ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/dermato.2018-61536

Clinical Features, Associated Systemic Diseases, Mortality Rates, and Treatment Protocols in a Group of Turkish Patients with Bullous Pemphigoid

Türkiye'de Bir Grup Büllöz Pemfigoid Hastasının Klinik Özellikleri, İlişkili Sistemik Hastalıkları, Mortalite Oranları ve Tedavi Protokolleri

Zehra AŞİRAN SERDAR,[a]
Ezgi AKTAŞ KARABAY,[a]
Şirin YAŞAR,[b]
Nihan KAZAZ[c]

[a]Department of Dermatology, Bahçeşehir University Faculty of Medicine,
[b]Clinic of Dermatology, University of Health Sciences İstanbul Haydarpaşa Numune Training and Research Hospital,
[c]Department of Biostatistics and Medical Informatics, İstanbul University Health Sciences Institute, İstanbul

Received: 23.05.2018
Received in revised form: 11.09.2018
Accepted: 12.09.2018
Available online: 02.11.2018

Correspondence:
Ezgi AKTAŞ KARABAY
Bahçeşehir University Faculty of Medicine, Department of Dermatology, İstanbul, TURKEY/TÜRKİYE
ezgiaktasmd@gmail.com

ABSTRACT Objective: The aim of the study was to investigate the clinical features, associated systemic diseases, treatment protocols, recurrence rates, and mortality rates in bullous pemphigoid (BP) patients. **Material and Methods:** The demographic and clinical characteristics of 47 patients with BP were evaluated. 47 age and gender-matched subjects without autoimmune bullous disease were included as the control group. The comorbidities accompanying to BP patients and the diseases in the control group were compared. **Results:** The mean age of the patients was 77.9±10.57 (36–96) years old, and the average disease duration was 39.30±29.54 months. The BP patients were compared with the control group in terms of systemic diseases using a chi-squared test with a 95% confidence interval. No significant differences were found between the BP patients and the control group with regard to the associated systemic diseases, including hypertension (HT), diabetes mellitus (DM), neurological disease, heart disease, malignancy, and other diseases. Systemic corticosteroids (methylprednisolone) were administered to 34 (72.3%) of the patients, while 12 (25%) patients were given methylprednisolone alone. Azathioprine and methotrexate were added to the treatments of 5 (10.6%) and 3 (6.4%) of the cases, respectively. Eight (17%) patients showed recurrences, and the mortality rate was 23.4%. **Conclusion:** Although the results of our study showed that a significant proportion of the BP patients had an accompanying systemic disease, most frequently hypertension and diabetes mellitus, there was not a statistically significant difference in terms of comorbidities between BP patients and controls. Systemic corticosteroids were the most commonly used treatments. Overall, our data from this 7-year period will contribute to the understanding of the characteristics of the BP patients in Turkey.

Keywords: Bullous pemphigoid; comorbidity; mortality; recurrence; therapy

ÖZET Amaç: Çalışmanın amacı büllöz pemfigoid (BP) hastalarında klinik özellikleri, ilişkili sistemik hastalıkları, tedavi protokollerini, nüks oranlarını ve mortalite oranlarını araştırmaktır. **Gereç ve Yöntemler:** 47 BP hastasının demografik ve klinik özellikleri değerlendirildi. Yaş ve cinsiyet açısından hasta grubuyla uyumlu olan otoimmün büllü hastalığı olmayan 47 kişi kontrol grubunu oluşturdu. BP hastalarına eşlik eden komorbiditeler ve kontrol grubunda bulunan hastalıklar karşılaştırıldı. **Bulgular:** Hastaların ortalama yaşı 77.9±10.57 (36-96) yıl ve ortalama hastalık süresi 39.30±29.54 ay idi. BP hastaları kontrol grubuyla sistemik hastalık bulunması açısından ki-kare test kullanılarak %95 güven aralığıyla karşılaştırıldı. BP hastaları ile kontrol grubu arasında hipertansiyon (HT), diabetes mellitus (DM), nörolojik hastalıklar, kalp hastalıkları, malignite gibi eşlik eden sistemik hastalıklar açısından belirgin fark bulunmadı. 34 hastaya (%72.3) sistemik kortikosteroid (metilprednizolon) tedavisi verilirken 12 hastaya (%25) sadece metilprednizolon tedavisi uygulandı. Azathiyoprin ve metotreksat sırasıyla 5 (%10.6) ve 3 (%6.4) olguya uygulandı. Sekiz hastada (%17) nüksler izlendi ve ölüm oranı %23.4 olarak bulundu. **Sonuç:** Çalışmanın sonuçları BP hastalarının önemli bir oranının en sık olarak HT ve DM olmak üzere eşlik eden bir hastalıkları olduğunu göstermişse de kontrol grubu ve BP hastaları arasında eşlik eden hastalık bakımından istatistiksel olarak anlamlı fark bulunamadı. En sık kullanılan tedavi sistemik kortikosteroidler idi. 7 yıllık verilerimizden oluşan bu çalışma Türkiye'deki BP hastalarının özelliklerini anlamaya katkıda bulunacaktır.

Anahtar Kelimeler: Büllöz pemfigoid; eşzamanlı hastalık; mortalite; nüks; tedavi

Bullous pemphigoid (BP) is a chronic autoimmune disease characterized by intensely pruritic eruptions with subepidermal bullae, and it affects elderly patients most frequently.[1] BP is one of the most common autoimmune blistering diseases found in European countries, including France, the United Kingdom, and Germany.[2,3] A number of previous studies have investigated whether there is a relationship between BP and hypertension (HT), diabetes mellitus (DM), neurological disease, malignancy, and other systemic diseases. However, it remains unclear whether BP is associated with other systemic comorbidities, or if there is a coincidental association.[4,5] In the literature, varying data on the clinical features and disease course have been reported based on the geographical region and ethnic group.[6,7]

The purpose of this study was to examine the demographic features, clinical course, associated diseases, recurrence rates, mortality rates, and the treatment protocols in patients with BP.

MATERIAL AND METHODS

The data from the clinical files of 47 patients who were hospitalized with BP diagnoses between February 2003 and December 2010 in an outpatient clinic were analyzed retrospectively. This data was compared with data obtained retrospectively from 47 control subjects who had no autoimmune bullous disease, and who were matched for age and gender. BP diagnosis was made based on the histopathological and direct immunofluorescence examination. The age, gender, clinical features, presence of itching, bullae features, bullae residue, urticarial papules or plaques and excoriations (as well as oral mucosal involvement), presence of Nikolsky's sign, laboratory findings, fecal occult blood were evaluated for each patient. In cases with abnormal test results and abnormal physical examination, upper gastrointestinal endoscopy, colonoscopy, and thoracoabdominal and pelvic computed tomography (CT) results, and superficial tissue ultrasound images evaluating the lymph nodes were performed if necessary. The presence of any accompanying disease, such as HT, DM, neurological disease, heart disease, malignancy, or other diseases, was investigated in both BP patients and the control subjects. Improvements with treatment were defined by the recurrence and mortality rates, which were evaluated.

The study was carried out according to the principles expressed in the Declaration of Helsinki.

The groups were compared statistically, in terms of the age, gender, and associated diseases, using a chi-squared test. The recurrence and mortality rates were also evaluated retrospectively, and they served as parameters for the treatment success. Descriptive statistics were used for demographic data, clinical characteristics, and laboratory investigations. The associations between the variables were calculated using the chi-squared and Fisher's exact tests.

RESULTS

The mean age of the patients was 77.9±10.57 (36-96) years. The female/male ratio was 1.6/1 [29 women (61.7%) and 18 men (38.3%)]. The mean age of the subjects in the control group was 78.00±10.42 (42-90) years. The female/male ratio was 1.6/1 [29 women (61.7%) and 18 men (38.3%)]. There was no statistically significant difference between the age and gender ratio between two groups (p=0.992, p= 1, respectively). The mean time between the disease onset and hospital admission was 39±29 months, and it ranged between 2 and 84 months. The number of hospitalizations ranged from 1 to 4 times. While the majority (83%) of the patients were hospitalized only once, 5 (10.6%) were hospitalized twice and 2 (4.3%) were hospitalized three times due to BP reactivation. Only one (2.1%) patient was admitted to the hospital four times. The average length of the hospital stay was 24 days when all the admissions (1-4) were taken into account. Forty-three (91.5%) patients presented with itching, 47 (100%) patients had bullae, and 24 (51.1%) patients had urticarial plaques.

Eosinophilia was detected in 16 patients and urticarial plaques were detected in 23 patients out of 43 patients with pruritus; however, there were no statistically significant relationships between the two parameters and pruritus (p=0.631 and

TABLE 1: Demographic features and clinical features of BP patients.

	BP patients n=47 (%)	**Control group n=47 (%)**	**p**
Gender	**Female 29 (61.7%) Male 18 (38.3%)**	**Female 29 (61.7%) Male 18 (38.3%)**	1
Mean age of patients	77.98±10.58 years (mean±SD)	78.00±10.42 years (mean±SD)	0.992
Mean age of disease onset	74.72±11.17 years (mean±SD)		
Mean duration of disease	39.30±29.54 months (mean±SD)		
Mortality	11 (23.4%) (number of patients)		
Mean age at death	83.91±8.91 years (mean±SD)		
Presence of pruritus	43 (91.5%) (number of patients)		
Presence of bullae	47 (100%) (number of patients)		
Presence of urticarial plaque	24 (51.1) (number of patients)		
Oral mucosa involvement	8 (17.0%) (number of patients)		
Nikolsky's sign positivity	7 (14.9%) (number of patients)		
Serum eosinophilia	18 (38.3%) (number of patients)		
High levels of serum IgE	4 (8.5%) (number of patients)		
Superficial LAP by USG imaging	4 (8.5%) (number of patients)		

p=0.348, respectively). Nikolsky's sign was present in 7 (14.9%) of the patients, while oral mucosal involvement was present in 8 (17%) of the patients. The fecal occult blood tests and tumor markers were negative, and the upper gastrointestinal endoscopy and colonoscopy results were within the normal limits among the subjects.

The superficial tissue ultrasound examinations detected lymphadenopathy in 4 (8.5%) cases (Table 1). In 45 (95.7%) patients, the thoracoabdominal and pelvic CT scan results showed no abnormalities. One patient had a sequela due to pneumonia, while another patient exhibited pulmonary cyst formation. In addition, 39 (82.98%) of the BP patients had an accompanying systemic disease. Among these diseases, HT was the most common, and it was present in 23 (48.9%) of the patients, followed by DM, which was found in 18 (38.3%) patients. Neurological diseases, heart diseases, malignancies, and other diseases were present in 12 (25.5%), 5 (10.6%), 4 (8.5%), and 19 (40.4%) patients, respectively. However, 8 (17%) patients had no systemic diseases.

TABLE 2: Accompanying diseases in the BP and contol group.

	BP patients n= 47 (%)	**Control group n= 47 (%)**	**p**
Accompanying diseases			
Hypertension	23 (48.9)	22(46.8)	1
Diabetes mellitus	18 (38.3)	9(19.1)	0.067
Neurological diseases	12 (25.5)	8(17)	0.45
Cardiovascular diseases	5 (10.6)	6(12.8)	1
Malignancies	4 (8.5)	1(2.1)	0.361
Lung cancer	2(4.3)	0	
Bladder cancer	1(2.1)	0	
Colon cancer	0	1(2.1)	
Skin, Squamous cell carcinoma	1	0	
Other	19 (40.4)	10(21.3)	0.073

Confidental interval: 95%

In the control group, HT, DM, neurological diseases, heart diseases, malignancies, and other diseases were detected in 22 (46.8%), 9 (19.1%), 8 (17%), 6 (12.8%), 1 (2.1%), and 10 (21.3%) patients, respectively (Table 2). The BP patients were compared with the control group in terms of systemic

diseases using a chi-squared test with a 95% confidence interval (CI). Based on the results, no significant differences were found between the groups with regard to the age, gender, and associated systemic diseases (p=0.992, p=1, and p=0.608, respectively). In addition, no significant relationships were found between the BP patients and the control group regarding the associated systemic diseases, including HT, DM, neurological disease, cardiovascular system disease, malignancy, and other diseases (95% CI, α=0.05; p=1, p=0.067, p=0.45, p=1, p=0.361, and p=0.073, respectively). When considering the difficulty in obtaining data from these patients, BP showed a significant association with DM when the confidence interval was 90% (p=0.067). The prevalence of DM in the BP patients was 38.3%, and it was 19.1% in the control group. All of these patients were diagnosed with DM before beginning systemic corticosteroid treatment.

Systemic corticosteroids (methylprednisolone) were given to 34 patients (72.3%), with doses ranging between 8 mg/day and 80 mg/day (mean: 37.06±28.568 mg/day). Twelve (25%) patients were given methylprednisolone alone; however, 5 (10.6%) received azathioprine at a dosage of 150 mg/day, and methotrexate (MTX) at a dosage of 15 mg/week was added in 3 (6.4%) cases. In addition to the systemic therapies, topical corticosteroid treatments (0.05% clobetasol 17-propionate) were applied in 18 (38.3%) patients. One patient was treated with only 0.05% clobetasol 17-propionate. Twenty (42.6%) patients, who could not tolerate systemic corticosteroid therapy or had side effects due to therapy, were treated with 2 g/day of tetracycline and 1,500 mg/day of nicotinic acid therapy (Table 3). However, in one patient with no response to the systemic corticosteroids and azathioprine therapy, intravenous immunoglobulin (IVIG), dapsone, and 2 g/day of mycophenolate mofetil were given.

The treatment period varied between 1 and 84 months, with an average treatment duration of 17.17±21.83 months. BP recurrences were observed in 8 cases (17%), and the mean treatment duration of these 8 patients was 53 months. In addition, recurrences were seen in the patients receiving combination therapy. One patient with psoriasis was treated with MTX and 0.05% clobetasol 17-propionate, while the remaining 7 patients were treated with methylprednisolone + azathioprine (n=3), methylprednisolone + MTX + 0.05% clobetasol 17-propionate (n=2), and tetracycline + nicotinic acid + 0.05% clobetasol 17-propionate (n=2). The three patients who were treated with prednisolone + azathioprine developed side effects; therefore, the treatment was switched to tetracycline + nicotinic acid therapy.

TABLE 3: Treatment modalities.

	n (%)
Systemic Steroid (methylprednisolone)	34 (72.3)
methylprednisolone -alone-	12 (25.5)
methylprednisolone + azathioprine	5 (10.6)
methylprednisolone + Methotrexate	3 (6.4)
Tetracycline + Nicotinic Acid	20 (42.6)
Topical Steroid (%0,05 clobetasol 17- propionate)- combined with other treatments	18 (38.3)
Topical Steroid (%0,05 clobetasol 17- propionate) -alone-	1 (2.1)

Of the 11 patients who died, 5 (45.49%) were male and 6 (54.4%) were female, and no statistically significant relationship was found between the gender and mortality. The mortality was highest in the 70-96 years old age range (mean 83±8.9 years). Although there were systemic diseases present in 10 of the patients who died (90.9%) [DM (n=3), HT (n=4), lung cancer (n=2), HT plus cardiovascular disease (n=1)], a statistically significant association between the mortality and the accompanying disease could not be determined. One of the patients died due to an acute myocardial infarction; however, no clear cause of mortality could be identified in others. No significant associations were observed between the mortality and the gender and age (p>0.05).

DISCUSSION

The incidence of BP has been reported as 2–10 individuals per million per year in different ethnic populations.[3,8] There are reports from Turkey eval-

uating patients diagnosed with BP separately in single centers; unfortunately, this data is insufficient with regard to the incidence of BP in Turkey.[9,10]

In the literature, a female dominance has been reported in patients with BP.[3,6,11] Similarly, in this study, there was also a female dominance with a female/male ratio of 1.6/1. The age of BP onset was reported as the 7th decade in Thailand, but this contradicts the data from Singapore, the United Kingdom, Romania, Greece, and Italy, which have reported the onset as usually occurring in the 8th decade.[3,12] In our study the mean age of onset of BP patients was found to be 77 which is consistent with the previous reports from Turkey with the mean age of onset as 78, 64, 71.[10,13,14]

Although mucosal involvement has been reported as an infrequent presentation of BP, Akay et al. reported that 12.9% of the BP patients and Kulthanan et al. reported that 15.5% of the BP patients presented with mucous membrane involvement.[6,9,15] In our study, oral mucosal involvement was detected in 17% of the cases. Similarly, in a study conducted by Ekiz et al. including 29 BP patients in Turkey, oral mucosal involvement was reported to be present in 17.24% of the patients. Moreover, Bushkell and Jordon reported a 5-43% rate of eosinophilia in the peripheral blood in BP patients.[16,17] In our study, peripheral blood eosinophilia was found in 38% of the patients.

Previously, a significantly higher (43%) number of neurological disorders were reported in the BP group than in the control group (19%), but no significant associations were found between BP and DM, malignant tumors, benign prostatic hypertrophy, HT, and ischemic heart disease.[18] It has been suggested that neurological diseases and immobility or age-related autoimmunity may be the triggers of BP.[19,20] In another study, stroke, HT, DM, hyperlipidemia, heart failure, atrial fibrillation, and coronary heart disease were observed to be more common among the BP patients when compared to the controls.[21] There have been studies reporting associations between BP and DM and malignancies and BP,[5] as well as reports observing no associations between BP and DM or malignancies.[4-6,9,22,23] Similarly, in a study conducted in Turkey, HT, DM, neurological diseases and coronary arterial diseases were reported to be the most common accompanying diseases in BP.[13] In a recent study, the increased prevalence of DM2 among newly diagnosed BP patients with the increasing use of dipeptidyl peptidase-4 (DPP-4) inhibitors as antidiabetic agents was shown to be related. It was also suggested that use of DPP-4 inhibitors might be associated with increased risk for developing BP.[24] Sim et al. also reported, HT, DM and neurological diseases to be common in patients with BP.[25] Moreover, they emphasized the high incidence of multimorbidity in patients with BP. In the present study, the DM prevalence in the patients with BP was significantly higher than in the control group. Although no statistically significant relationship was found between BP and malignancy in our study, four of the BP patients had malignancies, while only one patient had malignancy in the control group. No other statistically significant associations were found between the accompanying diseases and BP. In the present study the data on the therapies patients receiving for the comorbidities were missing, which is an important limitation since some medicines may cause BP or aggrevate BP symptoms.

The BP mortality rate has been reported to be between 8.6% and 41% in various studies.[26-28] In the subjects of our study, the mortality rate was 23.4%, which was consistent with the literature. The age, female gender, DM, hypertension, neurological disease, chronic lung disease, liver disease, and other systemic diseases (such as malignancy) are the major mortality risk factors.[26]

Several different modalities have been used in the treatment of BP, based mostly on clinical experience rather than controlled clinical studies.[15] The BP treatment options include, systemic/topical corticosteroids, tetracycline, and immunosuppressive agents.[15,26] Systemic corticosteroids are usually preferred as the first line treatment, either alone or in combination with azathioprine, dapsone, MTX, and cyclophosphamide or mycophenolate mofetil.[27,29] In our study group, 12 patients underwent adjuvant treatment, and 18 were

treated with additional topical corticosteroids. In another study, 62% of BP patients were treated with topical corticosteroid and tetracyclines and nicotinamide combination.[16]

Tetracyclines are usually preferred in patients with accompanying comorbidities, such as DM or HT, and in children due to their better safety profile. There is also evidence in favor of using immunosuppressants, such as azathioprine and MTX.[30]

In our study, those 20 patients who could not tolerate systemic corticosteroid therapy were treated with a combination therapy of tetracycline and nicotinic acid. IVIG, dapsone, and finally, mycophenolate mofetil were started in a patient after there was no response to the systemic corticosteroid therapy and azathioprine.

In conclusion, the mean age of the patients', disease onset age and gender ratio of the patients was consistent with the literature. Disease characteristics, such as mucosal involvement, concominant eosinophilia, features of cutaneous lesions, Nikolsky's sign presence were in line with the previous reports. There were systemic diseases accompanying the BP in 82.98% of the patients in our study. HT and DM were the most common accompanying systemic diseases. The high mortality rate in these patients may be associated with many factors, including advanced age in the majority of the patients, the presence of comorbid conditions, and the treatment side effects. Large population-based and controlled studies are still required, particularly to establish the treatment guidelines for patients with refractory BP.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Zehra Aşiran Serdar, Şirin Yaşar;* ***Design:*** *Zehra AŞiran Serdar, Ezgi Aktaş Karabay, Şirin Yaşar;* ***Control/Supervision:*** *Zehra Aşiran Serdar;* ***Data Collection and/or Processing:*** *Şirin Yaşar;* ***Analysis and/or Interpretation:*** *Ezgi Aktaş Karabay, Nihan Kazaz;* ***Literature Review:*** *Ezgi Aktaş Karabay, Şirin Yaşar;* ***Writing the Article:*** *Ezgi Aktaş Karabay, Şirin Yaşar;* ***Critical Review:*** *Zehra Aşiran Serdar;* ***References and Fundings:*** *Ezgi Aktaş Karabay, Şirin Yaşar.*

REFERENCES

1. Akın A. [Bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestationis: etiopathogenesis, clinic and treatment]. Turkiye Klinikleri J Dermatol-Special Topics 2008; 1(4):30-8.
2. Bernard P, Vaillant L, Labeille B, Bedane C, Arbeille B, Denoeux JP, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. Arch Dermatol 1995;131(1):48-52.
3. Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study. BMJ 2008;337:a180.
4. Chuang TY, Korkij W, Soltani K, Clayman J, Cook J. Increased frequency of diabetes mellitus in patients with bullous pemphigoid: a case-control study. J Am Acad Dermatol 1984;11(6):1099-102.
5. Ogawa H, Sakuma M, Morioka S, Kitamura K, Sasai Y, Imamura S, et al. The incidence of internal malignancies in pemphigus and bullous pemphigoid in Japan. J Dermatol Sci 1995;9(2):136-41.
6. Kulthanan K, Chularojanamontri L, Tuchinda P, Sirikudta W, Pinkaew S. Prevalence and clinical features of Thai patients with BP. Asian Pac J Allergy Immunol 2011;29(1):66-72.
7. Uzun S. Autoimmune bullous diseases. Archives of the Turkish of Dermatology and Venerology 2011;45(Suppl 1):1-3.
8. Mulyowa GK, Jaeger G, Kabakyenga J, Bröcker EB, Zillikens D, Schmidt E. Autoimmune subepidermal blistering disease in Uganda: correlation of autoantibody class with age of patients. Int J Dermatol 2006;45(9): 1047-52.
9. Akay BN, Bodamyalı P, Şanlı H, Akyol A. [10-year observation of bullous pemphigoid patients]. Türkderm 2010;44:61-4.
10. Uzun S, Durdu M, Akman A, Gunasti S, Uslular C, Memisoglu HR, et al. Pemphigus in the Mediterranean region of Turkey: a study of 148 cases. Int J Dermatol 2006;45(5):523-8.
11. Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med 2002;346(5):321-7.

12. Wong SN, Chua SH. Bullous pemphigoid seen at the National Skin Centre: a 2-year retrospective review. Ann Acad Med Singapore 2002;31(2):170-4.
13. Aktaş Karabay E, Aksu Çerman A, Kıvanç Altunay I. [Comorbidity profiles among patients with autoimmune bullous diseases; a retrospective study]. SETB-55376. Doi: 10.14744/SEMB.2018.55376.
14. Akbaş A, Kılınç F, Akkuş A, Şener S, Metin A. [A retrospective analysis of hospitalized autoimmune bullous disease patients]. Dermatoz 2015;4:15064a1.
15. Beissert S, Werfel T, Frieling U, Böhm M, Sticherling M, Stadler R, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. Arch Dermatol 2007; 143(12):1536-42.
16. Ekiz Ö, Bülbül Şen B, Rifaioğlu EN, Şen T, Atik E, Doğramacı AÇ. [Three-year observation of the patients with bullous pemphigoid: 29 cases]. Türkderm 2013;47:205-8.
17. Bushkell LL, Jordon RE. Bullous pemphigoid: a cause of peripheral blood eosinophilia. J Am Acad Dermatol 1983;8(5):648-51.
18. Jedlickova H, Hlubinka M, Pavlik T, Semradova V, Budinska E, Vlasin Z. Bullous pemphigoid and internal diseases-a case-control study. Eur J Dermatol 2010;20(1):96-101.
19. Bastuji-Garin S, Joly P, Lemordant P, Sparsa A, Bedane C, Delaporte E, et al; French Study Group for Bullous Diseases. Risk factors for bullous pemphigoid in the elderly: a prospective case-control study. J Invest Dermatol 2011;131(3):637-43.
20. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: a population-based case-control study. J Invest Dermatol 2011;131(3): 631-6.
21. Yang YW, Chen YH, Xirasagar S, Lin HC. Increased risk of stroke in patients with bullous pemphigoid: a population-based follow-up study. Stroke 2011;42(2):319-23.
22. Akarsu S, İlknur T, Erdemir Y, Gün M, Akyaz P, Bozkanat KM, et al. [Onset characteristics and accompanying autoimmune diseases in autoimmune bullous dermatoses]. DEÜ Tıp Fakültesi Dergisi 2010;24(2):57-63.
23. Venencie PY, Rogers RS 3rd, Schroeter AL. Bullous pemphigoid and malignancy: relationship to indirect immunofluorescent findings. Acta Derm Venereol 1984;64(4):316-9.
24. Gravani A, Gaitanis G, Tsironi T, Tigas S, Bassukas ID. Changing prevalence of diabetes mellitus in bullous pemphigoid: it is the dipeptidyl peptidase-4 inhibitors. J Eur Acad Dermatol Venereol 2018 Mar 23. Doi: 10.1111/jdv.14957. [Epub ahead of print].
25. Sim B, Fook-Chong S, Phoon YW, Koh HY, Thirumoorthy T, Pang SM, et al. Multimorbidity in bullous pemphigoid: a case-control analysis of bullous pemphigoid patients with age- and gender-matched controls. J Eur Acad Dermatol Venereol 2017;31(10):1709-14.
26. Joly P, Benichou J, Lok C, Hellot MF, Saiag P, Tancrede-Bohin E, et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. Arch Dermatol 2005;141(6):691-8.
27. Venning VA, Wojnarowska F. Lack of predictive factors for the clinical course of bullous pemphigoid. J Am Acad Dermatol 1992;26(4): 585-9.
28. Parker SR, Dyson S, Brisman S, Pennie M, Swerlick RA, Khan R, et al. Mortality of bullous pemphigoid: an evaluation of 223 patients and comparison with the mortality in the general population in the United States. J Am Acad Dermatol 2008;59(4):582-8.
29. Tirado-Sánchez A, Díaz-Molina V, Ponce-Olivera RM. Efficacy and safety of azathioprine and dapsone as an adjuvant in the treatment of bullous pemphigoid. Allergol Immunopathol (Madr) 2011;40(3):152-5.
30. Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. Br J Dermatol 2012;167(6):1200-14.