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DERMATOLOGIC THERAPY WILEY

LETTER

Generalized pustular psoriasis rapidly and successfully treated with ixekizumab in a Caucasian patient

Dear Editor,

Generalized pustular psoriasis (GPP), also known as Von Zumbusch psoriasis, represents the most severe form of pustular psoriasis, an immunological mediated inflammatory disease belonging to the group of neutrophilic pustulosis, characterized by the sudden outbreak of small sterile pustules over the majority of the body surface, possibly evolving in erythroderma. GPP is linked to systemic symptoms such as fever, malaise, asthenia, hydroelectrolytic imbalance with dehydration and potentially life-threating conditions such as hypocalcemia, bacteria superinfection and thus, sepsis.[1] Hence this condition must be diagnosed and treated promptly.

Herein we describe the case of a 53-year-old woman referred to our department due to the abrupt development of a painful pustular eruption arisen on erythemato-desquamative plaques, involving more than 70% of body surface area (Figure 1A). Patient's medical history was unremarkable, and she did not take any medications. The patient had negative family history of psoriasis. Clinical examination showed the presence of widespread erythemato-desquamative plaques roofed by 3–5 mm pustular lesions affecting the major skin folds, also depicted all over the trunk, the upper and lower limbs (Japanese Dermatological Association severity index of GPP = 5)[2] (Figure 1B). The patient recalled suffering from this condition since 1 years and that she was diagnosed with subcorneal pustular dermatosis being treated with topical corticosteroid plus acitretin (25 mg daily) for 1 year with transitory improvement. Subsequently, she was prescribed diaminodiphenylsulfone (100 mg daily) for 6 months, with only slight clinical benefit. Blood tests were within normal ranges except for ferritin values of 296 ng/ml (nv: 5–204 ng/ml). Microscopical examination showed negative results for fungal infection. A 3 mm punch biopsy for histological examination showed the presence of intradermal neutrophilic spongiform Kogoj–Lapière pustules with moderate lymphocytic and neutrophilic infiltrate and edema in the derma layer, supporting the diagnosis of GPP.

Due to the severity of the disease and the previous failure of acitretin and topical therapies, biological treatment with ixekizumab was chosen for its rapidity of action, safety profile and evidence of efficacy on GPP reported in literature even if mainly in Japanese patients.

Already at week one an impressive improvement was observed, showing the complete disappearance of pustules as well as an upgrade of patient's general condition (JDA severity index of GPP = 0, meaning complete clinical remission). At week 3, no erythema was present, and a complete resolution was achieved (Figure 2A,B). No side effects were reported by the patient.

Shared international guidelines regarding GPP treatment are lacking. Due to the rarity of this condition, recommendations are limited, and these patients are treated with the same therapeutical methods used for the common plaque psoriasis even if biologics are used off label in this condition; however, GPP is easily refractory to conventional therapies.[3] Thus, new treatment algorithm are focusing on biological agents since GPP can be a life-threatening condition hence prompt treatment is strictly required. Ixekizumab is an IL-17A antagonist approved for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis, being characterized by a very fast onset of action and high response rates.[4,5] Indeed, ixekizumab is reported as the second most rapid biologic drug, following brodalumab (e.g., PASI 75 reached in 25% of treated patients in 2.2 weeks vs. 2.1 of brodalumab),[6] being superior to ustekinumab and etanercept.[7,8] Ixekizumab has been successfully used for treating GPP in the Asian population. A subgroup analysis carried out by Okubo et al. reported that ixekizumab was efficacious and well tolerated on five patients with GPP up to 3 years of therapy.[9] while recently Nagata et al. reported a case series of 10 GPP patients successfully treated with ixekizumab.[10]

To date there is only one case report for ixekizumab Caucasian GPP patient: Dattola et al. reported a case of GPP with also psoriatic arthritis with significant improvement after only 2 weeks of therapy.[11]

Anti-IL17 efficacy in GPP is probably linked to IL17A capacity to stimulate IL-36α, IL-36β, and IL-36γ synthesis in keratinocytes. Indeed, loss-of-function IL-36 receptor antagonist (*IL36RN)* mutations have been identified in GPP. These mutations result in the hyperactivation of IL-36 signaling due to the unopposed stimulation of the IL-36 receptor by its ligands, IL-36α, IL36β, and IL-36γ, leading to neutrophil epidermal accumulation, and the formation of the spongiform pustules of Kogoj.[12]

Here we report a case of GPP in a Caucasian patient successfully and rapidly treated with ixekizumab. In our case, the patient did not

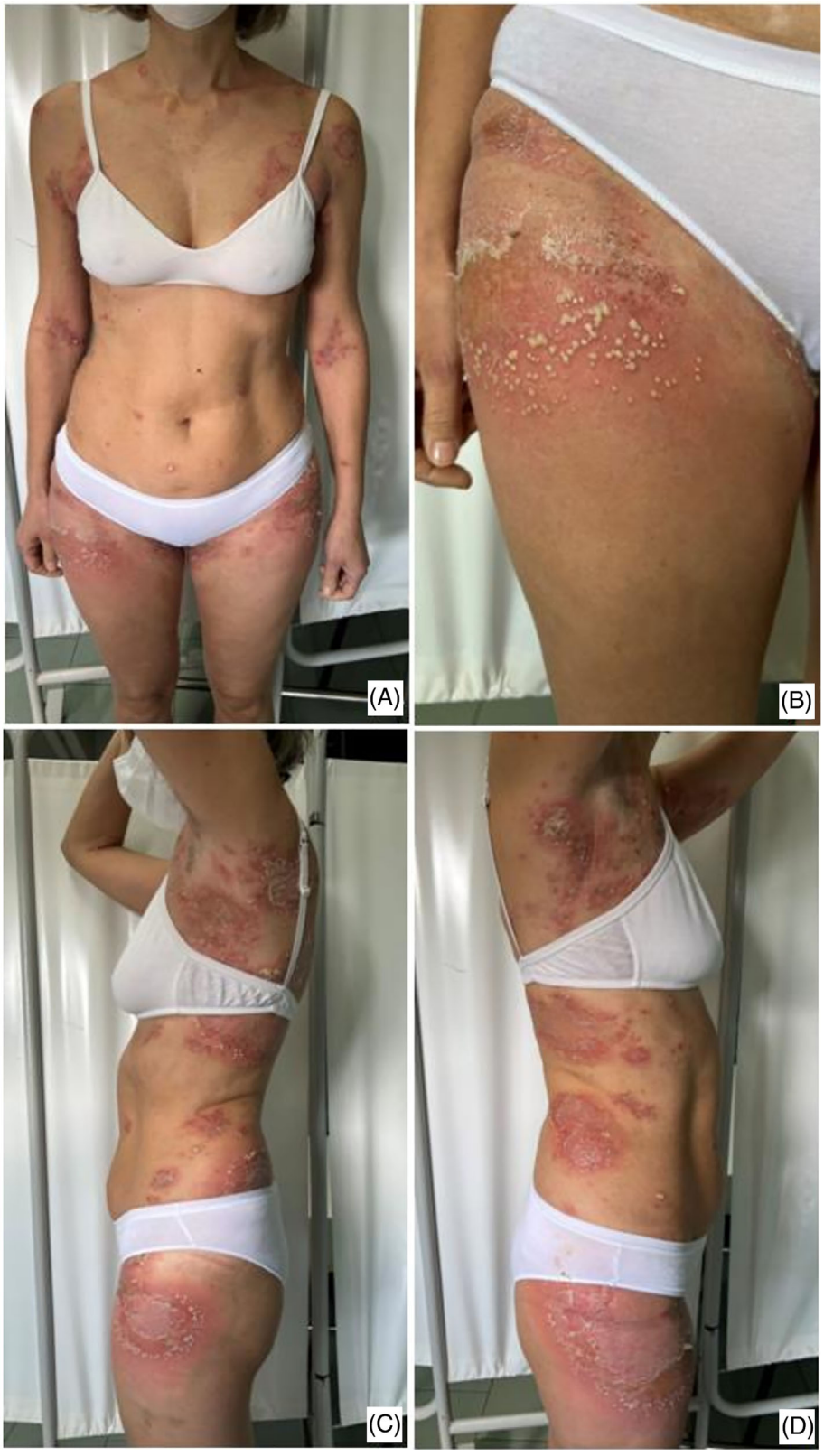

FIGURE 1 Patient at baseline (A–D): erythemato-desquamative plaques roofed by 3–5 mm pustular lesions affecting the major skin folds, also depicted all over the trunk, the upper and lower limbs

experience adverse events and achieved complete skin clearance and well-being after only 3 weeks of therapy.

In conclusion, our case further confirms the efficacy and the safety of ixekizumab in the treatment of GPP. However, deepening the knowledge of the pathogenetic mechanism underlying GPP will allow to efficiently guide treatment selection. Certainly, further studies are needed to determine globally shared therapeutic algorithm.

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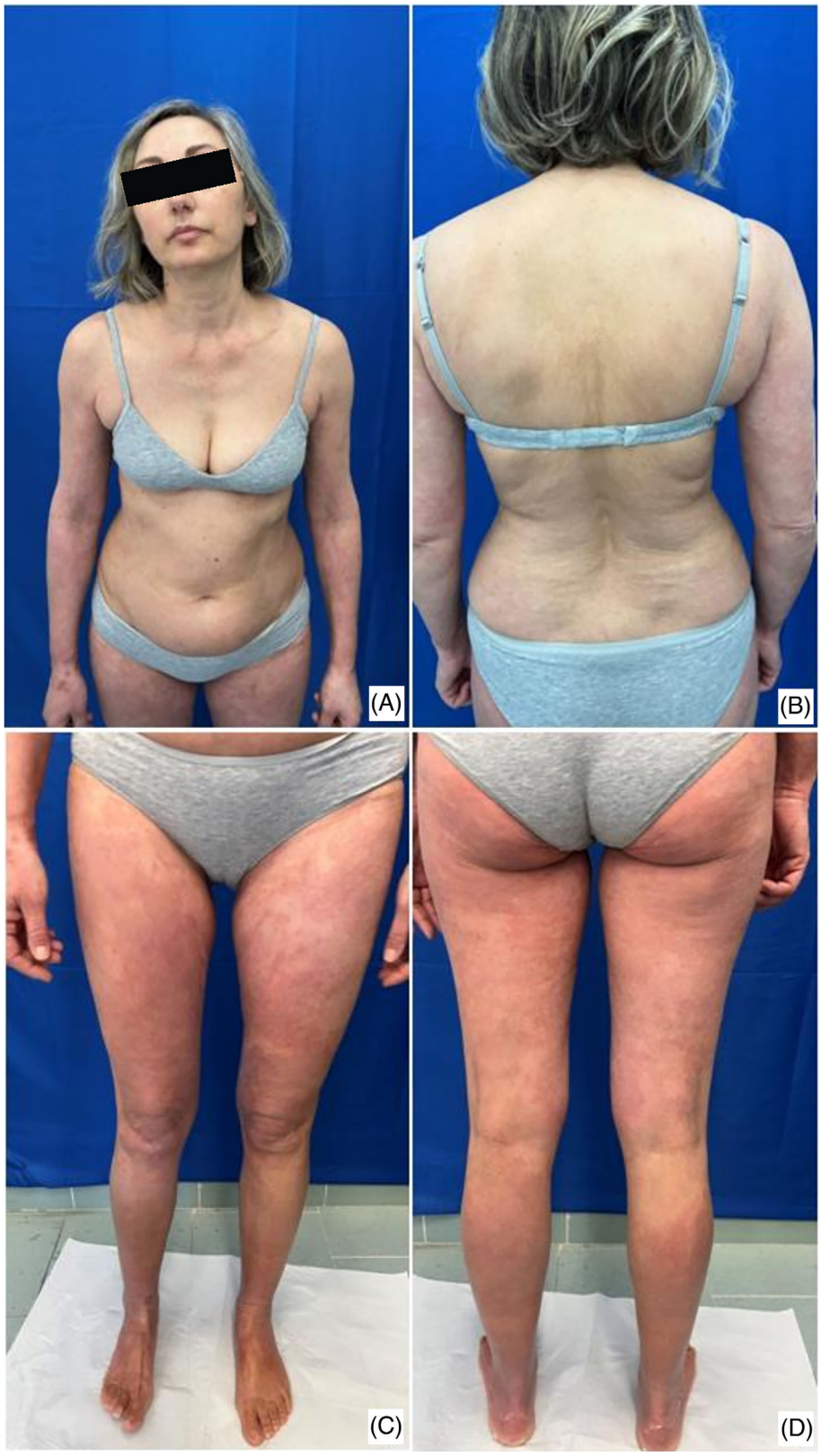

FIGURE 2 Patient after 3 weeks of therapy (A–D): complete skin clearance

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Matteo Megna has given substantial contributions to conception, acquisition of data, writing the article and final approval of the version to be published. **Luisa Abategiovanni** given substantial contributions to conception, acquisition of data, writing the article. **Alberto**

Annunziata acquisition of data, writing the article. **Ginevra Torta** acquisition of data, writing the article. **Tiziana Peduto** given substantial contributions to acquisition and interpretation of data. **Gabriella Fabbrocini** drafting article and has given final approval of the version to be published. **Wanda Lauro** substantial contributions to conception, acquisition of data, writing the article and final approval.

ETHICS STATEMENT

Not required.

PATIENT CONSENT

The authors have obtained the consent of the patient for clinical images.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Hoegler KM, John AM, Handler MZ, Schwartz RA. Generalized pustular psoriasis: a review and update on treatment. *J Eur Acad Dermatol Venereol*. 2018;32(10):1645-1651. doi:10.1111/jdv.14949
2. Morita A, Yamazaki F, Matsuyama T, et al. Adalimumab treatment in Japanese patients with generalized pustular psoriasis: results of an open-label phase 3 study. *J Dermatol*. 2018;45(12):1371-1380. doi:10.1111/1346-8138.14664
3. Menter A, Van Voorhees AS, Hsu S. Pustular Psoriasis: A narrative review of recent developments in pathophysiology and therapeutic options. *Dermatol Ther*. 2021;11(6):1917-1929. doi:10.1007/s13555-021-00612-x
4. Craig S, Warren RB. Ixekizumab for the treatment of psoriasis: up-to-date. *Expert Opin Biol Ther*. 2020;20(6):549-557. doi:10.1080/14712598.2020.1729736
5. Blegvad C, Skov L, Zachariae C. Ixekizumab for the treatment of psoriasis: an update on new data since first approval. *Expert Rev Clin Immunol*. 2019;15(2):111-121. doi:10.1080/1744666X.2019.1559730
6. Egeberg A, Andersen YMF, Halling-Overgaard AS, et al. Systematic review on rapidity of onset of action for interleukin-17 and interleukin-23 inhibitors for psoriasis. *J Eur Acad Dermatol Venereol*. 2020;34(1):39-46. doi:10.1111/jdv.15920
7. Gordon KB, Blauvelt A, Papp KA, et al. UNCOVER-1 study group; UNCOVER-2 study group; UNCOVER-3 study group. Phase 3 trials of Ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(4):345-356. doi:10.1056/NEJMoa1512711
8. Blauvelt A, Papp K, Gottlieb A, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe plaque psoriasis: 12-week efficacy, safety and speed of response from a randomized, double-blinded trial. *Br J Dermatol*. 2020;182(6):1348-1358. doi:10.1111/bjd.18851
9. Okubo Y, Mabuchi T, Iwatsuki K, et al. Long-term efficacy and safety of ixekizumab in Japanese patients with erythrodermic or generalized pustular psoriasis: subgroup analyses of an open-label, phase 3 study (UNCOVER-J). *J Eur Acad Dermatol Venereol*. 2019;33(2):325-332. doi:10.1111/jdv.15287
10. Nagata M, Kamata M, Fukaya S, et al. Real-world single-center experience with 10 cases of generalized pustular psoriasis successfully treated with ixekizumab. *J Am Acad Dermatol*. 2020;82(3):758-761.
11. Dattola A, Manfreda V, Esposito M, Bianchi L, Giunta A. A case of generalized pustular psoriasis and arthritis treated with ixekizumab. *J Dermatolog Treat*. 2020;31(7):754-755. doi:10.1080/09546634.2019.1606395
12. Krueger J, Puig L, Thaçi D. Treatment options and goals for patients with generalized pustular psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):51-64. doi:10.1007/s40257-021-00658-9