

# Recalcitrant generalized granuloma annulare treated successfully with dupilumab



Eingun James Song, MD,<sup>a</sup> Joshua Bezecny, MS, PA-C,<sup>b</sup> and Sterling Farrer, DO<sup>c</sup>  
*Mill Creek, Washington; and Lebanon and Salem, Oregon*

**Key words:** dupilumab; granuloma annulare.

## INTRODUCTION

Granuloma annulare (GA) is a chronic, inflammatory granulomatous disease of unknown etiology that can be therapeutically challenging. Based on preclinical studies and success of the tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitor class, GA has been thought to be primarily a helper T cell type 1 (Th1) immune-mediated disease.<sup>1</sup> Yet, there are patients who do not respond to TNF- $\alpha$  inhibitors, and paradoxical cases of GA have also been reported, suggesting that an alternate pathway may be implicated in certain individuals.<sup>2</sup> Min et al recently showed that in lesional GA skin, a wide array of inflammatory markers is expressed.<sup>3</sup> While Th1 cytokine levels were expectedly increased, the helper T cell type 2 (Th2) axis was surprisingly overly expressed as well. Dupilumab is a monoclonal antibody that binds to the alpha subunit of interleukin 4 (IL-4) receptor. Through blockade of IL-4R $\alpha$ , dupilumab modulates signaling of IL-4 and IL-13, both of which are key cytokines in the Th2 pathway. Herein, we report a patient with generalized GA that was refractory to adalimumab treatment who showed dramatic improvement with dupilumab.

## CASE REPORT

A 74-year-old woman with a past medical history of hypertension, hyperlipidemia, and depression presented with a 2-year history of dark-red annular dermal plaques with clearly distinguishable thickening involving the arms, chest, abdomen, and legs (Fig 1). Histopathology was consistent with GA. Previous treatment with ultrapotent topical steroids, oral antibiotics (rifampin, ofloxacin, and minocycline), hydroxychloroquine, methotrexate, niacinamide, allopurinol, and adalimumab had failed. Based on the results of a preclinical study showing

### Abbreviations used:

GA:	granuloma annulare
IL:	interleukin
Th1:	helper T cell type 1
Th2:	helper T cell type 2
TNF- $\alpha$ :	tumor necrosis factor alpha

that Th2 signaling may play a role in GA, the patient agreed to off-label treatment with dupilumab.<sup>3</sup>

A standard biologic screening was done, which included complete blood count, comprehensive metabolic panel, quantiferon gold, hepatitis B panel, and hepatitis C antibody. A loading dose of 600 mg of dupilumab was administered subcutaneously at week 0 and then decreased to 300 mg every 2 weeks thereafter. At her 4-week follow up, the patient had complete clearance of the plaques on her abdomen, distal shins, and dorsal aspect of the feet (Fig 2). She still had some residual annular dermal plaques on her arms and thighs, but the erythema and induration had significantly improved. At her 12-week follow up, the patient remained clear except for the proximal aspect of her arms and thighs. The patient overall was very satisfied with her improvement and stated that her skin had no-to-minimal impact on her quality of life.

## DISCUSSION

Despite our evolving understanding of the pathogenesis of GA, effective treatment has proved to be elusive. Multiple reports of successful treatment with TNF- $\alpha$  inhibitors suggest GA to be, in part, a Th1-mediated process.<sup>1,4,5</sup> Paradoxically, there have also been reports of GA induced by infliximab, adalimumab, and etanercept.<sup>2</sup> Min et al recently provided evidence that GA may also be driven by other

From North Sound Dermatology, Mill Creek<sup>a</sup>; Western University of Health Sciences, Lebanon<sup>b</sup>; and Silver Falls Dermatology, Salem.<sup>c</sup>

Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

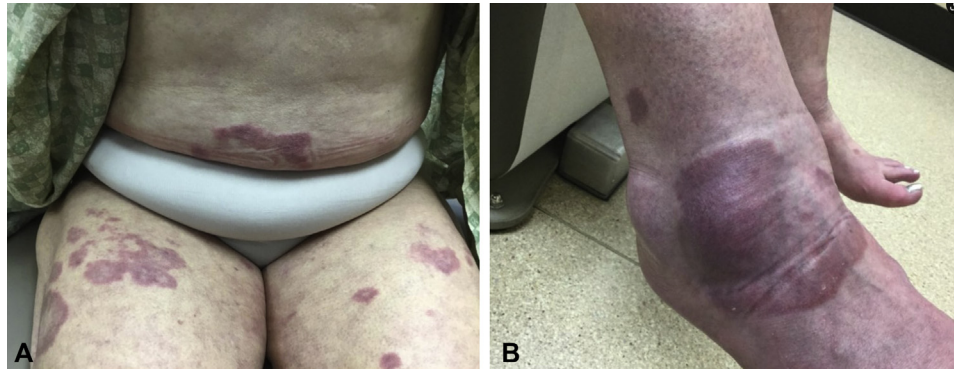
Correspondence to: Sterling Farrer, DO, 1793 13th St SE, Salem, OR 97302. E-mail: [Sterl.farrer@gmail.com](mailto:Sterl.farrer@gmail.com).

JAAD Case Reports 2021;7:■-■.

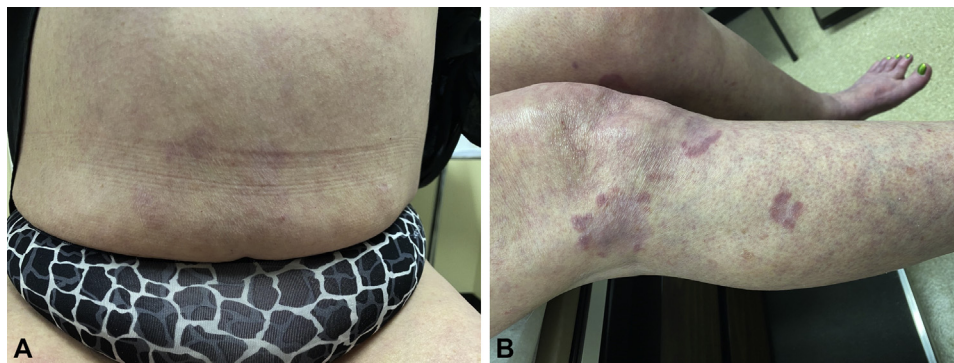
2352-5126

© 2020 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jdcrr.2020.10.021>



**Fig 1.** GA on the trunk, thighs (A) and right ankle (B) prior to initiating dupilumab. GA, Granuloma annulare.



**Fig 2.** Complete clearance of GA plaques on abdomen after 4 weeks of dupilumab (A). Residual GA plaques on lower extremities with significant improvement of erythema and induration after 4 weeks of dupilumab (B). GA, Granuloma annulare.

immune pathways, including Th2 and Janus kinase signaling.<sup>3</sup>

Macrophage polarization has been recognized as an important mediator in GA pathogenesis, with classically activated macrophages contributing to the early development of GA and alternatively activated macrophages contributing to the late development of GA. Classically activated macrophages are characterized by the expression of high levels of proinflammatory cytokines and promotion of a Th1 response. Alternatively activated macrophages are stimulated by Th2 cytokines, such as IL-4, IL-10, and IL-13, and are involved in extracellular matrix remodeling, which is a key feature of GA.<sup>6</sup> One can speculate that the response to Th1 or Th2 inhibition will depend on the stage of granuloma formation. Given that our patient had a long history of GA and failed treatment with a TNF- $\alpha$  inhibitor, it would stand to reason that her disease was being driven primarily by Th2 signaling, which would explain her dramatic response to dupilumab. The patient did not have any associated comorbid asthma, atopic dermatitis, or chronic rhinosinusitis, which would have correlated with a positive response to dupilumab.

To our knowledge, this is the first reported case of generalized GA being successfully treated with dupilumab. Further studies need to be done to corroborate our preliminary findings. It would be of interest to know whether inhibition of the Th2 pathway would lead to the same high level of efficacy as seen with TNF- $\alpha$  inhibitors or whether it should be reserved for those in whom more traditional treatment that targets Th1 signaling has failed.

#### REFERENCES

1. Min MS, Lebwohl M. Treatment of recalcitrant granuloma annulare (GA) with adalimumab: a single-center, observational study. *J Am Acad Dermatol.* 2016;74(1):127-133.
2. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A, Drosos AA. Granuloma annulare induced by anti-tumour necrosis factor therapy. *Ann Rheum Dis.* 2008;67(4):567-570.
3. Min MS, Wu J, He H, et al. Granuloma annulare skin profile shows activation of T-helper cell type 1, T-helper cell type 2, and Janus kinase pathways. *J Am Acad Dermatol.* 2020;83(1):63-70.
4. Chen A, Truong AK, Worswick S. The role of biologics in the treatment of chronic granuloma annulare. *Int J Dermatol.* 2019; 58(5):622-626.
5. Lukács J, Schliemann S, Elsner P. Treatment of generalized granuloma annulare — a systematic review. *J Eur Acad Dermatol Venereol.* 2015;29(8):1467-1480.
6. Asai J. What is new in the histogenesis of granulomatous skin diseases? *J Dermatol.* 2017;44(3):297-303.