spongiotic lichenoid dermatitis with eosinophils with no TCR clonality was strongly suggestive of a drug eruption rather than recurrent disease.

In conclusion, dupilumab may be an effective and justifiable therapy in patients with known early-stage CTCL and good prognosis who experience the eruption, given that the role of IL-13 in CTCL pathogenesis is unclear. If exposure to dupilumab is limited, the benefit of swift, durable eruption elimination may balance the possible risk of CTCL relapse/exacerbation. Further studies are warranted to elucidate the influence of dupilumab on Th2 stimulatory cytokine signaling in CTCL.

Conflicts of interest

Dr Trum and author Abad have no conflicts to declare. Dr Zain is a consultant to Kyowa Kirin, Seattle Genetics, and Mundi Pharma. Dr Rosen is a consultant to Novartis Pharmaceuticals Corporation, Pepromene Bio, Inc, Exicure, and Apobiologix/Apotex Inc.; education advisory board to Seattle Genetics, NeoGenomics, and Aileron Therapeutics, Inc; has stock options with Pepromene Bio, Inc, and Exicure, Speaker's bureau for Celgene, Global Education Group and Paradigm Medical Communications, LLC, and Abbvie. Dr Querfeld is a

consultant to MiRagen, Helsinn/Actelion, Medvir, Stemline Therapeutics, Trillium, Bioniz, and Kyowa Kirin; contracted clinical investigator/researcher to MiRagen, Helsinn/Actelion, Bioniz, Kyowa Kirin, Celgene, Trillium, Esai, Soligenix, and Elorac; received research grant from Celgene.

REFERENCES

1. Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19(9):1192-1204.
2. Kasamon YL, Chen H, de Claro RA, et al. FDA approval summary: Mogamulizumab-kpkc for mycosis fungoides and Sézary syndrome. *Clin Cancer Res*. 2019;25(24):7275-7280.
3. Geskin LJ, Viragova S, Stolz DB, Fuschiotti P. Interleukin-13 is overexpressed in cutaneous T-cell lymphoma cells and regulates their proliferation. *Blood*. 2015;125(18):2798-2805.
4. Russomanno K, DeKlotz CMC. Acceleration of cutaneous T-cell lymphoma following dupilumab administration. *JAAD Case Rep*. 2021;8:83-85.
5. Espinosa ML, Nguyen MT, Aguirre AS, et al. Progression of cutaneous T-cell lymphoma after dupilumab: case review of 7 patients. *J Am Acad Dermatol*. 2020;83(1):197-199.
6. Steck O, Bertschi NL, Luther F, et al. Rapid and sustained control of itch and reduction in Th2 bias by dupilumab in a patient with Sezary syndrome. *J Eur Acad Dermatol Venereol*. 2021;35(6):1331-1337.
7. Mollanazar NK, Savage KT, Pousti BT, et al. Cutaneous T-cell lymphoma and concomitant atopic dermatitis responding to dupilumab. *Cutis*. 2020;106(3):131-132.
8. Masuda Y, Tatsuno K, Kitano S, et al. Mogamulizumab-induced photosensitivity in patients with mycosis fungoides and other T-cell neoplasms. *J Eur Acad Dermatol Venereol*. 2018;32(9):1456-1460.
9. Trum NA, Zain J, Martinez X, et al. 453 mogamulizumab associated rash (MAR) frequently mimics CTCL recurrence: A case series. *J Invest Dermatol*. 2021;141(5):S78.