SUN EXPOSURE AS A TRIGGER FOR EXACERBATION OF PEMPHIGUS-TYPE BULLOUS DERMATOSES

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Summary

Autoimmune bullous dermatoses, particularly pemphigus vulgaris (PV), are rare chronic diseases characterized by blisters and post-bullous erosions on the skin and mucous membranes. While genetic predisposition plays a crucial role in their development, various environmental factors, including solar radiation, medications, infections, and stress, can trigger or exacerbate the disease. This study evaluates the impact of sun exposure on the exacerbation of PV, focusing on four patients under medical care at the Dermatology and Venereology Clinic in Iași. These patients experienced flare-ups after prolonged sun exposure during summer months.

The study highlights UV radiation's role in triggering PV flare-ups, with all patients showing worsened lesions after sunlight exposure. Exacerbation was observed mainly in sun-exposed areas such as the thorax, limbs, and scalp. Patients were treated with systemic corticosteroids, topical treatments, and immunosuppressive therapy, with clinical improvement noted.

The findings suggest that sun exposure, particularly during warmer months, can worsen PV symptoms. High SPF sunscreens and avoidance of direct sunlight are recommended for PV patients to minimize flare-ups. In conclusion, UV radiation and high temperatures may contribute to the increased incidence of PV exacerbations and hospitalizations, emphasizing the importance of preventive measures to reduce environmental triggers during active disease phases.

Keywords: *Pemphigus Vulgaris, Autoimmune Bullous Dermatoses, Sun Exposure, Ultraviolet Radiation, Exacerbation, Corticosteroids.*

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Introduction

Autoimmune bullous dermatoses represent a heterogeneous group of rare chronic diseases clinically characterized by the presence of blisters and post-bullous erosions on the skin and mucous membranes. They are classified into two major groups: the pemphigoid group and the pemphigus group, depending on the depth of the autoimmune process in the skin [1]. The pemphigus group includes various forms such as pemphigus vulgaris (PV), vegetative pemphigus, erythematous pemphigus, foliaceus pemphigus, and paraneoplastic pemphigus.

Currently, it is considered that genetic predisposition is essential for the development of these autoimmune diseases, but exogenous factors play a significant role in triggering and exacerbating them. For example, solar radiation or various medications such as Captopril, Penicillamine, Aspirin, Rifampicin, and Levodopa, as well as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and calcium channel blockers, have been implicated as triggering factors for PV [2]. Moreover, the hypothesis that PV and foliaceus pemphigus can develop following infection with the herpes simplex virus or cytomegalovirus, as well as after

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artificial immunizations, has been supported by many authors, suggesting that this phenomenon is not so rare [3]. Additionally, PV can be aggravated by other factors such as certain foods (garlic), pesticides, other autoimmune diseases, or neoplasms.

The primary characteristic of these diseases is the presence of autoantibodies against structural adhesion proteins in the skin and mucous membranes. In recent years, the understanding of their mechanism of action has deepened due to extensive characterization of their targets.

In bullous pemphigoid (BP), the most common subepidermal autoimmune bullous disease, autoantibodies are directed against the hemidesmosomal anchoring proteins BP180 and BP230. In contrast, in pemphigus vulgaris (PV), IgG autoantibodies targeting desmoglein 1 (Dsg-1) and desmoglein 3 (Dsg-3) are responsible for the formation of bullous lesions. These desmogleins are found in desmosomes of keratinocytes near the basal layer of the epidermis. The formation of the antibody-desmoglein complex leads to the separation of keratinocytes and their replacement with fluid, resulting in blister formation. Additionally, aggressive and aberrant immune responses contribute to PV development and progression through different mechanisms, including autoantibody production by plasma B lymphocytes and activation of CD4+ helper T lymphocytes and CD8+ T lymphocytes [4].

While PV is predominantly found in individuals aged 40–60 years, BP more frequently affects individuals over 60 years old. Moreover, PV is more commonly seen in women than in men and is predominant among Mediterranean, Jewish, and Asian (especially Indian and Japanese) populations.

Clinically, PV is characterized by flaccid blisters with thin walls filled with clear fluid, which rupture easily, causing painful post-bullous erosions and pruritus. In most cases, the oral mucosa is the first to be affected, with cutaneous lesions developing subsequently. Oral involvement appears to be less common in other variants, such as erythematous pemphigus and foliaceus pemphigus [5]. Furthermore, bullous lesions and post-bullous erosions most often appear on the upper anterior-posterior thorax, face, and scalp. Nikolsky's sign is positive.

For PV diagnosis, a concise clinical evaluation of the patient, a Tzanck cytodiagnosis from a blister, and a biopsy of the skin adjacent to the bullous lesion are required. The diagnosis is subsequently confirmed by direct immunofluorescence of skin biopsy sections, revealing IgG antibodies or complement on the keratinocyte cell surface. Additionally, histopathology usually shows rounded and separated keratinocytes just above the basal layer of the epidermis - an intraepidermal acantholysis.

Regarding the mechanism of ultraviolet (UV) radiation on the skin, it is known that UVA radiation penetrates the epidermis easily, acting indirectly on the basal proliferative layer and cellular components through oxidative mechanisms involving the formation of reactive oxygen species. These contribute to premature skin aging. On the other hand, UVB radiation has higher energy than UVA and is directly absorbed by various cellular components (nucleic acids, proteins, urocanic acid), leading to mutagenic effects on the skin and being responsible for the development of skin cancer [6].

Concerning the mechanism of UV radiation in pemphigus, the acantholytic process induced by UVB irradiation in the skin of pemphigus patients has been studied immunohistologically using monoclonal antibodies that bind to antigenic determinants present in the C5b9 complex. This membrane attack complex was detected five hours after irradiation, at which point no acantholysis was observed. However, after 24 hours, suprabasal intraepidermal cleavage with acantholytic epidermal cells was observed. These findings suggest that UVB radiation may be involved in the intraepidermal acantholysis process in PV patients [7].

Several studies in the literature address the impact of solar exposure on pemphigus exacerbation. As early as 1995, some authors reported, based on a study conducted in Bulgaria between 1980 and 1995, that the first manifestations of PV occurred in the spring and summer in about three-quarters of patients, while disease onset or exacerbation was less common in winter [8].

Another study conducted in Italy between 2006 and 2020 over 15 years on a sample of 892 patients diagnosed with PV and BP (530 women and 362 men) aimed to evaluate how seasonality

affects exacerbation trends in these two bullous dermatoses. The total number of hospital admissions over 12 months was analyzed, and a peak in PV and BP exacerbations with hospital presentations was recorded in June, July, and September [9].

A study conducted in Turkey between 1989 and 2018, which included 68 patients with foliaceus pemphigus, reported a higher incidence of pemphigus onset and relapses in spring and summer. Retrospective data analysis of these patients concluded that 42 of them experienced 117 relapses during spring and summer [10].

Another study used data from the National Inpatient Sample (2002–2012) in the USA, comprising 68,476,920 patients (children and adults). The study aimed to highlight the impact of UV exposure, climatic factors, and pollutants on pemphigus and whether these factors are associated with disease exacerbation. It was found that most hospital visits for pemphigus exacerbation occurred in the summer and fall months (June–November), with the highest rates in July and October. The study concluded that high temperatures, UV exposure, and air pollution are associated with an increased hospitalization rate in pemphigus patients [11].

Materials and Methods

We report four cases of medically controlled pemphigus vulgaris known to the Dermatology and Venereology Clinic in Iași, who presented with exacerbation of bullous skin lesions following prolonged sun exposure between June and July 2024.

The first patient, a 67-year-old man known to have COPD and persistent dysphonia, presented for the first time at the Clinic in June 2024 due to the appearance and persistence of bullae and post-bullous erosions for approximately three weeks before presentation, located on the entire body, oral cavity, and inguinal region (Fig. 1). He also presented conjunctival hyperemia with ectropion and moderate serous secretions in the left eye. In June, direct immunofluorescence, Tzanck cytodiagnosis, and skin biopsy were performed, confirming the diagnosis of pemphigus vulgaris. During hospitalization, systemic corticosteroids, antibiotics, topical corticosteroids, and oral corticosteroid rinses were administered, with favorable clinical evolution.

In July 2024, the patient returned to the clinic with significantly worsened PV lesions, much more severe clinically compared to the first hospital presentation. The lesions were located on the anterior-posterior thorax, upper and lower limbs, scalp, and trunk, alternating with areas of sunburn, following repeated and prolonged sun exposure, as the patient believed that "the sun dries the blisters" (Fig. 2).

Another patient, 46 years old, diagnosed and confirmed anatomopathologically with pemphigus vulgaris in December 2020 (Fig. 3), currently undergoing chronic systemic treatment with immunosuppressants and corticosteroids, presents in July 2024 at the Clinic due to the appearance and persistence of flaccid blisters and post-bullous erosions, painful, well-defined, located on the anterior hairline of the scalp and the anterior-posterior thorax (Fig. 4), after repeated and excessive sun exposure in agriculture, the patient being a farmer by profession.

Another patient, 23 years old, known and confirmed anatomopathologically with pemphigus vulgaris since April 2024, when she presented with blisters and post-bullous erosions, with yellowish crusts on the surface, painful, localized at the site of a cesarean scar and the right axilla (Fig. 5), and for which various topical preparations were applied, as well as systemic treatment with Diprophos, showing a slow, clinically favorable progression, returned to the Dermatology Clinic in Iași in July 2024 for the exacerbation of pemphigus lesions at the previously mentioned scar site and the appearance of new lesions on the scalp (Fig. 6), after prolonged sun exposure during the day (38-40°C).

The last patient, 41 years old, known to the Dermatology Clinic in Iași with a diagnosis of pemphigus vulgaris confirmed anatomopathologically since May 2023 (Fig. 7), currently undergoing systemic corticosteroid treatment, presents in July 2024 with the appearance of new post-bullous erosions, well-defined, and numerous flaccid, round-oval, well-defined blisters, disseminated on the anterior chest (Fig. 8), after prolonged sun exposure during a seaside vacation in the two weeks prior to the presentation.

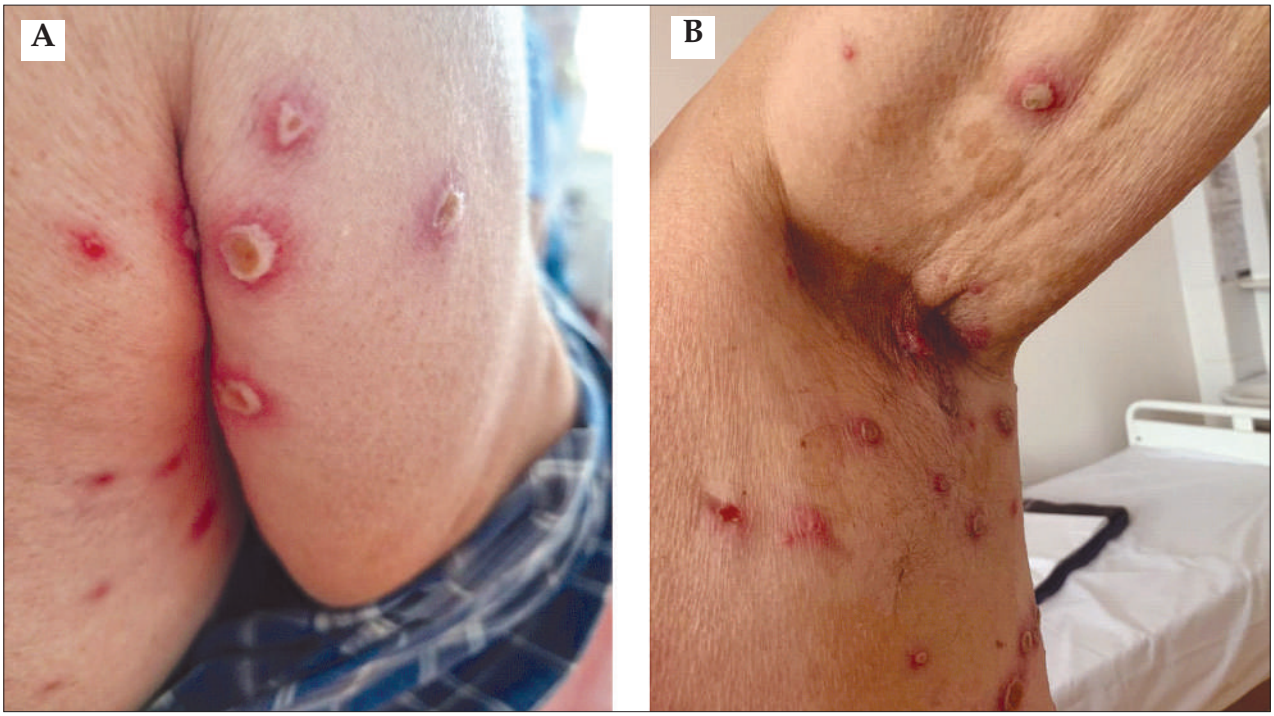

Figure 1. CASE 1 - Images taken at the first presentation in the Clinic. A. Post-bullous erosions and flaccid blisters on the dorsal surface of the right arm. B. Post-bullous erosions and flaccid blisters in the left axillary region.

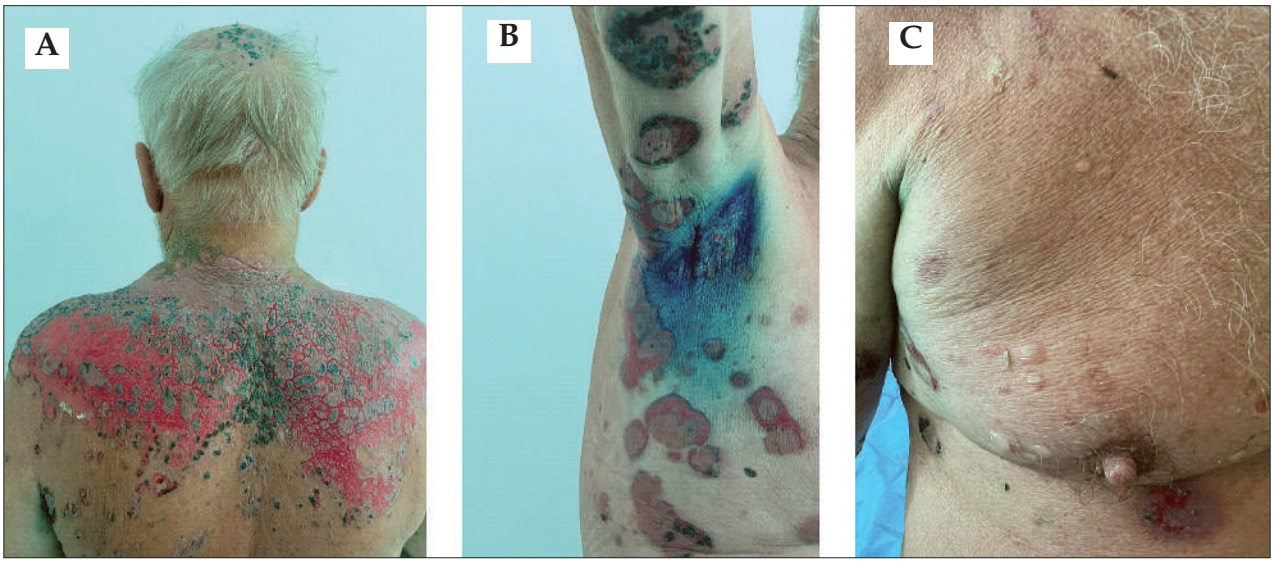

Figure 2. *CASE 1 - Images taken at the second presentation in the Clinic. A. Post-bullous erosions with areas of sunburn. B. Post-bullous erosions and flaccid blisters in the right axillary region. C. Flaccid blisters on the right mammary gland.*

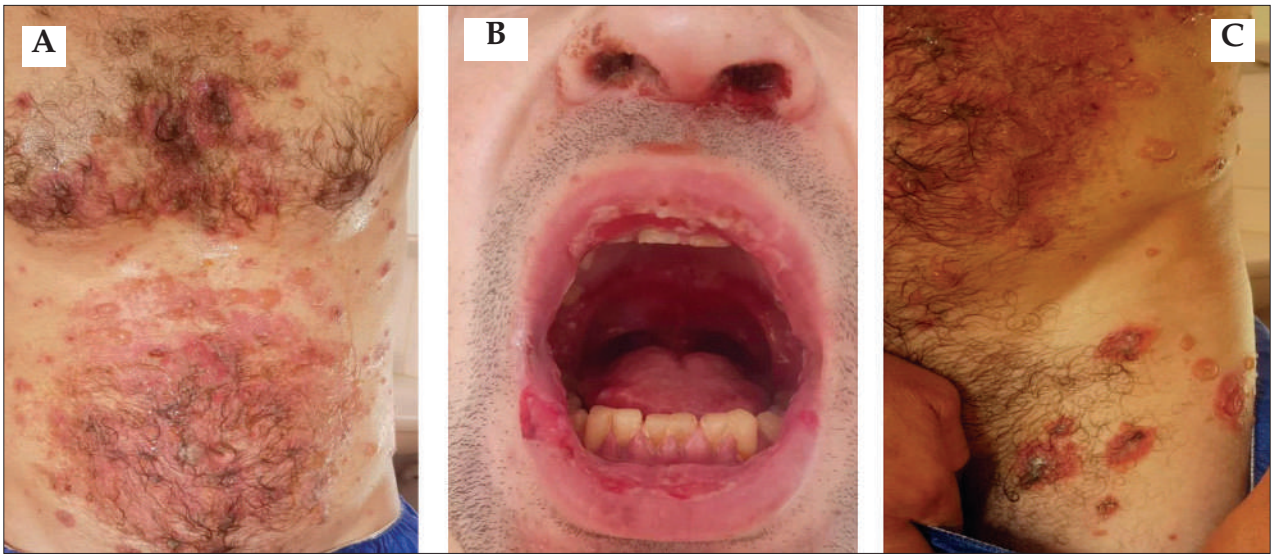

Figure 3. CASE 2 - Images taken at the first presentation in the Clinic (2020). A. Post-bullous erosions and flaccid blisters located on the anterior chest and abdomen. B. Post-bullous erosions in the oral cavity and nasal vestibule. C. Post-bullous erosions and flaccid blisters located in the left inguinal region and the anterior part of the left thigh.

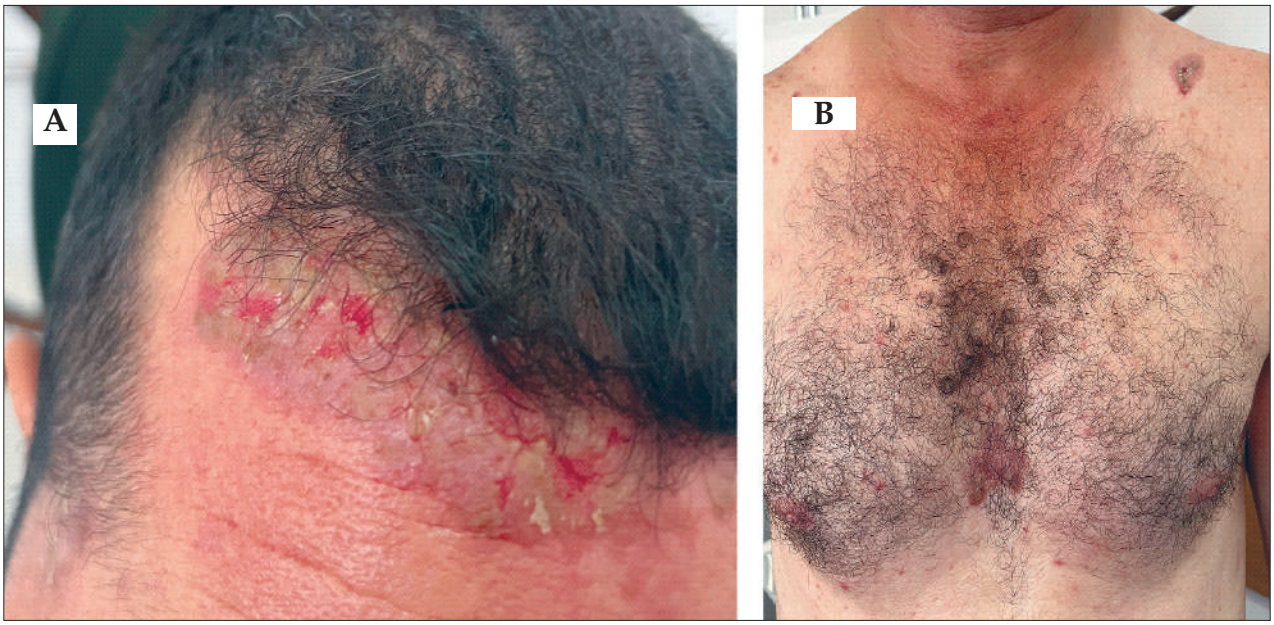

Figure 4. CASE 2 - Images taken at the second presentation in the Clinic (July 2024). A. Post-bullous erosions located at the anterior hairline of the scalp. B. Post-bullous erosions and flaccid blisters located on the anterior chest.

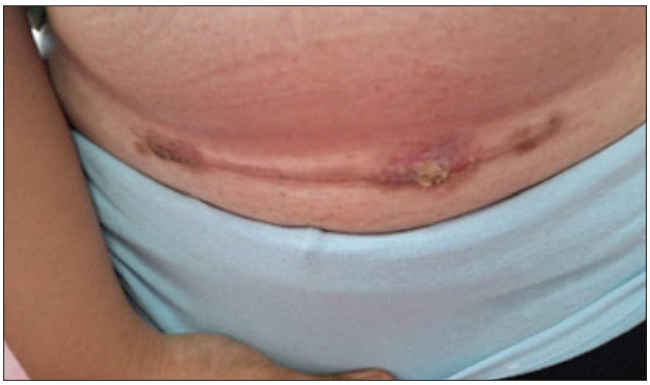

Figure 5. CASE 3 - Images taken at the first presentation in the Clinic (April 2024). A. Post-bullous erosion located at the site of the cesarean scar.

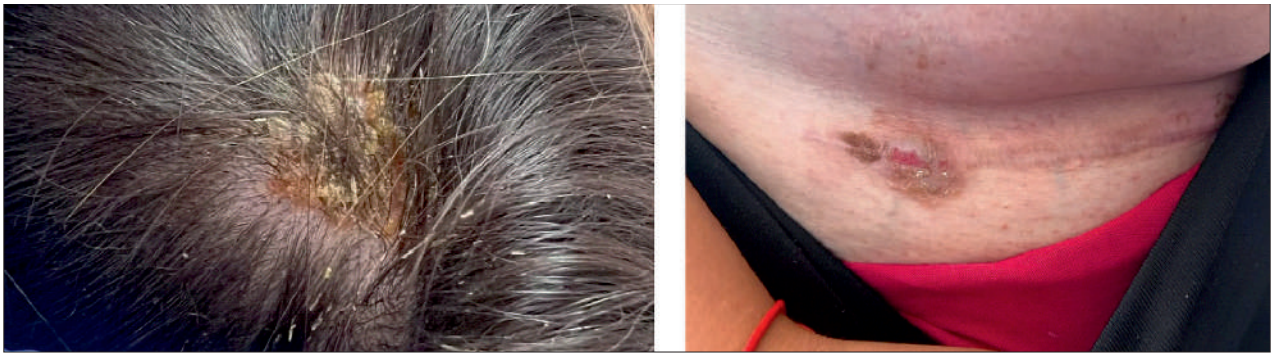

Figure 6. CASE 3 -Images taken at the second presentation in the Clinic (July 2024). A. Post-bullous erosion located at the site of the scalp. B. Post-bullous erosion located at the site of the cesarean scar.

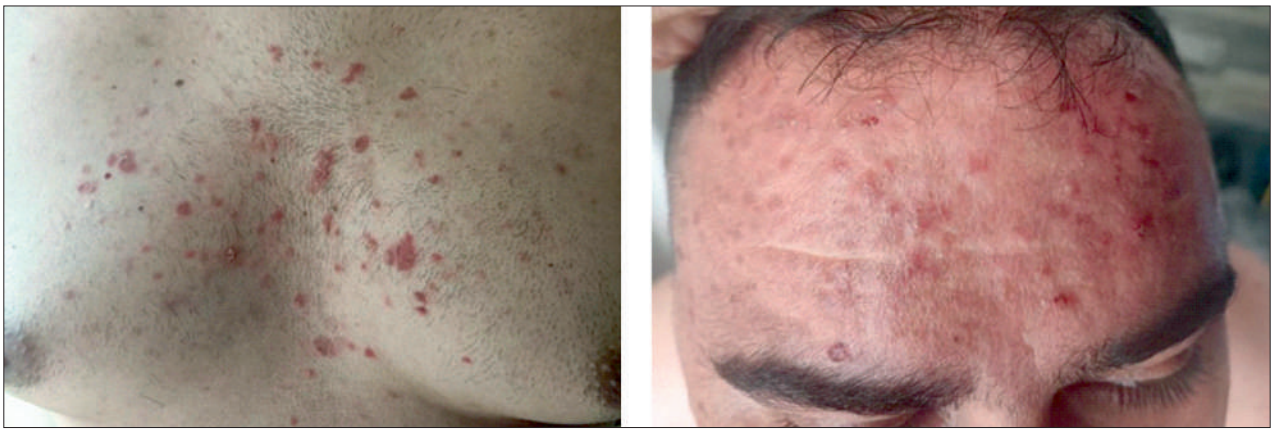

Figure 7. CASE 4 - Images taken at the presentation in the Clinic (May 2023). A. Post-bullous erosions located on the anterior chest. B. Post-bullous erosions located on the frontal area.

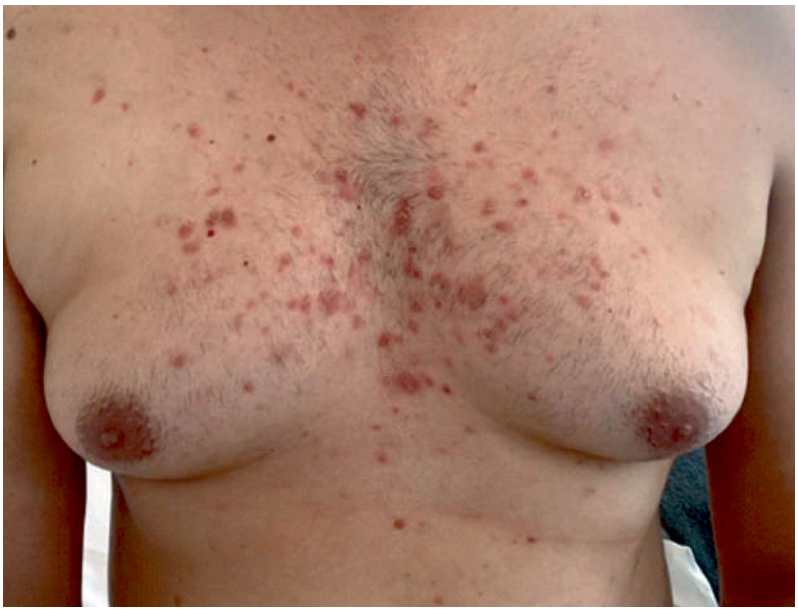

Figure 8. CASE 4 - Image taken at the second presentation in the Clinic (July 2024). A. Post-bullous erosions located on the anterior chest.

Results

Four patients with medically controlled pemphigus vulgaris (PV) were included in the study, all presenting with exacerbations following prolonged sun exposure. The patients were aged between 23 and 67 years, and their lesions primarily appeared on sun-exposed areas such as the thorax, limbs, and scalp. All patients exhibited flaccid blisters and post-bullous erosions, with varying degrees of severity based on the extent of sun exposure. All patients showed a significant increase in lesion severity after sun exposure. The exacerbations ranged from mild worsening to severe lesions with increased pain and pruritus. Lesions appeared on the anterior and posterior chest, upper limbs, and scalp in the majority of patients. The exacerbation was most notable during the summer months, with lesions becoming more severe with continued exposure to sunlight. For each patient, PV was confirmed through direct immunofluorescence, Tzanck cytodiagnosis, and skin biopsies. These diagnostic tests confirmed the presence of intraepidermal acantholysis, characteristic of PV. Direct immunofluorescence revealed IgG autoantibodies targeting desmoglein 1 and 3, aligning with the diagnosis of PV.

Discussions

The etiology of pemphigus is largely unknown. Several triggering factors have been described that induce or exacerbate the disease, such as medications, vaccines, pregnancy, radiation, emotional stress, infections, diet, or other external factors. These act synergistically with predisposing factors such as genetic susceptibility and coexisting comorbidities [12]. Pemphigus vulgaris results from a reaction with serum IgG autoantibodies directed against desmosomes on keratinocytes in the cell membrane, disrupting desmosomal activity. Desmosomal molecules, especially desmoglein 3 and desmoglein 1, belong to the cadherin family, which is responsible for epithelial cell adhesion. In the early stages of the disease, oral lesions are present due to the development of autoantibodies against desmoglein 3. In more advanced stages of the disease, when both skin and oral lesions appear, antibodies against both desmoglein 1 and desmoglein 3 are implicated. This is because desmoglein 3 is primarily expressed in the mucosal epithelium, whereas both types of desmoglein are present in the skin. Serum IgG antibodies are primarily responsible for the development of PV, considering that IgG1

indicates the remission phase, while IgG4 indicates the active phase of the disease. Both the cases mentioned in the literature and those in the Dermatology Clinic of Iași suggest an exacerbation of PV hospitalizations during the summer months. This phenomenon could be associated with sun exposure and air temperature. In fact, high temperatures during spring and summer, as well as more frequent sun exposure compared to winter and autumn, may contribute to these seasons' impact on the epithelialization process and, consequently, on the induction of PV. Moreover, despite autoimmune blistering diseases not being considered photodermatoses, the use of a sunscreen with SPF50+ and avoiding sun exposure is recommended for these patients.

Conclusions

UV radiation, involved in immunosuppression and immunomodulation beneficial in conditions such as psoriasis, is unfavorable in autoimmune blistering pathologies by inducing acantholysis at the epidermal level. The increase in temperature and exposure to UV radiation could be associated with an increase in the incidence of hospitalization for pemphigus vulgaris.

Pemphigus patients may benefit from avoiding these potential environmental triggering factors and should minimize activities that may traumatize the skin and mucous membranes during active phases of the disease.

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Conflict of interest
NONE DECLARED

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