ORIGINAL ARTICLE

Prevalence, Spectrum and Clinical Implications of Malignancies in Patients with Bullous Pemphigoid

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Current research on the malignancy rate and spectrum of malignancies in patients with bullous pemphigoid is contradictory. The aims of this study were to determine the prevalence and spectrum of malignancy in patients with bullous pemphigoid and to compare demographic, clinical, therapeutic and outcome data between bullous pemphigoid patients with and without malignancy. This retrospective cohort study enrolled 335 patients (194 women and 141 men; mean age at diagnosis of bullous pemphigoid 77.5 ± 12 years) followed up at an Israeli tertiary centre between January 2009 and December 2019: 107 (32%) had malignancy and 228 (68%) did not. Malignancy occurred before and after bullous pemphigoid diagnosis in 82 (77%) and 25 (23%) patients, respectively. Bullous pemphigoid patients with cancer were older ($p = 0.02$) and had a higher mortality rate ($p < 0.0001$) than those without malignancy. The 2 groups did not differ in terms of sex, comorbidities, or clinical characteristics. Those who developed malignancy before bullous pemphigoid were younger than those who developed malignancy after bullous pemphigoid (mean age 69.3 vs 82.4 years, $p < 0.0001$). Overall malignancy rates did not differ between patients with bullous pemphigoid and the general population; therefore, comprehensive malignancy workup may be unnecessary. However, patients with bullous pemphigoid had a greater risk of melanoma (10.7% vs 4.3%, $p = 0.0005$); therefore, routine skin screening may be recommended.

Key words: bullous pemphigoid; bullous dermatoses; malignant melanoma; mortality rate.

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SIGNIFICANCE

The aims of this study were to determine the prevalence and spectrum of cancer in patients with bullous pemphigoid (BP), and to compare BP patients with and without cancer. The results show that there is no increased rate of overall malignancy in BP, while the frequency of melanoma increases. Patients with both BP and cancer are older, but there are no differences in severity or clinical features. These results suggest that routine skin screening in patients with BP is necessary to improve treatment and outcomes.

Bullous pemphigoid (BP) is the most prevalent autoimmune blistering disorder that primarily affects older individuals (1). Over the last 20 years, the prevalence of BP has increased by 1.9–4.3 time, as reported in data from the UK, France, Germany, and Israel. This trend has been attributed to population ageing, drug-induced cases, and the increased identification of non-bullous presentations (1). The overall prevalence of BP in the US is 12 cases per 100,000 individuals, with cases among women slightly outnumbering those among men (12.7/100,000 vs 11/100,000). The prevalence rate of BP is highest (123.6 cases/100,000 persons) among patients aged ≥ 90 years (2). The annual incidence of BP varies from 2.4 to 21.7 cases per million persons worldwide, with 2.5–42.7, 2.6–7.4, and 10 cases per million people in Europe, Asia, and the USA, respectively (3, 4). With increasing age, the incidence rate rises very rapidly, reaching 190–312 and up to 507 cases per million persons among individuals aged > 80 and ≥ 85 years, respectively, worldwide (1, 5).

BP is clinically distinguished by pruritic skin eruptions with the formation of tight bullae on erythematous skin, together with urticarial papules and plaques. Only papular urticarial eczematous lesions or excoriations are observed in the early stages or in atypical non-bullous variants. Most patients have severe pruritus. In 10–30% of cases, mucosal involvement may occur (6). The pathogenesis of BP is linked to tissue-bound and circulating autoantibodies directed against hemidesmosomal proteins (BP antigen 180, BP antigen 230, or both) involved in dermal-epidermal cohesion. Binding of these antibodies triggers an inflammatory cascade and the formation of subepidermal blisters (6). Histopathology reveals a subepidermal blister with an inflammatory infiltrate frequently harbouring eosinophils. Direct immunofluorescence (DIF) shows linear deposition of immunoglobulin G and/or C3 at the dermo-epidermal junction (7).

The diagnosis of BP is based on a combination of clinical features, histological findings, including positive DIF, and the detection of specific circulating immunoglobulin G (IgG) anti-basement membrane autoantibodies using indirect immunofluorescence investigations or enzyme-linked immunosorbent assays (ELISAs) (7).

BP has been linked with a variety of comorbidities, including neurological illnesses (multiple sclerosis, dementia, Parkinson's disease, epilepsy, and stroke) (8); an elevated risk of thromboembolic events (9); psychiatric disorders (10); dermatoses (psoriasis and lichen planus) (11, 12); and various medications (13). The link between BP and malignancy has also been studied with conflicting results. Some studies have shown an association with malignancies (either solid tumours and/or haematological malignant disorders) (14–17), while others claim that this association is coincidental and may be explained by confounding factors, such as age (18, 19). Several reports have described unusual clinical BP variants in patients who also have malignancies (20, 21). Because the prevalence of BP varies by geographical area and ethnicity (22, 23), it is probable that comorbidities, such as malignancy, will also vary.

The objectives of this study were to compare the frequency of malignancies in patients with BP with that in the general population in Israel, and to describe their spectrum and range. In addition, the study aimed to evaluate the demographics, medical histories, clinical features, therapies employed, and mortality rates among BP patients with and without malignancy.

MATERIALS AND METHODS

This cohort study evaluated the medical records of patients diagnosed with BP. The patients were diagnosed, treated, and followed up in the dermatology department and dermatology outpatient clinic at the Sheba Medical Center, the largest and most comprehensive tertiary centre in the middle east, between January 2009 and December 2019. The study was approved by the institutional review board (7172-09-SMC). The medical records of the patients diagnosed with BP were collected from the Sheba Hospital Chameleon System computerized files and reviewed. Inclusion criteria were: patients of any age with: a confirmed diagnosis of BP based on the typical clinical picture; typical histological appearance of subepidermal splitting; positive DIF results confirmed in Sheba Medical Center's laboratory or in a certified laboratory at another medical centre; and follow-up of at least 10 months after BP diagnosis. Patients with a misdiagnosis or incomplete files were excluded.

Demographic data, comorbidities (general, cutaneous, and malignancy), clinical parameters (presence or absence of bullae, mucosal involvement, pruritus, and disease severity at onset), treatment received, and follow-up time-span were collected. Data were gathered on the type of malignancy and chronology of its diagnosis in relation to BP diagnosis, and all patients were divided into 2 groups: (i) those without comorbid malignancy, and (ii) those with malignancy. Patients with comorbid malignancy were subdivided into those who developed malignancy before and after BP diagnosis. All collected parameters were compared between the groups. The mortality rate of BP patients with malignancy was estimated and compared with that of BP patients without malignancy.

The malignancy rate and spectrum in the cohort of patients with BP were compared with those in the general population. To achieve this, data from the study group were compared with that from the general population (adjusted for age) using the Israel National Cancer Registry (INCR) database for 2015, which was the midpoint of the follow-up period of the study cohort.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics, version 25 (IBM Corp., Armonk, NY, USA). Dichotomous variables were compared using the χ^2 test, while dichotomous and quantitative variables (age and follow-up duration) were compared using the student's *t*-test for unpaired samples. A comparison of the invasive cancer proportions was performed using the Z test. All tests were performed at a confidence level of 95% (significance level 0.05), with a statistical power of 80%.

RESULTS

Patient demographics and overall malignancy rates

The study included a final total of 335 patients, after excluding 409 patients due to misdiagnosis or uncertain diagnosis, 41 due to lack of access to data, and 41 due to loss to follow-up. The patients' follow-up duration from BP diagnosis ranged from 10 to 129 (mean 17.4 ± 25.6) months. Of the 335 included patients, 194 were women and 141 were men, with a mean age at BP diagnosis of 77.5 ± 12 years: women 78.5 ± 11 years; men 76.2 ± 13.3 years ($p = 0.07$). Out of all the patients, 107 (32%) had at least 1 malignancy, whereas 228 (68%) had no malignancy. Among the BP patients with malignancy, 14 (13%) had 2 distinct malignancies. The malignancy preceded BP onset in 82 (77%) of the 107 patients (the duration between cancer diagnosis and BP onset ranged between 4 months and 42 years; mean 9.8 ± 1.80 years), and BP preceded the malignancy in 25 (23%) patients (duration between BP diagnosis and malignancy ranged between 1 month and 7 years; mean 2.6 ± 0.85 years). Of the 107 patients with BP and associated malignancy, 7 received immunosuppressive treatment before the diagnosis of malignancy. Patients with malignancy were significantly older than those without ($p = 0.02$). There were no differences in sex, comorbidities, and clinical characteristics between the patient groups. Data on epidemiology, clinical characteristics, and treatments received are shown in **Table I**.

Comorbidities, clinical characteristics, and mortality rates in bullous pemphigoid patients with and without malignancy

The patients with BP and malignancy had comparable comorbidities and clinical characteristics. The case mortality rate in patients with BP linked with malignancy was significantly higher ($p < 0.0001$) (Table I).

Comparison of patients with bullous pemphigoid onset before and after malignancy

Table II shows the comparison of demographics, comorbidities, clinical characteristics, and treatments received by patients who were diagnosed with malignancy before and after BP diagnosis. Sex, comorbidities, and clinical characteristics did not differ significantly between the 2

Table I. Comparison of demographics, comorbidities, clinical features, and treatments between bullous pemphigoid (BP) patients with and without malignancy

Sub-category	All patients with BP $n=335$	BP with malignancy $n=107$	BP without malignancy $n=228$	p-value
Demography				
Age at BP diagnosis, years, mean (SD)	77.5 (12.0)	79.2 (10.1)	76.7 (12.8)	0.02
Female sex *n* (%)	194 (58)	57 (53)	137 (60)	0.40
Comorbidities, *n* (%)				
Smoking *n* (%)	19 (6)	5 (5)	14 (6)	0.58
Cardiovascular	149 (44)	52 (48)	97 (42)	0.31
Diabetes mellitus	153 (46)	44 (41)	109 (48)	0.25
Hypertension	248 (74)	83 (77)	165 (72)	0.31
Endocrine	69 (21)	23 (21)	46 (20)	0.78
Pulmonary	57 (17)	18 (17)	39 (17)	0.34
Neuro-psychiatric	144 (43)	39 (36)	105 (46)	0.09
Coagulation	2 (0.6)	2 (2)	0 (0)	0.03
Gastrointestinal	49 (15)	19 (18)	30 (13)	0.26
Dyslipidaemia	169 (50)	50 (47)	119 (52)	0.35
Dermatological comorbidities, *n* (%)				
Dermatoses (any)	21 (6)	6 (6)	15 (7)	0.73
Papulosquamous diseases	14 (4)	4 (4)	10 (4)	0.78
Autoimmune dermatosis[a]	8 (2)	3 (3)	5 (2)	0.73
Clinical parameters, *n* (%)				
Pruritus	282 (84)	85 (79)	197 (86)	0.10
Bullae	308 (92)	98 (91)	210 (92)	0.87
Mucosal involvement	66 (20)	24 (22)	42 (18)	0.39
Mucosal involvement, *n* (%)				
No	269 (80)	83 (78)	186 (82)	0.70
Oral involvement	64 (19)	22 (20)	42 (18)	0.64
Genital involvement	13 (4)	3 (3)	10 (4)	0.48
Moderate-severe disease	296 (88)	92 (86)	204 (89)	0.35
Treatment, *n* (%)				
Systemic Treatment	296 (88)	92 (86)	204 (89)	0.35
Dapsone/tetracycline	257 (77)	78 (73)	179 (78)	0.25
High-dose corticosteroids	41 (12)	13 (12)	28 (12)	0.97
MTX/azathioprine	33 (10)	5 (5)	28 (12)	0.02
Mycophenolate mofetil	30 (9)	10 (9)	20 (9)	0.86
Rituximab	6 (2)	1 (1)	5 (2)	0.41
DPP4i	8 (2)	6 (6)	2 (1)	0.08
Follow-up duration of BP, months range, mean (SD)	10–129, 17.4 (25.6)	10–117, 20.9 (25.7)	10–129, 15.8 (25.4)	0.09
Case-mortality rate, *n* (%)	78 (23)	49 (46)	29 (13)	0.000

[a]Alopecia areata, vitiligo, urticaria.

MTX: methotrexate; SD: standard deviation; DPP4i: Dipeptidyl peptidase 4 inhibitors.

groups. While the age at which BP was diagnosed was not different, the age at which malignancy was discovered was much lower in patients who had malignancy before BP (69.3 vs 82.4 years, $p<0.0001$). The case mortality rate was significantly higher among patients who had been diagnosed with malignancy prior to BP diagnosis (52% vs 24%, $p=0.01$).

Malignancy types and rates

Table III describes the distribution of malignancies in patients with BP compared with that in the general adult age-matched population. There were no differences in the overall malignancy rates between the patients with BP and the general population. Significant differences were observed in the rates of melanoma, lung cancer, and colon cancer.Patients with BP had a higher rate of melanoma than that in the general population (10.7% vs 4.3%, respectively, $p=0.0005$). Of the 13 cases of melanoma, 8 (61.5%) and 5 (38.5%) preceded and followed BP diagnosis, respectively. In addition, compared with the general population, patients with BP had lower rates of lung (4.1% vs 10.9%, $p=0.01$) and colon (2.4% vs 12.2%, $p=0.0008$) cancers. No significant differences were found in the other malignancy rates. Breast cancer (14.8%), squamous cell carcinoma (SCC) (13.2%), prostate cancer (11.5%), melanoma (10.7%), and bladder cancer (7.4%) were the 5 most common cancer types in patients with BP. Breast cancer (20.4%), prostate cancer (12.9%), colon cancer (12.2%), lung cancer (10.9%), and bladder cancer (7.7%) were the 5 most common cancer types in the general population.

It should be noted that Israel's National Cancer Registry does not collect information on squamous cell skin cancers. Among the 107 patients with malignancies, 93 had solid malignancies, 10 had haematological

Table II. Comparison of epidemiological and clinical characteristics and treatments between patients diagnosed with malignancy before and after the diagnosis of bullous pemphigoid (BP)

Sub-category	Malignancy preceded BP, $n=82$	BP preceded malignancy, $n=25$	p-value
Demography			
Age at BP diagnosis, years, mean (SD)	79.1 (10.5)	79.7 (8.6)	0.29
Age at malignancy diagnosis, years, mean (SD)	69.34 (11.8)	82.4 (8.8)	<0.0001
Time period between BP onset and malignancy – diagnosis range, mean (SD)	4 months–42 years, 9.8 (1.80) years	1 months–7 years, 2.6 (0.85) years	<0.0001
Female sex, *n* (%)	46 (56)	11 (44)	0.28
Comorbidities, *n* (%)			
Smoking *n* (%)	5 (6)	0 (0)	0.20
Cardiovascular	40 (49)	12 (48)	0.94
Diabetes mellitus	33 (40)	11 (44)	0.73
Hypertension	63 (77)	20 (80)	0.73
Endocrine	20 (24)	3 (12)	0.18
Pulmonary	13 (16)	5 (20)	0.77
Neuro-psychiatric	30 (36)	9 (36)	0.95
Coagulation	2 (2)	0 (0)	0.43
Gastrointestinal	14 (17)	5 (20)	0.73
Dyslipidaemia	36 (44)	14 (56)	0.28
Dermatological comorbidities, *n* (%)			
Dermatoses (any)	4 (5)	2 (8)	0.55
Papulosquamous diseases	3 (4)	1 (4)	0.93
Autoimmune dermatoses[a]	1 (1)	2 (8)	0.07
Clinical features, *n* (%)			
Pruritus	65 (79)	20 (80)	0.93
Bullae	75 (91)	23 (92)	0.93
Mucosal involvement	18 (22)	6 (24)	0.83
Mucosal involvement, *n* (%)			
No	64 (78)	19 (76)	0.81
Oral involvement	18 (22)	4 (16)	0.51
Genital involvement	1 (1)	2 (8)	0.07
Moderate-severe disease	72 (88)	20 (80)	0.32
Treatment, *n* (%)			
Systemic Treatment	72 (88)	20 (80)	0.32
Dapsone/tetracycline	62 (76)	16 (64)	0.25
High-dose steroids	9 (11)	4 (16)	0.50
vMTX/azathioprine	3 (4)	2 (8)	0.36
Mycophenolate mofetil	7 (8)	3 (12)	0.60
Rituximab	1 (1)	0 (0)	0.57
Immunosuppressive Tx before malignancy	4 (5)	3 (12)	0.20
Follow-up duration of BP, months range, mean (SD)	10–107, 18.1 (23.1)	10–117, 29.8 (31.8)	0.04
Case mortality rate, *n* (%)	43 (52)	6 (24)	0.01

[a]Alopecia areata, vitiligo, urticaria.

SD: standard deviation; BP: bullous pemphigoid; MTX: methotrexate.

Table III. Distribution of malignancies in bullous pemphigoid (BP) patients compared with the general population

Malignancy	Patients with BP *n* (%)	New patients in 2015 *n* (%)	*p*-value
Breast	18 (14.8)	4,044 (20.4)	0.11
Invasive SCC	16 (13.2)	–	
Prostate	14 (11.5)	2,550 (12.9)	0.61
Melanoma	13 (10.7)	855 (4.3)	0.0005
Bladder	9 (7.4)	1,524 (7.7)	0.86
Renal	8 (6.6)	890 (4.5)	0.28
Lung	5 (4.1)	2,159 (10.9)	0.01
NHL	5 (4.1)	1,209 (6.1)	0.32
Thyroid	4 (3.3)	796 (4.0)	0.65
Stomach	4 (3.3)	749 (3.7)	0.77
Colon	3 (2.4)	2,412 (12.2)	0.0008
Brain	3 (2.4)	343 (1.7)	0.54
Uterus	3 (2.4)	727 (3.6)	0.47
Leukaemia	2 (1.6)	730 (3.7)	0.21
MDS	2 (1.6)	335 (1.6)	1.00
MM	2 (1.6)	395 (2.0)	0.74
Other[a]	10 (8.2)	–	
Total	121 (100)	27,303 (100)	

[a]Other included larynx, malignant fibrous histiocytoma, soft tissue, ureter, penile cancer, pancreas, parotid gland, and unknown.
MM: multiple myeloma; MDS: myelodysplastic syndrome; SCC: squamous cell carcinoma; NHL: non-Hodgkin lymphoma.

malignancies, and 4 had both solid and haematological malignancies. Compared with the general population, solid malignancies accounted for a larger proportion of all malignancies (solid and haematological) in patients with BP (91.1% vs 87%).

DISCUSSION

In this study patients with BP in the malignancy group were older and had higher mortality rates than the non-malignancy group. The literature describes BP as a disease that primarily affects older individuals (1). The average mean age of the patients in the current study was 77.5 ± 1.2 years, which is within the previously reported range of 76–80 years. There was a significant difference in the age at BP onset between the groups with and without associated malignancy, with patients in the malignancy group being much older than those in the non-malignancy group (79.2 ± 10.1 vs 76.7 ± 12.8 years, respectively, $p = 0.02$). As both BP and several common malignancies become more prevalent with age, these findings might be attributed to either the increasing frequency of malignancy or a demographic characteristic of BP associated with malignancy. Previously, contradictory results were obtained in patients with BP, with some studies indicating an increase in the prevalence of malignancy with age, and others not (14–19, 24, 25). This could be related to variation in the occurrence of a range of cancers among the different populations. Moreover, the current study found that, in BP patients with associated malignancy, the case mortality rate was nearly 4 times higher. This could be because the patients in the subgroup with concomitant malignancies were older.

Patients diagnosed with cancer before developing BP had a mortality rate more than twice as high as that of patients who were diagnosed with BP first. A possible explanation is that, in this study, the length of time spent with existing malignancy was longer in the group with malignancy before BP onset than in the group with BP prior to cancer (9.8 vs 2.6 years).

In addition, patients with BP had a higher incidence of melanoma, but no higher overall malignancy incidence. The fact that there were no differences in the overall malignancy rates between patients with BP and the general population is consistent with those of earlier studies, although inconsistent with those of others (14–19). Consistent with previous findings, the current study showed that patients with BP had a significantly higher rate of melanoma than that in the general population (10.7% vs 4.3%, respectively, $p = 0.0005$) (33). There are several suggested mechanisms underlying this association, including keratinocyte dysfunction and increased anti-BP230 autoantibodies, all of which have been observed in patients with melanoma, and human leukocyte antigen polymorphisms linked to both melanoma and BP (HLA-DQB1*03:01) (33–36). Melanoma has also recently been recognized as a risk factor for BP development after treatment with Immune checkpoint inhibitors (ICIs) (33). Notably, none of the patients in the current cohort received treatment with ICIs. In this study, 61.5% and 38.5% of the melanoma cases occurred before and after BP diagnosis, respectively. These findings indicate a causal associationbetween BP and melanoma (not only therapy) and suggest that routine melanoma screening should be considered in patients with BP.

This study found that patients with BP have a lower prevalence of lung and colon cancers than in the general population (4.1% vs 10.9% and 2.4% vs 12.2%, respectively). According to the Israel National Registry of Cancer Mortality data 2021, lung cancer is the leading cause of cancer mortality in Israel, with a low 5-year survival rate and 75% of all fatalities occurring in people aged ≥ 50 years. According to the same data, colorectal cancer is the second leading cause of cancer death in Israel, with a mortality rate close to the global mean rate, and older individuals accounting for most cancer deaths. Colorectal cancer mortality rates have also been reported to increase after the age of 55 years, peaking in patients aged ≥ 75 years. It is reasonable to assume that the prevalence of lung and colorectal cancers in the current study was understated; some of the patients with cancer may not have been referred to a dermatologist, but instead were treated by an oncologist. This is also true for other types of malignancy for which no association was found, as further discussed in the study limitations section.

In addition, the current study found that a vast majority of the cancers appeared before the diagnosis of BP. Researchers have suggested a link between BP and cancer and several pathogenic mechanisms have been proposed, most of which are reliant on the sequence in which the disorders appear; In cases where malignancy

preceded the onset of BP, a hypothesis of paraneoplastic autoimmunity emerging from the disruption of central and peripheral immunity, as well as self-antigen modification, has been proposed (26). Consequently, antibodies targeting tumour-specific antigens may cross-react with basement membrane antigens, such as BP antigens, causing skin blistering (26). One putative antigen is laminin-332, a protein involved in keratinocyte-basal cell membrane adhesion, which is produced by a variety of solid malignancies (breast, pancreatic, colon, and lung cancers). Putative pathogenetic processes include tumour-produced anti-BMZ cross-reactive antigens and the creation of molecules that disrupt the basal membrane, resulting in anti-BMZ antibody production (27).

Anticancer treatments, radiotherapy, and surgery, have also been described as triggers for bullous dermatoses (28–30). When cancer develops following the onset of an autoimmune bullous disorder, it has been hypothesized that the constant activation of the immune system, the creation of proinflammatory cytokines, tissue damage, and extended inflammation all contribute to carcinogenesis (31). Chronic immunosuppressive therapy has also been linked to an increased risk of cancer in patients with BP (32). In the current study, malignancy preceded BP manifestation in most patients (77%). Thus, BP as a result of an immune response to tumour cells or anticancer therapy may be a more common scenario than BP as a primary cause of carcinogenesis. Among the anticancer drugs, ICIs are specifically linked to BP (28), as pointed out previously. The pathomechanism is not entirely known; however, M2 macrophages may play a role (29). The time between drug exposure and BP onset varies, ranging from early onset following treatment initiation to late onset after treatment discontinuation (28). Radiotherapy may cause BP by altering the antigenic properties of the basement membrane and by inducing autoantibody production (30). Notably, none of the patients in the current cohort had had any radiotherapy before BP onset.

The rate of immunosuppressive therapy differed significantly between the groups, with the malignancy group receiving immunosuppressive medication (methotrexate and/or azathioprine) at a lower rate ($p=0.02$). This could be related to their poorer overall health, desire to avoid tumour aggravation, or concurrent anticancer treatment that prevented additional immunosuppression. It is also possible that BP associated with cancer may resolve following anticancer treatment, precluding the need for these immunosuppressive medications (37). There were no differences in clinical characteristics, symptoms, or illness severity between patients with and without cancer in the current study cohort. This is in contrast to several previous reports of unusual clinical BP variants (atypical presentation and refractory disease) in patients with associated malignancies (20, 21, 38–40).

Study limitations and strengths

This study has several limitations. There was no information regarding the patients' anti-BP180 and anti-BP230 antibody titres, since indirect immunofluorescence (IIF) and enzyme-linked immunoassay (ELISA) are not part of the routine BP workup in our centre. Furthermore, because the data were obtained from a single tertiary centre, the sample size was limited, and there is a possibility of selection bias. While dermatologists refer most patients with severe BP to tertiary centres where they are followed closely, it is possible that less severe cases are treated in the community or by oncologists without being referred to a dermatologist, and therefore without a definitive diagnosis of BP. This can result in an underestimation of the association between BP and malignancy, especially in non-skin cancers; while most patients with skin cancer most probably see a dermatologist, patients with non-skin cancer may not be evaluated by a dermatologist, leading to an underestimation of the association between their non-skin cancer and BP. The strengths of the current study include its well-defined cohort, long-term follow-up, and reliance on data files containing complete data on clinical features and treatments provided by expert dermatologists. Several population-based studies lack complete clinical information and are prone to classification bias.

Conclusion

A comprehensive workup for solid or haematological malignancy in patients with BP is considered unnecessary, as no higher risk of general malignancy was found in patients with BP comperd with the general population. The sample of patients with BP had a higher prevalence of melanoma, indicating that routine skin screening may be recommended. Furthermore, large sample, multicentre prospective studies are warranted.

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REFERENCES

1. Kridin K, Ludwig RJ. The growing incidence of bullous pemphigoid: overview and potential explanations. Front Med (Lausanne) 2018; 5: 220.
2. Wertenteil S, Garg A, Strunk A, Alloo A. Prevalence estimates for pemphigoid in the United States: a sex-adjusted and age-adjusted population analysis. J Am Acad Dermatol 2019; 80: 655–659.
3. Miyamoto D, Santi CG, Aoki V, Maruta CW. Bullous pemphigoid. An Bras Dermatol 2019; 94: 133–146.
4. Colbert RL, Allen DM, Eastwood D, Fairley JA. Mortality rate of bullous pemphigoid in a US medical center. J Invest Dermatol 2004; 122: 1091–1095.
5. Daniel BS, Murrell DF. Review of autoimmune blistering

diseases: the pemphigoid diseases. J Eur Acad Dermatol Venereol 2019; 33: 1685–1694.
6. Bernard P, Antonicelli F. Bullous pemphigoid: a review of its diagnosis, associations and treatment. Am J Clin Dermatol 2017; 18: 513–528.
7. Saschenbrecker S, Karl I, Komorowski L, Probst C, Dähnrich C, Fechner K, et al. Serological diagnosis of autoimmune bullous skin diseases. Front Immunol 2019; 10: 1974.
8. Egami S, Yamagami J, Amagai M. Autoimmune bullous skin diseases, pemphigus and pemphigoid. J Allergy Clin Immunol 2020; 145: 1031–1047.
9. Ungprasert P, Wijarnpreecha K, Thongprayoon C. Risk of venous thromboembolism in patients with bullous pemphigoid: a systematic review and meta-analysis. Indian J Dermatol Venereol Leprol 2018; 84: 22–26.
10. Pourali SP, Gutierrez Y, Kohn AH, Rajkumar JR, Jones ME, Ortiz I, et al. Bullous dermatoses and depression: a systematic review. JAMA Dermatol 2021; 157: 1487–1495.
11. Phan K, Goyal S, Murrell DF. Association between bullous pemphigoid and psoriasis: systematic review and meta-analysis of case-control studies. Australas J Dermatol 2019; 60: 23–28.
12. Hübner F, Langan EA, Recke A. Lichen planus pemphigoides: from lichenoid inflammation to autoantibody-mediated blistering. Front Immunol 2019; 10: 1389.
13. Verheyden MJ, Bilgic A, Murrell DF. A systematic review of drug-induced pemphigoid. Acta Derm Venereol 2020; 100: adv00224.
14. Li J, Zuo YG, Zheng HY, Qiu-Ning S. Association between bullous pemphigoid and internal diseases. J Dtsch Dermatol Ges 2013; 11: 263–264.
15. Pankakoski A, Sintonen H, Ranki A, Kluger N. Comorbidities of bullous pemphigoid in a Finnish cohort. Eur J Dermatol 2018; 28: 157–161.
16. Venning VA, Wojnarowska F. The association of bullous pemphigoid and malignant disease: a case control study. Br J Dermatol 1990; 123: 439–445.
17. Atzmony L, Mimouni I, Reiter O, Leshem YA, Taha O, Gdalevich M, et al. Association of bullous pemphigoid with malignancy: a systematic review and meta-analysis. J Am Acad Dermatol 2017; 77: 691–699.
18. Cai SC, Allen JC, Lim YL, Tan SH, Tang MB. Association of bullous pemphigoid and malignant neoplasms. JAMA Dermatol 2015; 151: 665–667.
19. Lucariello RJ, Villablanca SE, Mascaró JM, Reichel M. Association between bullous pemphigoid and malignancy: a meta-analysis. Australas J Dermatol 2018; 59: 253–260.
20. Jackson SR, Koestenbauer J, Carroll AP, Oo TH, Chou S, Indrajit B. Paraneoplastic bullous pemphigoid – a sign of clear cell renal carcinoma. Urol Case Rep 2020; 30: 101119.
21. Das A, Das S, Das SK, Basuthakur S. A case of paraneoplastic bullous pemphigoid in association with squamous cell carcinoma of lung. J Postgrad Med 2015; 61: 197–199.
22. Kridin K, Bergman R. Ethnic variations in the epidemiology of bullous pemphigoid in Israel. Int J Dermatol 2018; 57: 34–39.
23. Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two autoimmune bullous diseases: pemphigus and bullous pemphigoid. Arch Dermatol Res 2015; 307: 291–298.
24. Iwashita K, Matsuyama T, Akasaka E, Mizutani K, Yamamoto K, Kondoh A, et al. The incidence of internal malignancies in autoimmune bullous diseases. Tokai J Exp Clin Med 2007; 32: 42–47.
25. Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. J Invest Dermatol 2015; 135: 1445–1447.
26. Balestri R, Magnano M, La Placa M, Patrizi A, Angileri L, Tengattini V, et al. Malignancies in bullous pemphigoid: a controversial association. J Dermatol 2016; 43: 125–133.
27. Moro F, Fania L, Sinagra JLM, Salemme A, Di Zenzo G. Bullous pemphigoid: trigger and predisposing factors. Biomolecules 2020; 10: E1432.
28. Wang LL, Patel G, Chiesa-Fuxench ZC, McGettigan S, Schuchter L, Mitchell TC, et al. Timing of onset of adverse cutaneous reactions associated with programmed cell death protein 1 inhibitor therapy. JAMA Dermatol 2018; 154: 1057–1061.
29. Tanita K, Fujimura T, Kambayashi Y, Tsukada A, Sato Y, Hashimoto A, et al. Intensity-modulated radiotherapy triggers onset of bullous pemphigoid in a patient with advanced melanoma treated with nivolumab. Case Rep Oncol 2018; 11: 114–118.
30. Choi R, Cowper S, Young M, Leventhal J. Bullous pemphigoid exacerbated by radiation therapy: an atypical presentation. Adv Radiat Oncol 2022; 7: 100794.
31. Kumar N, Chugh H, Tomar R, Tomar V, Singh VK, Chandra R. Exploring the interplay between autoimmunity and cancer to find the target therapeutic hotspots. Artif Cells Nanomed Biotechnol 2018; 46: 658–668.
32. Hsu DC, Katelaris CH. Long-term management of patients taking immunosuppressive drugs. Aust Prescr 2009; 32: 68–71.
33. Kridin K, Hundt JE, Ludwig RJ, Amber KT, Bitan DT, Cohen AD. Melanoma is associated with an increased risk of bullous pemphigoid: a large population-based longitudinal study. Arch Dermatol Res 2022; 314: 77–83.
34. Hwang BJ, Zhang Y, Brozowski JM, Liu Z, Burette S, Lough K, et al. The dysfunction of BP180/collagen XVII in keratinocytes promotes melanoma progression. Oncogene 2019; 38: 7491–7503.
35. Bateman AC, Turner SJ, Theaker JM, Howell WM. HLA-DQB1*0303 and *0301 alleles influence susceptibility to and prognosis in cutaneous malignant melanoma in the British Caucasian population. Tissue Antigens 1998; 52: 67–73.
36. Büdinger L, Borradori L, Yee C, Eming R, Ferencik S, Grosse-Wilde H, et al. Identification and characterization of autoreactive T cell responses to bullous pemphigoid antigen 2 in patients and healthy controls. J Clin Invest 1998; 102: 2082–2089.
37. Caccavale S. The association of bullous pemphigoid and malignancy: a case control study. G Ital Dermatol Venereol 2015; 150: 764–765.
38. Gilmour E, Bhushan M, Griffiths CE. Figurate erythema with bullous pemphigoid: a true paraneoplastic phenomenon. Clin Exp Dermatol 1999; 24: 446–448.
39. Grilletta EA, Ellis DL. Paraneoplastic bullous pemphigoid presenting with erythema gyratum repens-like figurate erythema. JAAD Case Rep 2021; 12: 37–39.
40. Shrestha P, George MK, Baidya S, Rai SK. Bullous pemphigoid associated with squamous cell lung carcinoma showing remarkable response to carboplatin-based chemotherapy: a case report. J Med Case Rep 2022; 16: 184.