Dear Editor,

Title: Generalized prurigo nodularis with dramatic response to dupilumab treatment, case report

Name of Journal: *World Journal of Dermatology*

Manuscript NO: 80847

Manuscript Type: CASE REPORT

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Thank you very much for your kind e-mail, which gave us the possibility to revise our manuscript. We emended the paper according to the reviewers' comments. We hope this revision will make our manuscript better to be accepted in your journal. Each comment has been answered accordingly in the manuscript.

We hope that the revised version will fulfill the requirements for publication in the World Journal of Dermatology.

Thank you very much.

Reply to editorial comments:

1- Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

Answer: This was done accordingly

2- Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are

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Answer: This was done accordingly

3- Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Answer: Considering your suggestion, we made additions from the literature to our manuscript using RCA. We think these additions improve our article, thank you for your suggestion.

- Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, Suprun M, Estrada Y, Xu H, Peng X, Silverberg JI, Menter A, Krueger JG, Zhang R, Chaudhry U, Swanson B, Graham NMH, Pirozzi G, Yancopoulos GD, D Hamilton JD. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol. 2019 Jan;143(1):155-172. doi: 10.1016/j.jaci.2018.08.022. Epub 2018 Sep 5. PMID: 30194992.

- Hashimoto T, Nattkemper LA, Kim HS, Kursewicz CD, Fowler E, Shah SM, Nanda S, Fayne RA, Paolini JF, Romanelli P, Yosipovitch G. Itch intensity in prurigo nodularis is closely related to dermal interleukin-31, oncostatin M, IL-31 receptor alpha and oncostatin M receptor beta. Exp Dermatol. 2021 Jun;30(6):804-810. doi: 10.1111/exd.14279. Epub 2021 Feb 1. PMID: 33428793.

Reply to reviewer's comments:

Reviewer #1:

1- Authors report on a case of generalized prurigo nodularis who showed a dramatic response to dupilumab treatment. The case report is interesting, but some points need to be addressed by Authors in a revised In Discussion Authors should mention the key involvement of the cytokine interleukin-31 (IL-31) in the symptomatology of pruritus, and both IL-31 and its receptor have become potential therapeutic targets for a range of pruritic diseases, including prurigo nodularis.

Answer: We took your suggestion into consideration and added a paragraph about IL-31 to our article.

The mechanisms underlying the development of PN are still not fully known. The pathogenesis of PN involves T cells and their cytokines, particularly IL-31. IL-31 is mainly produced by activated Th2 cells, CD45R0 CLA+ T cells, and mast cells. IL-31 has an important role in the induction of chronic cutaneous inflammation. It has been shown to have an important role in the etiology of atopic dermatitis and has been accepted as a major dermal pruritogen [7, 8]. Messenger RNA for IL-31 is more abundant in PN lesional skin when compared with healthy skin [3]. IL-31 and its receptor have become potential therapeutic targets for a range of pruritic diseases, including PN [9].

2- Iron deficiency is a commonly regarded cause of this symptom. Authors should provide information about the anemia of their patient (i.e. mean corpuscular volume, iron and total iron binding capacity. In some cases, iron replacement leads to complete cessation of pruritus very shortly after commencement of therapy, thus resolving what may otherwise be a debilitating and frustrating condition. (Millington GWM et al. British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. Br J Dermatol 2018;178:34–60).

Answer: Thank you for your important reminder. The patient used oral iron replacement therapy and did not benefit. We have added this important detail to our article after your warning. Patient's mean corpuscular volume 74.5 fL (normal range:

87–102.2 fL), iron 17 ug/dL (normal range: 70–180 ug/dL); and total iron binding capacity 421 ug/dL values have also been added to our article.

Reviewer #2:

The title is informative and relevant. The references are relevant and recent. The cited sources are referenced correctly. Appropriate and key studies are included. The introduction reveals what is already known about this topic. The research question is clearly outlined. The case is well-described, the used methods methods for diagnosing and therapy are valid and reliable. The patient data is presented in an appropriate way. The illustrative materials are relevant and clearly presented. Data is discussed from different angles and placed into context without being overinterpreted. The conclusions are supported by references and own results. This paper added to what is already in the topic. The article is consistent within itself. Specific comments on weaknesses of the article and what could be improved: Major points - none Minor points:

1- Add units when reporting test results (i.e., IgE levels, etc.)

Answer: This was done accordingly

In the blood tests of the patient, serum IgE 9330 IU/mL (normal range: 0-100 IU/mL), WBC 14,8 10^3/µL (normal range: 3,39-8,86 10^3/µL), eosinophil 7.6% (1,13 10^3/µL (normal range: 0,03-0,27 10^3/µL)), lymphocyte 16.10% (2,38 10^3/µL), neutrophil 69.30% (10,25 10^3/µL (normal range: 1,5-5 10^3/µL)), hemoglobin 10.2 g/dL (normal range: 11,1-14,7 g/dL), hematocrit 32.4% (normal range: 36,9-49,1 %) , mean corpuscular volume 74,5 fL (normal range: 87-102,2 fL), platelet 542 10^3/µL (normal range: 158-374 10^3/µL), iron 17 ug/dL (normal range: 70-180 ug/dL), total iron binding capacity 421 ug/dL, CRP 7 mg/L (normal range: 0-5 mg/L), ESR 67 mm/h (normal range: 1-30 mm/h), glucose 151 mg/dL (normal range: 74-106 mg/dL), B 12 83 ng/L (normal range: 180-914 ng/L), Anti-HIV (-), Anti-HCV (-), HBsAg (-) were measured.

2- Add more information about the immunological background of the disease before introducing the biologic treatement

Answer: We added more information about the immunological background of the disease.

Immune and neural dysregulation are implicated in the pathogenesis of PN. Immune cells and neuropeptides play an important role in cutaneous inflammation. Interleukin (IL)-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides are only a few of the mediators that immune cells in the skin release to cause a significant inflammatory response and severe itching. This immune response is central to the pathogenesis of PN. Additionally, eosinophils play an important role in the cutaneous inflammation and pruritus associated with PN. There is an accumulation of eosinophils in the dermis of PN lesional skin. It is believed that the pathophysiology of PN is a cutaneous reaction pattern brought on by recurrent cycles of chronic itching and scratching [3].

3- **Add a paragraph discussing the prognosis and follow-up of the patient and recommendations based on the case report.**

Answer: We added a paragraph discussing the prognosis and follow-up of the patient and recommendations based on the case report.

As a result, complete remission was observed in our patient in a short time after dupilumab treatment. No side effects were observed in the follow-up of dupilumab treatment. No itching was observed in the patient's follow-up. Significant improvements in sleep and quality of life were observed. Based on our case, it can be predicted that dupilumab treatment is an effective and safe treatment for patients with refractory generalized PN.

Thank you for considerating the review.

Sincercely yours

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10.11.2022