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Evaluation of the risk of venous thromboembolism in patients with bullous pemphigoid: a single-centre retrospective cohort study

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Abstract

Objective: Bullous pemphigoid (BP) is an autoimmune blistering disease that predominantly affects elderly individuals. It has been associated with various comorbidities, including neuropsychiatric disorders and diabetes mellitus. In patients with BP, elevated levels of prothrombin and D-dimer, as well as increased tissue factor expression, have been frequently observed, which may lead to endothelial activation. Its pathophysiology and predilection for older age may contribute to an increased risk of venous thromboembolism (VTE). Therefore, in this study, we aimed to retrospectively investigate the clinical characteristics, survival, frequency of VTE, and its impact on survival in patients diagnosed with BP.

Methods: In this study, the clinical characteristics, survival duration, VTE incidence, and its impact on survival were retrospectively evaluated in patients who presented to Zonguldak Bülent Ecevit University between 2010-2024 and had a clinical and histopathological diagnosis of BP.

Results: A total of 53 patients (37 female, 16 male) were included in the study. The mean age at diagnosis was 75.15 years (± 9.7). The most common comorbidities were diabetes mellitus (n=35) and hypertension (n=30). The median survival time was estimated at 39 months according to survival analysis. VTE was observed in 3 patients (5.7%). The incidence rate of VTE in BP patients was 42.6 per 1,000 person-years. The incidence rate of VTE in BP was found to be statistically significantly higher compared with the incidence rate of VTE in the population over 18 years of age and in the elderly population in population-based studies ($p<0.001$ and $p<0.001$). Thromboembolic events developed within one year following the diagnosis of BP. According to the survival analysis, VTE did not affect mortality ($p=0.978$).

Conclusion: In our study, an increased incidence of VTE was demonstrated in patients diagnosed with BP. However no significant effect on survival was observed. The increase is attributed to the prothrombotic state induced by inflammatory pathways and comorbidities. We believe that this elevated risk, particularly in the acute phase, is an important factor affecting prognosis that should be considered by clinicians in patient follow-up

Keywords: bullous pemphigoid, venous thromboembolism, survival

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Büllöz pemfigoid hastalarında venöz tromboemboli riskinin değerlendirilmesi: tek merkezli retrospektif kohort çalışma

Öz

Amaç: Büllöz pemfigoid (BP), genellikle yaşlı bireylerde görülen otoimmün büllöz bir hastalıktır. Nöropsikiyatrik hastalıklar, diyabetes mellitus gibi birçok hastalık ile ilişkilendirilmektedir. BP hastalarında sıklıkla endotel aktivasyonuna yol açabilecek artmış protrombin ve D-dimer yüksekliği ile artmış doku faktörü ekspresyonunun olduğu gösterilmiştir. Patofizyolojisi ve ileri yaşta görülmesi venöz tromboemboli (VTE) riskini arttırabilmektedir. Bu nedenle çalışmamızda BP tanısı almış hastaların klinik özelliklerini, sağkalım sürelerini, VTE sıklığını ve bunun sağkalıma etkisini retrospektif olarak incelemeyi planladık.

Yöntemler: Bu çalışmada Zonguldak Bülent Ecevit Üniversitesi'ne 2010-2024 yılları arasında başvurmuş klinik ve histopatolojik olarak BP tanısı almış hastaların klinik özellikleri, sağkalım süreleri, VTE sıklığı ve bunun sağkalıma etkisi retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya 53 (37 kadın, 16 erkek) hasta dahil edildi. Tanı anında yaş ortalaması 75.15'di(± 9.7). En sık eşlik eden hastalıklar diyabetes mellitus (n=35) ve hipertansiyondu (n=30). Yapılan yaşam analizi sonucunda medyan yaşam süresi 39 ay olarak hesaplandı. VTE, 3 hastada (%5.7) gözlendi. BP hastalarında VTE görülme insidans oranı 1,000 kişi-yıl başına 42.6 olarak hesaplandı. Bu çalışmadaki BP'de VTE insidansı, toplum bazlı çalışmalardaki VTE'nin 18 yaş üzerinde ve yaşlı popülasyonda görülme sıklığı ile karşılaştırıldığında, istatiksel olarak anlamlı derece yüksek bulundu ($p<0.001$ ve $p<0.001$). Tromboembolik olay gelişimi BP tanısından sonraki bir yıl içinde gözlendi. Yaşam analizi sonucuna göre, VTE'nin mortalite üzerine etkisi bulunmadı ($p=0.978$).

Sonuç: Çalışmamızda BP tanılı hastalarda VTE insidansının arttığı gösterilmiştir. Ancak sağkalım üzerine anlamlı etkisi gösterilememiştir. Artış, inflamatuar yolakların tetiklediği protrombotik durum ve komorbiditelere bağlanmaktadır. Özellikle akut dönemde artmış bu riskin klinisyenler için hasta takibinde dikkate alınması gereken, prognozu etkileyen önemli bir unsur olduğunu düşünmekteyiz.

Anahtar kelimeler: büllöz pemfigoid, venöz tromboembolizm, yaşam analizi.

INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune bullous disease, usually affecting the elderly. The incidence of this disorder has increased in recent years, possibly due to an aging population, cases arising from medication, and increased awareness of the diagnosis of non-bullous forms of the disease[1]. Etiopathogenesis includes the development of IgG and IgE-type autoantibodies against hemidesmosome proteins (BP180 and BP230). Bullous pemphigoid, a process initiated by the breakdown of the basement membrane zone triggered by complement activation, neutrophil chemotaxis, and protease and elastase release at the antibody binding site, classically manifests with tense vesicles accompanied by pruritus on urticarial plaques on the trunk and extremities[1]. It is associated with various diseases, including neuropsychiatric disorders, diabetes mellitus, anemia, and renal disease[2-4].

Together with this, increased VEGF expression, which may lead to endothelial activation, has been frequently observed in patients with BP[5]. This condition leads to increased endothelial activation and may predispose to thrombosis. Venous thromboembolism includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) and can lead to serious morbidity and mortality[6]. Studies in patients with BP have shown that the presence of acquired VTE risk factors, such as advanced age and comorbidities, as well as increased tissue factor expression with elevated prothrombin and D-dimer levels, increases the susceptibility of these patients to develop VTE[7-10].

This retrospective study aimed to evaluate the clinical characteristics and overall survival of patients diagnosed with bullous pemphigoid,

determine the incidence of VTE, and assess its prognostic impact on survival.

METHODS

The present study included patients diagnosed with bullous pemphigoid based on clinical, histopathological, and immunofluorescence examinations who were followed up at the Zonguldak Bülent Ecevit University Department of Dermatology between 2010 and 2024 (Ethics committee approval no: 2025/02). Clinical and demographic characteristics, medication history, history of VTE, hospitalization data, follow-up duration, and survival status were recorded.

Statistical Analysis

The normal distribution of the numerical data was evaluated using the Shapiro-Wilk test. Numerical variables with a normal distribution were expressed as mean and standard deviation, and those without a normal distribution were expressed as median, minimum, and maximum values. Survival analyses of the patients who followed up were calculated using the Kaplan-Meier survival analysis, and the log-rank test was used for comparisons when examining the effect of gender and VTE on survival. Statistically significant results ($p < 0.05$) were identified, and the SPSS 29.0 software package (Statistical Package for the Social Sciences, SPSS Inc.) was utilized for data analysis.

RESULTS

The present study comprised 53 patients, 69.8% (n=37) female and 30.2% male. The mean age at diagnosis was 75.15 years (± 9.7). The median follow-up period was 16 months (minimum: 0 and maximum: 77 months). The most common comorbidities were diabetes mellitus (66%, n=35) and hypertension (56.6%, n=30). Neurological diseases were present in 28.3% (n=15) of the patients, including stroke (n=5) and Alzheimer's disease (n=5). 15.1% (n=8) of the patients had a history of malignancy. The comorbidities of the patients are detailed in Table 1.

Table I: Comorbidities of the patients (n:53)

	Number of cases(%)
Diabetes mellitus	35 (66%)
Hypertension	30 (56.6%)
Neurological diseases	15 (28.3%)
Alzheimer's disease	5
Stroke	5
Parkinson's Disease	2
Spinal cord trauma	2
Epilepsy	1
Malignancy	8 (15.1%)
Rectal Adenocarcinoma	1
Prostate Cancer	1
Ovarian Granulosa Cell Tumor	1
Papillary Thyroid Cancer	1
Pancreatic Cancer	1
Merkel Cell Carcinoma	1
Myelodysplastic Syndrome	1
Chronic Lymphocytic Leukemia	1
Asthma and Chronic Obstructive Pulmonary Disease	6
Coronary Artery Disease	6
Heart Failure	6
Hyperlipidemia	4
Arrhythmia	4
Thyroid Disease	3
Chronic Renal Failure	2
Benign Prostatic Hyperplasia	2
Rheumatoid Arthritis	1

The overall mortality rate was 41.5% (n=22). Survival analysis revealed a median survival period of 39 months. No statistically significant difference in survival outcomes between male and female patients was observed (p=0.077). At the most recent follow-up, the disease was controlled with medication in 35.8% of cases

(n=19), while 22.6% (n=12) were not receiving any treatment.

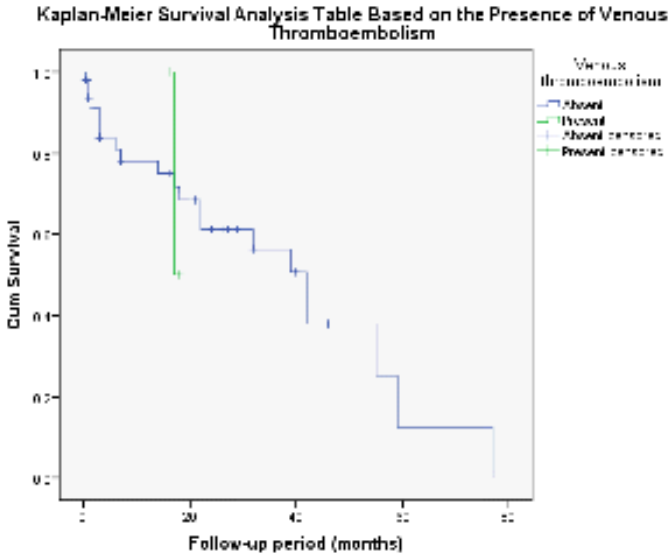
During the follow-up period, 49.1% (n=26) of patients required hospitalization for treatment of BP.

The mean eosinophil count at the time of diagnosis in 51 patients was 632.2 (median=300, min=0, max=4200). The total immunoglobulin E level which was evaluated before treatment was analyzed in 36 patients, with a mean value of 1050.9 (median=431, min=24, max=5000).

Venous thromboembolic events were observed in 3 patients (5.7%). The incidence rate of VTE in BP patients was 42.6 per 1,000 person-years. A study conducted in the USA found the incidence rate of VTE in patients over 18 years of age to be 3.02 per 1,000 person-years[11]. A comparison of the incidence rates from the two studies revealed a statistically significant difference (p<0.001). In the same study, the incidence rate of VTE in the advanced age group was 7.76 per 1,000 person-years[11], which was still significantly lower than the rate observed in our study(p<0.001).

It was observed that all patients with venous thromboembolic events were female, with two cases demonstrating ultrasonographically confirmed DVT and one case exhibiting chronic PTE. These patients experienced thromboembolic events within one year following the diagnosis of BP. All three patients received systemic corticosteroids as first-line treatment; in one, combined with azathioprine, and in another, with a topical corticosteroid. Two patients had a history of hospitalization due to widespread BP lesions; however, thromboembolic events were diagnosed before these hospitalizations. One patient was diagnosed with DVT, and the other with chronic PTE, both before admission for lesion exacerbation. Notably, the patient diagnosed with chronic PTE had undergone hip replacement surgery one month before the diagnosis of PTE. The presence of VTE did not affect overall mortality (p=0.978, Table 2).

Table II: Kaplan-Meier Survival Analysis Based on the Presence of Venous Thromboembolism



DISCUSSION

Bullous pemphigoid is an autoimmune bullous disease that usually occurs in the elderly and is associated with various comorbidities. The most common comorbidities are neurological and psychiatric disorders[4]. The incidence of diabetes mellitus, arterial hypertension, and heart disease also increases in the population of patients with BP[4]. In our study, the most common comorbidities were diabetes mellitus and hypertension. Recently, there is evidence of an increased association of venous thromboembolic events in patients with BP, which may lead to serious morbidity and mortality[8-10].

Venous thromboembolism (VTE) is defined as an acute process followed by a chronic disease, including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), affecting approximately 10 million people in the world every year[6]. Numerous factors influence the general incidence of VTE worldwide. The most significant acute risk factors include major

trauma, surgery, and prolonged immobilization. The presence of active cancer and antiphospholipid antibody syndrome, et cetera, are considered acquired triggers with a strong association with VTE[6]. It is well established that stasis, vascular wall damage or dysfunction, and hypercoagulability, also known as the Virchow triad, play a role in thrombus formation. However, a complex interaction between coagulation and inflammation, known as immunothrombosis, also plays a role in the etiopathogenesis of the condition[6].

It has been hypothesized that neutrophilic activation and neutrophilic extracellular trap structures (NETosis) may also be effective in developing venous thrombosis[12]. A direct relationship between circulating neutrophils and NETosis in BP has been demonstrated in studies[13]. In addition, eosinophils are also very important in the pathogenesis of BP and VTE[14-18]. In our patients, the mean eosinophil count was found to be high. The presence of increased eosinophils in lesional and peripheral blood in BP patients has been reported in the literature[14]. A meta-analysis showed that peripheral blood eosinophilia may be associated with increased arterial and venous thrombosis[18]. Eosinophils may trigger thrombosis by disrupting endothelial integrity with EPO release or secreting tissue factor[17].

We have also observed increased total IgE levels in our patients before the treatment. There are studies and case reports on the role of total IgE concentration in venous thromboembolism[19]. The effects are thought to be due to interactions with mast cells, which can trigger platelet activity and promote tissue factor and plasminogen activator inhibitor-1 release.

In the present study, 5.7% of patients developed venous thromboembolism (VTE) following a diagnosis of bullous pemphigoid. The incidence rate of VTE in BP patients was 42.6 per 1,000 person-years, significantly higher than in the general population[11]. BP is predominantly observed in elderly individuals, and the incidence of VTE increases with age[6,11]. Also, a statistically significant increase in the development of venous thromboembolism (VTE) was observed in patients with BP compared with a similar age group in the present study[11]. However, the literature lacks precise data on the effect of VTE on survival in BP. The present study found no effect of VTE development on survival.

A multicenter cohort study by Cugno et al. observed that the incidence of VTE generally increased in BP, and this risk was higher in the acute period compared to the clinical remission period[8]. For this increased risk, it was stated that the inflammatory process in the acute period may play a role in the development of thrombosis, and controlling the disease may reduce this risk. In this study, VTE was observed in the first year after the diagnosis of BP. Several reasons have been suggested for the increase in this risk in the acute period. Especially in the acute period, elevated prothrombin and D-dimer associated with coagulation activation in serum and increased tissue factor expression in the lesional skin have been demonstrated, and normalization of these values has been observed when the disease is controlled [7,16]. It has been observed that the tissue factor in the lesional skin of BP patients is eosinophil-derived; this tissue factor triggers thrombin production by initiating the extrinsic coagulation pathway, and this thrombin both increases the permeability of blood vessels and plays a role in the coagulation cascade[16].

In addition to the aforementioned inflammatory and prothrombotic pathways, the fact that the patients are predominantly elderly, require hospitalization for treatment, have comorbidities such as additional cancer, and have decreased mobilization due to lesions may also pose a risk for VTE[6]. In this study, approximately half of the patients required hospitalization at least once for BP

management. Two patients in our cohort had a history of hospitalization due to extensive BP lesions; however, thromboembolic events occurred prior to these admissions. One patient was diagnosed with DVT and the other with chronic PTE, both preceding hospitalization for lesion exacerbation. Notably, the patient with chronic PTE had undergone hip replacement surgery one month before the PTE diagnosis. Furthermore, there may be other comorbidities such as neurological diseases and cancer that may increase immobilization in BP patients.

Nevertheless, therapies used to control BP, such as systemic corticosteroids, may increase this risk further. Although corticosteroids have been associated with an increased risk of VTE, no definitive study has yet examined their specific impact on VTE development in BP patients[20]. These agents are usually given to patients with more active and severe disease, whose inflammatory and prothrombotic pathways may also predispose them to VTE. Therefore, it remains difficult to determine whether the use of systemic corticosteroids exerts a protective or detrimental effect on VTE in this context. Further large-scale, randomised studies are required to clarify this issue.

CONCLUSION

In this study, we observed that the incidence of VTE increased in patients with BP, aligning with findings from other studies. However, no effect of VTE development on survival was identified. Both the prothrombotic state triggered by inflammatory pathways involved in the etiopathogenesis and the presence of existing comorbidities in patients contribute to the heightened risk of VTE. Therefore, managing this inflammatory process through disease treatment and considering the increased risk of VTE during the acute phase are important factors in patient follow-up and treatment regarding VTE development.

Ethics Committee Approval: Zonguldak Bülent Ecevit University Department of Dermatology between 2010 and 2024 (Ethics committee approval no: 2025/02).

Conflict of Interest: The authors declared no conflicts of interest.

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