Dermatology Practical & Conceptual

Bullous Pemphigoid and Epidemiological Patterns in Northern Greece: Insights from an 8-Year Observational Study

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ABSTRACT

Introduction: Bullous pemphigoid (BP) is an autoimmune disorder causing tense blisters on the skin and sometimes mucous membranes, primarily affecting older adults. It results from autoantibodies attacking the epidermal basement membrane. The incidence of BP is rising globally, particularly due to drug-induced cases.

Objectives: This study aimed to present epidemiological data on BP patients, response to systemic corticosteroid therapy, relapse rates, need for additional therapy, and overall prognosis.

Methods: This retrospective study included patients diagnosed with BP and admitted to the Dermatology Department of a referral center in northern Greece from 2014 to 2022. The registry included parameters such as sex, age at onset, comorbidities, drug associations, hospitalization, additional immunosuppressive therapy or doxycycline use, time to tapering, and number of relapses.

Results: Among the 188 patients (88 females, 100 males; mean age 76 years), 97% received systemic corticosteroid therapy, while 1.6% were treated with potent topical steroids alone. Doxycycline was administered to 8% of patients, and 11.7% received additional immunosuppressive agents. The most common comorbidity was diabetes mellitus (60.6%). BP was associated with gliptin intake in 36% of cases. Hospitalization was required for 79% of patients with corticosteroid tapering initiated on average by day twenty-three. Disease recurrence occurred in 34% of cases.

Conclusion: The high incidence rates in older adults and DPP-4 inhibitor users underscore the need for continued vigilance and research. Systemic corticosteroids remain the primary treatment at our center. Continuous monitoring and refinement of prevention and management strategies are crucial for effectively addressing BP.

Introduction

Definition and Epidemiology

BP is a prevalent autoimmune disorder characterized by the formation of tense blisters or bullae, primarily on the skin but occasionally that affect mucous membranes such as the oral cavity, pharynx, esophagus, and genitalia [1]. It was first identified as a distinct clinical entity in 1953 by Lever [2]. The pathogenesis of BP involves a complex interplay between genetic and environmental factors which trigger an aberrant immune response. Autoantibodies play a critical role, targeting hemidesmosomal proteins BP180 and BP230 in the epidermal basement membrane, leading to complement activation, leukocyte recruitment, and subsequent tissue damage [3]. Recent evidence indicates a noteworthy increase in the occurrence of BP, with reported rises of 1.9 to 4.3-fold over the past two decades [4-6]. Although the incidence exhibits geographic variation and is considered low, there is an upward trend [6]. This increase is partially attributed to drug-induced cases, with dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) playing a significant role. DDP-4 inhibitors may disrupt the plasmin formation, leading to improper cleavage of BP180, thus inducing BP. Other drugs implicated include loop diuretics, aldosterone antagonists, penicillin and cephalosporins, further emphasizing the need for careful monitoring of medication-related risks in susceptible populations [7]. The true disease burden may be underestimated, emphasizing the necessity for more epidemiological studies on this autoimmune condition[8,9]. BP is recognized as a condition affecting the elderly, with the typical age at onset ranging from 66 to 83 years in various global cohorts. The incidence escalates significantly with advancing age, peaking at 190 to 312 cases per million per year in individuals aged 80 years and above [9, 10]. There is evidence suggesting a genetic predisposition to BP, with certain human leukocyte antigen (HLA) alleles, such as HLA-DQB10301, HLA-DRB10401, and HLA-DQB1*0503, identified as potential risk factors. However, the association between HLA alleles and BP varies across different ethnic groups [11].

Clinical Presentation

The characteristic clinical presentation involves the development of tense blisters, which may develop on skin with normal appearance or on inflamed skin [12]. Before this, an urticarial or eczematous rash may occur. The level of itchiness can vary from none to intense, and it might precede the development of blisters that contain either clear or bloodstained fluid. These blisters typically manifest across the whole body and are more likely to appear on the limbs. There are also localized forms of the condition. BP can extend to affect mucosal surfaces, such as the mouth, and is generally not associated with scarring [13].

Diagnosis and Therapeutic Strategies

The most reliable diagnostic method for BP involves a perilesional skin biopsy for immunopathological analysis. A direct immunofluorescence technique conducted on the individual's skin reveals deposits of immunoglobulin G (IgG) autoantibodies and complement component 3 (C3) at the dermoepidermal junction, binding to BP230 and BP180 autoantigens. Enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence utilizing serum can demonstrate circulating autoantibodies directed against basement membrane proteins and especially the NC16A portion of BP180 antigen [14, 15]. Direct immunofluorescence (DIF) is the standard diagnostic method for immunobullous diseases. DIF in pemphigoid diseases allows for the identification of two antibody deposition patterns at the dermal-epidermal junction: u-serrated and n-serrated. The u-serrated pattern is associated with epidermolysis bullosa acquisita, while the n-serrated pattern is present in all other pemphigoid diseases [16]. However, it is not consistently effective in distinguishing between different subtypes of subepidermal immunobullous diseases. Immunofluorescence techniques on split skin,

introduced in the late 1980s, enable a more precise localization of the antigen-antibody-binding site. The procedure involves incubating punch biopsy specimens in 5 mL of 1 mol/L NaCl at 4° C for 24 hours, after which the epidermis is separated from the dermis using fine forceps [17]. Incubation of skin tissue in one molar sodium chloride results in the separation of the dermis from the epidermis within the lamina lucida level of the basement membrane, visible under electron microscopic examination [18]. This differentiation is essential to distinguish BP from other autoimmune bullous diseases, such as epidermolysis bullosa acquisita and bullous systemic lupus erythematosus. In BP, fluorescence is typically at the roof (epidermal binding), whereas in other diseases, it is often at the floor of the blister (dermal binding) [19]. Immunoelectron microscopy and immunoblotting offer greater specificity in investigations and may even lead to a change in diagnosis in some cases [20]. However, these advanced investigations are primarily limited to research centers, while ELISAs for detecting circulating IgG autoantibodies to BP180 and BP230 antigens are now widely available. One limitation of ELISAs is that they only detect autoantibody binding to BP180 and BP230 autoantigens, leaving other autoantigens undetected by this method [21]. BP runs a chronic course and thus requires long-term treatment. Current therapeutic options involve topical and oral steroids as well as immunosuppressants. For severe cases, plasma exchange, anti-inflammatory antibiotics, nicotinamide, biologics like rituximab, and intravenous immunoglobulins are considered [22-25] . However, these treatments pose risks of severe adverse effects and financial burden. Historically, oral corticosteroids were standard, but recent evidence suggests high-potency topical steroids, like clobetasol propionate cream, may be equally effective [26], while some studies state that topical treatment is superior to oral corticosteroid treatment [9]. Antibiotics with anti-inflammatory properties, notably in an aging population, have demonstrated efficacy and safety [27]. Biological therapies, including anti-CD20 monoclonal antibodies (rituximab), omalizumab, and dupilumab, are emerging as treatment options [28, 29]. Additionally, plasma exchange and intravenously applied pooled immunoglobulins are considered for selected cases [30]. Continuous exploration of new treatment options aiming to improve healing and minimize adverse effects is ongoing, although the clinical efficacy of these options requires further establishment.

Objectives

This study aimed to share recent epidemiological data from BP patients in a northern Greece tertiary hospital and the treatment protocol we have been following for the past eight years. Focusing on this specific region provides insights into local prevalence and trends. Additionally, the study explored the recurrence rate of BP and evaluated the effectiveness of current treatments. By doing so, the research contributes practical knowledge to improve the care of individuals with BP.

Methods

This observational retrospective cross-sectional study was designed to follow the STROBE statement [31]. Patients diagnosed with BP and admitted to the Dermatology Department of our hospital during the study period from 2014 until 2022 were included in this study. The sources of the present data were patient report files, admission files, and the hospital's record system (SAP).

The parameters of inclusion in the study were based on the fulfilment of clinical, histological, and immunological confirmations of BP. Specifically, only patients who exhibited clinical (urticarial, eczematous, excoriated, and/or bullous lesions accompanied by varying degrees of pruritus), histological (subepidermal clefts, eosinophilic spongiosis, and/or dermal infiltration of eosinophils), and immunological (immunofluorescence microscopy showing linear deposition of IgG and C3 in a linear band at the dermo epidermal junction of perilesional skin) features were included. The exclusion criteria included inadequate documentation to confirm the diagnosis of BP and a lack of follow-up information. Data on patient age at the time of onset of the disease, sex, concomitant medications, history of hospitalization, and length of stay were included. In terms of treatment documentation, the following parameters were measured: the duration of systematic corticosteroid therapy, the additional administration or not of immunosuppressive agents, the initiation of steroid tapering, the duration of maintenance therapy, and the presence or absence of relapses.

Results

In this retrospective study, a total of 188 patients were included. The patients' ages ranged from 43 to 95 years, with an average age of 76 years and a male/female (M/F) ratio of 1.13:1. Out of 188 patients, 148 (79.0 %) BP patients needed hospitalization, and 92 (48.9%) were hospitalized at first diagnosis. The average duration of hospitalization was 11.78 days. Out of 92 women, 79 were hospitalized, and out of 98 men, 76 were hospitalized. In 182 (96.8%) patients, systemic corticosteroid therapy was administered as the main treatment, while in only three (1.6%) patients, the disease was controlled exclusively with potent topical steroids (clobetasol propionate). In conjunction with topical steroids, 15 (8%) patients received therapy with doxycycline, and in

Table 1. Treatment modalities.

Treatment	Number of patients	Percentage %
Systemic corticosteroids	182	96.8
Potent topical steroids	3	1.6
Doxycycline and topical steroids	15	8.0
Immunosuppressive agents and topical steroids	22	11.7
-Azathioprine	8	4.25
-Dapsone	15	7.97

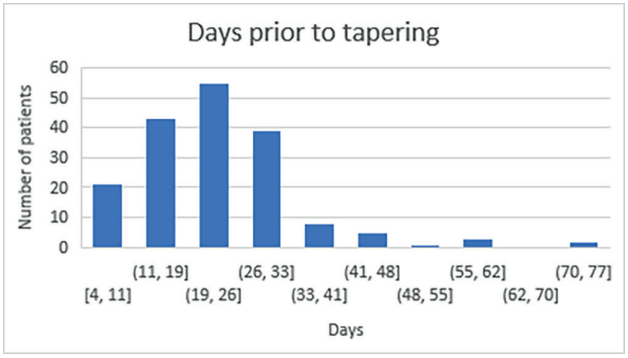

Figure 1. Corticosteroid Treatment Tapering Period Measured in Days.

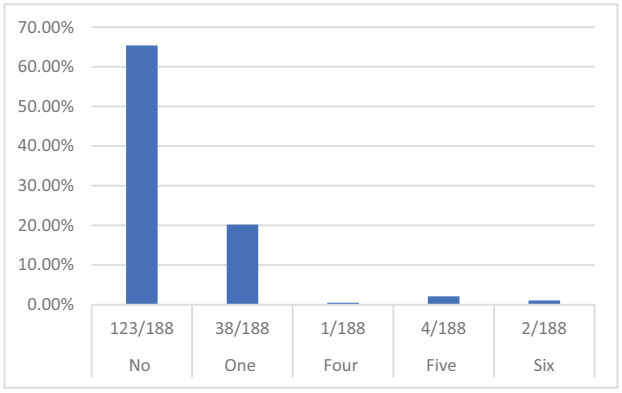

Figure 2. Frequency of Relapses.

22 patients (11.7%), additional treatment with immunosuppressive agents such as azathioprine (4.25%) and dapsone (7.97%) was prescribed (Table 1). Prednisone was given once daily, with a dosage of 0.5 mg/kg of body weight per day for patients with moderate disease and 1 mg/ kg per day for those with extensive disease. Extensive disease involved widespread blistering, significant skin involvement, and/or systemic symptoms, often causing substantial impact on the patient's quality of life or requiring more aggressive management (Bullous Pemphigoid Disease Area Index (BPDAI) >57 [32]), while moderate disease was characterized by a limited number of blisters and less extensive skin involvement, with no significant impairment in daily activities or systemic symptoms(BPDAI 20–56 [33]).The initial dose was maintained for 15 days after achieving disease control, followed by a gradual reduction of 15% every three weeks. The treatment was concluded after a duration of 12 months. Tapering of the oral corticosteroid treatment was initiated on average on the 23rd day. Patients on topical corticosteroids were prescribed a daily dose of 40 g of clobetasol propionate applied twice daily over the entire body surface until 15 days after disease control. Following this, a gradual reduction plan was implemented: decreasing to 20 g daily for one month, 10 g daily for two months, 10 g every other day for four months, and eventually settling at 10 g twice a week for the subsequent four months (Figure 1). A relapse was characterized by the presence of a minimum of three bullae daily for three consecutive days while undergoing treatment. For patients experiencing a relapse during the phase of dose reduction, the dosage was escalated to the prior level that had effectively maintained disease control. In total, 34% of cases exhibited disease recurrence, whereas the number of relapses was on average 0.70. Specifically, 123 of the patients had no relapses, 38 had one relapse, one had four relapses, four had five relapses and two had six relapses (Figure 2). Total duration of systematic steroid therapy was on average 16 months, and duration of maintenance treatment was approximately 13.8 months.

Comorbidities

The most common type of comorbidity found in our study was diabetes mellitus, which affected 60.6% (N=114) of the patients. BP was also associated with the following comorbidities: hypertension (45.2%, N= 85), chronic kidney disease (8%, N=15), cardiac disease (10%, N=19), and neurological disease (11.8 %, N=22). The number of patients that had been diagnosed with any type of cancer/malignancy five years before or five years after the diagnosis of BP was also calculated (4.25%). It should be taken into consideration that those patients' ages was an average of 82.125 years at the time of the BP diagnosis The onset of BP was correlated with a previous intake of DPP-4 inhibitor in 36% (68 cases), while vildagliptin was the most common inducible DPP-4 inhibitor (Figures 3 and 4). Scheduled follow-up visits were organized on days 7, 14, 21, 30, 90, 180, and 360. During these visits, meticulous records were kept, noting the occurrence and date of any relapse. Recognizing the heightened one-year mortality rate documented in recent series, the follow-up protocol was designed to span 12 months exclusively. Over the course of the one-year follow-up, 26 patients (13.8%) died. The primary cause of death was identified in 19 cases (Figure 5), with predominant factors including

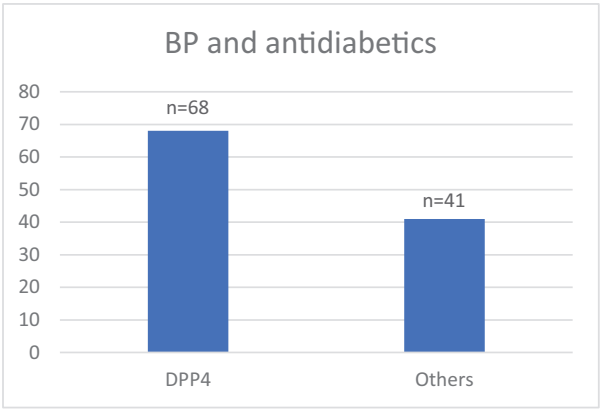

Figure 3. Number of Patients with Bullous Pemphigoid and Diabetes Mellitus Treated with D-PP4 Inhibitors in Comparison with Those Treated with Different Agents.

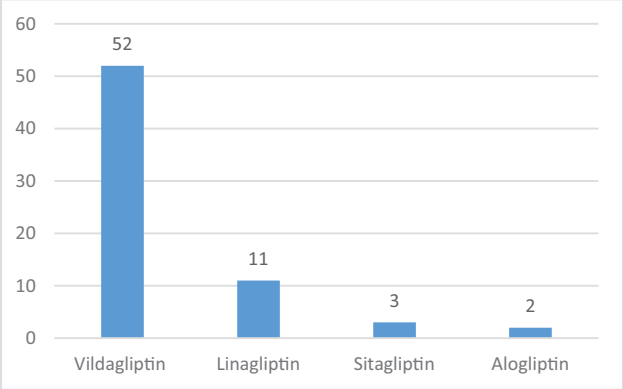

Figure 4. Comparison of DPP-4 Agents.

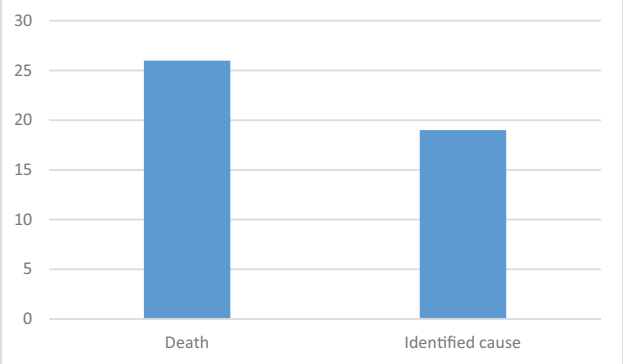

Figure 5. The Number of Deaths after a 12-month Period of Follow-Up.

cardiovascular disease (observed in 10 patients, including eight heavy smokers), stroke (two individuals), and sepsis (seven cases, 5 of which caused by pneumonia) (Figure 6).

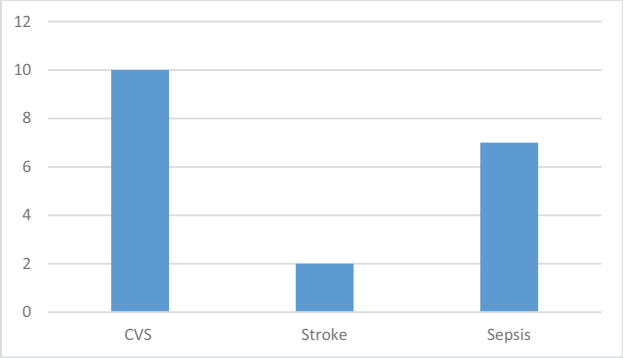

Figure 6. Identified Causes of Death after a 12-month Period. Abbreviations: CVS: cardiovascular diseases.

Discussion and Conclusions

BP accounts for 70% of subepidermal blistering diseases, predominantly affecting the elderly [10]. Its annual incidence among different populations worldwide ranges from 12 to 66 cases per 1 million people [34]. In this study, the average age at onset was 76 years, aligning with recent reviews. The male-to-female (M/F) ratio of 1.13:1 observed in our study, while indicating a slightly higher prevalence in males, does not represent a marked divergence from the ratios reported in other studies. This finding aligns with some larger retrospective studies but contrasts with the reported female preponderance in the literature, which shows M/F ratios ranging between 1:1.04 and 1:5.1. It is worth considering whether this difference was statistically significant or whether it falls within the expected variability seen across studies. Further analysis is needed to determine if this reflects a true population-specific trend or a result of sampling differences [35-37]. A series of comorbidities have been reported in BP patients, including autoimmune, neuropsychiatric, cardiovascular and renal disease, malignancy, hypertension, and diabetes mellitus [38]. In the current study, the most common comorbidities found in BP patients were diabetes mellitus (60.6%), hypertension (45.2%), kidney disease (8%), and cardiovascular (10%) and neuropsychiatric diseases (11.8%). These findings are in line with the current literature [39]. It is significant to consider that the intake of immunosuppressants can lead to the worsening of preexisting pathologies in patients with BP. The increased relapse rate prompts exploration of identifying high-risk patients and optimal management strategies. Administering adjuvant immunosuppressive agents may result into potential severe side effects, emphasizing the vulnerability of the elderly population commonly affected by BP [40]. This study underscores the impact of DPP-4 inhibitors, such as vildagliptin and linagliptin, in increasing BP risk. Another study conducted in Greece exhibited similar results [41]. In a large series of case reports, the findings suggest that DPP-4 inhibitors such as vildagliptin, sitagliptin, linagliptin, anagliptin, and alogliptin were identified as inducing agents for BP. Furthermore, a recent retrospective study demonstrated that the use of this class of

medication, especially vildagliptin and, to a lesser extent, linagliptin, relates to an increased risk of BP, independently of the metformin intake [42]. Although DPP-4 is a plasminogen receptor expressed in various tissues, including the skin, the exact mechanism underlying BP development remains unclear. It is proposed that DDP-4 inhibitors hinder the plasmin formation, which may be responsible for the unsuitable cleavage of BP180. Various cell types within the epidermis and the dermis, including keratinocytes and T-cells, express DPP-4. Its suppression induces proinflammatory cytokines, such as *eotaxin* (CCL11 chemokine), and leads to cutaneous eosinophil activation and blister formation[43]. Other mechanisms that have been proposed for gliptin's mechanism of action include the modification of the immune response, the alteration of the antigenic properties of the epidermal basement membrane zone, and the modification of the activity of proteases, resulting in abnormal processing and/or destruction of BP180 antigen [44]. At the referral Center of Autoimmune Bullous Diseases of our hospital, the primary treatment strategy is systemic steroid monotherapy (78.7% of patients), consistent with European Academy of Dermatology and Venereology (EADV) guidelines [45]. The average time to initiate steroid tapering was 23 days, with a total treatment duration of 16 months. Adjuvant immunosuppressive agents were avoided due to their potential severe side effects and limited benefits. Significantly, the study revealed a 13.8% mortality rate over the 1-year follow-up period, with cardiovascular disease, sepsis, and stroke identified as the primary causes. It is noteworthy that the prevalence of sepsis as a cause of death may have been influenced by the recent COVID-19 pandemic. Overall, disease control corresponds either to no new lesion occurrence or pruritus or established BP lesions under the healing process [46]. The average time to start tapering (disease control) in our study was on day 23. The mean duration of maintenance therapy (minimal 0.1 mg/kg per day) was one year and two months (13.8 months). Overall, the average total treatment duration, including the consolidation phase and maintenance treatment, was sixteen months. This total treatment duration was longer than that proposed by experts (9-12 months) [45]. Additionally, the relapse rate (36%) found in the study aligns well with data from the current literature, which demonstrates a range of relapse rates from 27.87% to 53%. Interestingly, most relapses tended to occur early, within six months during the remission [47, 48]. A relapse of BP is defined as the appearance of at least three new lesions within one month or one large (diameter larger than 10 cm) lesion that does not heal in one week, or the extension of original exanthem or daily pruritus in patients in remission [49]. Questions that emerge are how to identify patients at a higher risk of relapse and what the optimal therapeutic option for the management of a relapse is. Several studies have shown that patients with numerous lesions at disease onset have a significant risk of relapse [50, 51]. By using the BPDAI score for the assessment of disease severity, more precise conclusions may be reached during baseline and follow-up visits [45]. This observational study plays a significant role in identifying new areas of investigation that may require further validation through fundamental or experimental research. Nevertheless, it is crucial to acknowledge the limitations that can arise in such studies, due to factors like small sample sizes, residual confounding, multiple comparisons, or subgroup analyses conducted without prespecified hypotheses or sufficient statistical power [31].

The findings of this study confirm the higher incidence rates of BP in elderly patients and DPP-4 inhibitor users, reflecting trends observed globally. Systemic corticosteroids remain the primary therapeutic strategy at our center. However, the observed relapse rates highlight the chronic nature of BP, while its associated mortality underscores the urgent need for optimized management. Continuous monitoring of BP epidemiology and further research into preventive and management strategies are crucial to mitigate the disease burden worldwide.

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