Original Investigation
Orijinal Araştırma

DOI: 10.4274/turkderm.23922
Turkderm - Arch Turk Dermatol Venerology 2016;50

Retrospective analysis of the forty-six patients with bullous pemphigoid followed-up in our clinic

Kliniğimizde takip edilen kırk-altı büllöz pemfigoid olgusunun retrospektif analizi

Serkan Yazıcı, Emel Bülbül Başkan, Şükran Tunalı, Kenan Aydoğan, Hayriye Sarıcaoğlu

Uludağ University Faculty of Medicine, Department of Dermatalogy, Bursa, Turkey

Abstract

Background and Design: Bullous pemphigoid (BP) is an autoimmune disease characterised by widespread itchy plaques and subepithelial blisterings and usually affects the elderly population. Due to the chronic nature of the disease, to prevent the side effects of chronic steroid treatment, adjuvant immunosuppressive (mycophenolate mofetil, azathioprine, methotrexate) and anti-inflammatory (tetracycline, nicotinamide, dapsone) agents may be used. In this study, we retrospectively evaluated the clinical and demographic characteristics and applied treatments of 46 patients with the diagnosis of BP and compared with literature data.

Materials and Methods: We retrospectively evaluated the records of 46 patients who received clinical and histopathological diagnosis of BP and followed up in our clinic between 2006 and 2013.

Results: Of the 46 patients, 22 were female and 24 male. The mean age of onset was 69.54 years (range: 18-105). The duration of the lesion ranged from 1 week to 10 months with a median duration of 8 weeks. The most frequent comorbid chronic disease was hypertension detected in 28 (60.8%) patients. Only four patients had a history of malignancy before the onset of the disease. Nineteen patients (42%) used more than 5 agents for comorbid diseases. Thirty-two patients (69.5%) used systemic corticosteroids alone and ten (22%) patients needed additional adjuvant therapies.

Conclusion: BP is a major cause of morbidity in the elderly population receiving multiple drug treatment. To avoid the side effects of steroid therapy, especially in patients with severe disease, short-term use of additional immunosuppressive agents appears to be safe and effective.

Keywords: Bullous pemphigoid, adjunctive therapy, comorbidities, multiple drug use

Öz

Amaç: Büllöz pemfigoid (BP) ileri yaş popülasyonu etkileyen yaygın kaşıntılı plaklar ve subepitelyal büllerle karakterize otoimmün bir hastalıktır. Yaygın lezyonlu, şiddetli hastalığı olan olgularda sistemik steroidler tercih edilir. Hastalığın kronik seyri nedeniyle steroid tedavisinin yan etkilerinden korunmak için ek immünsüpresif ve anti-enflamatuvar ajanlar kullanılabilmektedir. Bu çalışmada kliniğimizde BP tanısı ile takip edilen 46 olgunun klinik, demografik özellikleri ve uygulanan tedaviler retrospektif olarak değerlendirilerek literatür verileri ile karşılaştırıldı.

Gereç ve Yöntem: Klinik, histopatolojik ve immünohistokimyasal (direkt immünofloresan) bulgularla BP tanısı alan ve topikal tedaviye yanıtsızlık, şiddetli hastalık nedeniyle klinik izlem yapılan 46 olgunun arşiv dosya kayıtları retrospektif olarak incelendi.

Bulgular: Toplam 46 olgunun 22'si kadın, 24'ü erkek olarak saptandı. Hastalığın başlangıç yaşı 18 ile 105 arası değişmekte olup ortalama 69,54 olarak saptandı. Lezyon süresi 1 hafta ile 10 ay arası değişmekteydi. En sık eşlik eden kronik hastalık; 28 olguda hipertansiyon (%60,8) saptandı. Sadece dört olguda hastalığın ortaya çıkışından önce malignite tanısı mevcuttu. Olguların 19'unda (%41) 5'ten fazla ilaç kullanımı mevcuttu. Olguların 32'sinde (%69,5) sistemik steroid tek başına kullanılırken on (%21,7) olguda ek adjuvan tedavilere ihtiyaç duyuldu.

Sonuç: BP çoklu ilaç kullanımı olan ileri yaş popülasyonunda önemli bir morbidite nedenidir. Özellikle şiddetli olgularda steroid tedavisinin yan etkilerinden korunmak için ek immünsüpresif ajanlar hastalık yönetiminde etkili ve kısa dönemde güvenli görünmektedir.

Anahtar Kelimeler: Büllöz pemfigoid, adjuvan tedavi, komorbidite, çoklu ilaç kullanımı

Address for Correspondence/Yazışma Adresi: Serkan Yazıcı MD, Uludağ University Faculty of Medicine, Department of Dermatalogy, Bursa, Turkey
Phone.: +90 224 295 07 21 E-mail: serkanyazici@uludag.edu.tr **Received/Geliş Tarihi:** 29.04.2015 **Accepted/Kabul Tarihi:** 28.09.2015

Introduction

Bullous pemphigoid (BP) is an auto-immune disease, affects advanced age population (>70 years) and characterized by sub epidermal bulla[1]. It is reported that the disease is a significant health problem which is the most common auto-immune bullous disease in Europe, and the incidence of it increased approximately three-fold in the last decades, corresponding 4.5-14 per million[2-4]. Although the ethiopathology is not known clearly, antibodies producing against basal membrane hemidesmosomal antigens (BP180 and BP230) in genetically predisposed individuals (the most evident susceptibility locus in White race is HLA-DQB1*0301) are considered to play the main role in disease formation. Clinical skin lesions are substantially polymorphic; it is in addition to bullous lesions, characterized by excoriate, eczematous, papular or urticaria-like lesions accompanied by an itch. Associations between BP and mainly neurological, psychiatric, immunological, haematological, and auto-immune diseases, and malignancies were reported[5]. Various medications in broad spectrum such as penicillin antibiotics up to anti-tumour necrosis factor agents were accused in the ethiopathogenesis[6]. Although the primary treatment of the disease is high potency topical corticosteroids, it is not convenient to use topical treatment in advance age population affected by the disease, and short term systemically steroid treatment should primarily be preferred particularly in cases with extensive disease. Based on the chronical process of the disease characterized by remissions and relapses, immunosuppressive (Mycophenolate mofetil, azathioprine, methotrexate) and anti-inflammatory (tetracycline, nicotinamide, dapsone) agents, and intravenous immunoglobulin (IVIG) treatment in cases not responding to conventional treatments might be used in order to avoid potential side effects of steroid treatment[7-9]. Studies investigating clinical and demographical characteristics of cases with BP diagnose are significant in understanding and managing the ethiopathogenesis of the disease, and determining optimal treatment. In the current study, we aimed to assess retrospectively the clinical, demographical characteristics and the treatments of the 46 cases with BP diagnose we follow up and treat in our service, and compare these data with the literature data.

Materials and Methods

Study population

Archive records of 46 patients, who had a BP diagnose with clinical, histopathological, and immunohistochemical [direct immunofluorescence (DIF)] evidence, and clinically followed-up due to a severe disease (>30% involvement) and being non-response to topical therapies between January 2006 to July 2013, have been analyzed retrospectively[10,11]. The diagnosis in all clinically suspicious patients was done by lesional, histopathological and perilesional DIF findings. Various clinical and demographical characteristics, such as the age of onset of the disease, sex, duration of lesions, co-morbidities, drug use, distribution of lesions, oral mucosal involvement and itching, agents used for treatment, treatment response, complications caused by treatment, relapses and mortality rates, have been analyzed from the archive records of the patients. A detailed history was obtained from all patients regarding to drug use as a triggering factor of the disease, as well as detailed laboratory tests including complete blood count, sedimentation rate, liver and kidney function tests. In addition, for age and sex-matched malignancy scanning in suspicious cases, fecal occult blood and tumor markers were evaluated, if positive, upper gastrointestinal endoscopy and/or colonoscopy were done, as well as mammography in female patients, and if required, hematologic evaluation and abdominal, pelvic, thoracic tomographic evaluations. Antibody response against BP180 and/or BP230 target antigens could not be performed either indirect immunofluorescence analysis (salting out) or serologically (enzyme-linked immunosorbent assay).

Statistical Analysis

SPSS package program (Statistical Programmes for Social Sciences) was used in an IBM compatible computer, in order to evaluate the results statistically. Variables in the study were presented with mean, standard deviation, and maximum-minimum values. Categorical variables were specified with number and percentage ratios.

Results

A total of 46 cases, including 22 female and 24 male, were followed up in a period of seven years. Female to male ratio of the cases was found as 0.91. The age of onset of the disease ranges between 18 and 105 years, and the mean was found as 69.54 years. Linear IgG and C_3 deposition in dermoepidermal junction was detected in 40 of the cases, but no immune deposition was found in four cases (8.69%). The duration of lesions ranged between 1 week and 10 months, and the median of the duration was found as 8 weeks. The most common accompanying diseases in cases were hypertension in 28 cases (60.8%), cerebrovascular diseases in 21 cases (39.1%) and diabetes mellitus in 17 cases (36.9%). Only four cases had malignancies before the onset of the disease, which were multiple myeloma in two cases, plague cell leukemia and prostate cancer. Nineteen of the patients using medications due to their co-morbidities (41%) were taking more than 5 medications. While systemically steroid treatment (0.75 mg/kg/day; 4 weeks) was used alone in 32 patients (69.5%) since they had extensive body lesions and were non-response to topical treatment (clobetasol propionate 0.05% 40 gr/day; 4 weeks), additional adjuvant treatments were required in ten cases (22%). Methotrexate 15 mg/week in two cases, plasmapheresis in three cases, IVIG in two cases, and azathiopurine 100 mg/day were used in combine with systemically steroid treatment. The most frequent side effect of the treatments applied was dysregulation of the blood glucose in four cases (8.6%). No side effect due to adjuvant treatments was seen. Two patients died, one of them was 62 years old, had plague cell leukemia and developed neutropenic fever, and the other one was 66 years old and had co-morbidities such as hypertension, cerebrovascular disease and chronic renal failure. These deaths were not found in association with BP disease or the applied treatments of the disease. Relapses were seen in seven patients while follow-up. Two of them had relapse a year after the cessation of the therapy, one had 6 months later, and the rest had early relapses in periods ranging from one to three months. It is notable that in cases who had relapses used systemically steroid treatment but no adjuvant therapy. Clinical and demographical characteristics of our cases and the treatment parameters were showed in Table 1.

Table 1. Clinical and demographical characteristics of the cases	
n	46
Sex	
Female/male	22/24
Age of onset of the disease (years)	
Mean±SD	69.54±14.65
Median; minimum-maximum	73.0; 18-105
Duration of lesion (week)	
Mean±SD	9.86±8.61
Median; minimum-maximum	8.0; 1-40
Co-morbidity (n)	
Hypertension	28
Diabetes mellitus	17
Cerebrovascular disease	18
Coronary artery disease	7
Chronic renal failure	3
Chronic obstructive pulmonary disease	5
Dyslipidaemia	6
Benign prostate hyperplasia	5
Goitre	2
Osteoporosis	2
Cataract	3
Gastrointestinal system hemorrhage	3
Peptic ulcer	3
Malignancy	4
Hairy cell leukemia	1
Prostate cancer	1
Multiple myeloma*	2
Drug use	
None	4
0-3 agent(s)	13
3-5 agents	10
>5 agents	19
Localization	
Whole body	46
Oral mucosal involvement	
No	33
Yes	13
Itching	
No	12
Yes	34
Therapy applied	
Systemical steroid	32
Systemical steroid+azathioprine	4
Systemical steroid+IVIG	2
Systemical steroid+plasmapheresis	3
Systemical steroid+methotrexate	2
Complications due to therapy	
Dysregulation of blood glucose	4
Pneumonia	2
Dysregulation of arterial blood tension	1
Lumbar fracture	1
Herpetic keratitis	1
Herpes zoster	1
Cataract	1
Follow-up	
Relaps	7
Mortality	2

IVIG: Intravenous immunoglobulin, SD: Standard deviation

Discussion

The incidence of BP, which is a significant cause of morbidity and mortality in advanced age population, is knows as increasing with age, however, rarely cases in childhood were reported[12]. A retrospective study conducted in the UK with 869 cases reported the median age of onset of the disease as 80 years[13]. As in the previous studies conducted in Turkey, the mean age of our cases was above 60 years (Table 2)[14-17]. While the mean age of our cases was 69.54 at the time of diagnosis, the youngest patient in this study was 18 years old. Although the disease affects both genders, it is seen slightly more frequent in females[18]. A like the results of studies by Ekiz et al.[16], BP in this study was found slightly more in male patients (male to female ratio: 1.09).

It is considered in this disease, of which ethiopathogenesis is not known well, that various environmental factors induce the formation of anti-epidermal basal membrane antibodies[19]. In particular, it is considered that drug use could induce the autoimmunity in the ethiopathogenesis, and these possible auto-antibodies against drugs cross-react with the antigens in the basal membrane. The accused agents mostly include sulfhydryl groups (Thiols: D-penicillamine, captopril, penicillin and its derivatives, furosemide)[20].

In a retrospective study conducted by Daye et al.[17], a possible association was reported between the onset of the disease and drug use in 37.5% of the cases with BP, and Thiazide group diuretics were accused as an inducing factor in 66.6% of the cases. Although various drugs were defined in association with BP formation, it is quite difficult in practice to define the precise association since patients in advanced age group generally use multiple drugs[6,21]. Indeed, in the current study, it is notable that cases with no drug use were just 4 (8.69%), while 19 patients (41.3%) were using more than 5 agents. Although Nisa Akay et al.[15] did not report a possible association between BP and drugs, the high rate in this study could be provided with reliable anamnesis inquiry we did during clinical follow-up.

The immune reaction, which occurs against structural proteins similar to epidermal basal membrane antigens, is defined as "epitope spreading phenomenon", and the close association between BP and neurological diseases is explained by this phenomenon[1]. Hemidesmosomal BP auto-antigens are $BPAG_1$ and $BPAG_2$; BPAG1 is an antigen produced

by distonin gene and there are specific isoforms of BPAG1: BPAG1-e is produced primarily in epithelial tissues, while $BPAG_1$-a and $BPAG_1$-b are produced in neural and muscular tissues. The relationship between BP and neurological diseases was showed in various large series, and this tight relationship was explained by the similarity of BP antigens and neuronal antigens[22]. In a prospective, case-controlled, multicentre study, where the risk factors of BP were assessed, neurological problems (Parkinson, dementia), psychiatric problems (unipolar/bipolar disorders), immobility and chronic drug use (Spironolactone, aliphatic side chain phenothiazines) were reported as independent risk factors[23]. In this study, cerebrovascular diseases were found as the second most common chronic disease, with a rate of 39.1%. The period before the appearance of bullous lesions might last weeks to months, non-specific itchy eczematous, papular, urticarial-like lesions may be seen in this period. The disease duration in our cases ranged up to 10 months, which is consistent with the literature. Clinical lesions are characterized by typically extensive, itchy plagues and 1-3 cm tense bulla; these lesions are localized on trunk, flexor areas of extremities, axilla and inguinal folds in general. Intense itching accompanying to lesions is in the foreground. Localized cases of 30% have been reported in the literature. Localized cases may remain limited, as well as turning into a widespread form. Oral mucosal involvement may be seen in 10-30% of patients.[24] Although oral mucosal involvement in our cases (28%) was consistent with the literature data, its rate in this study was approximately 2 times higher than the other studies conducted in Turkey, and it might have been associated with severe clinical lesions of our patients. While an association between BP and malignancies is controversial, a possible malignancy should be excluded in severe, treatment-resistant BP cases[4,25]. A total of four internal malignancies (8.6%), three haematological malignancies, and one solid organ malignancy were found in our cases. This result may be in association with the disease, as well as a possible result in this age and sex group. In DIF analysis of the disease, which is characterized by subepidermal bulla, it is seen that characteristically linear IgG and C_3 deposition in basal membrane, and IgM and IgA deposition to a lesser extent. IgG and C_3 deposition were detected in 87% of our cases, but no IgM or IgA deposition was found[4]. A like in the study of Nisa Akay et al.[15], IgG and C_3 deposition was the most frequently seen DIF finding in 77.4% of the cases.

The primary treatment of the disease is topical and systemical steroids. Topical steroid therapy seems not practical in the older population in need of care, and systemically steroid treatment is primarily preferred particularly in cases with extensive lesions. Systemically steroid treatment could be used alone successfully in 32 of our cases, and the most common side effect due to this treatment was found as reversible dysregulation of blood glucose. Although literature data regarding to usage of immunosuppressive and anti-inflammatory agents in the management of BP is limited, they could be used in clinical practice in order to reduce chronic steroid usage requirement and to provide a quick control of the disease. Adjuvant therapies can be used during the dose reduction of systemic steroids, as well as an initial treatment in patients who cannot have systemic steroids due to co-morbidities[7,8]. One-year mortality rate of BP cases in literature is reported as ranging between 6% and 41%[11]. Nisa Akay et al.[15] reported the mortality rate

Table 2. Studied conducted in Turkey

Author	**Uzun et al.[14]**	**Nisa Akay et al.[15]**	**Ekiz et al.[16]**	**Daye et al.[17]**	*****
Year	2006	2009	2013	2013	2014
Region	Antalya	Ankara	Hatay	Konya	Bursa
Duration (years)	6	9	3	6	7
n	29	31	29	32	46
Sex					
Female/male	17-12	19-12	14-15	20-12	22-24
Age (years)					
Mean	64	78.8±8.67	70.17±16.98	70	69.54±15.05
Minimum-maximum	40-89	60-96	34-100	?	18-105
Duration of the disease (month)					
Mean	?	16.58±18.48	15.41±14.04	?	9.86±8.61[&]
Minimum-maximum	?	1-60	1-48	?	1-40[&]
Oral mucosal involvement	?	4; 12.9%	5; 17.2%	5; 15.6%	13; 28%
Itching	?	24; 77.4%	24; 82.8%	?	34; 73%
Internal malignancy	?	Ø	1; 3.44%	?	4; 8.6%
Drug use	?	Ø	3; 10.34%	12; 35.7%	42
Treatment (n, %)					
Systemical steroid	?	8; 25.8%	10; 34.4%	20; 62.5%	32; 69.5%
SS+AZT	?	16; 51.6%	1; 3.4%	8; 25%	3; 6.5%
Relaps	?	11; 35%	7; 24.13%	6; 18.8%	7; 15.2%
Mortality	?	6; 19.3%	2; 6.9%	?	2; 6.5%

*Our study; n: Case number, %: Percentage, SS: Systemical steroid, AZT: Azathioprine, ?: Unevaluated, Ø: Undetermined, &: Weeks

as 19.4%, while Ekiz et al. reported mortality in 6.9% of the cases. Ekiz et al.[16] associated the low mortality rate with less disease severity of the patients. Low death rate in our cases (two cases only; 4.34%) might be associated with the close follow-up of severe cases, and the early diagnose and management of the complications which could be developed due to primary diseases and/or their possible treatments.

Study Limitations

No serological evaluation has done in cases, the study is retrospective, and included particularly severe cases who were taken under clinical follow-up, however, clinical and demographic characteristics of the cases were consistent with the literature data.

Conclusion

BP is a significant cause of morbidity in advanced age population who generally use multiple drugs. Additional immunosuppressive agents to avoid possible side effects of steroid treatment particularly in severe cases are effective in management of the disease, and can be used safely in short term. In particular, close follow-up of severe cases is significant in management of possible complications which might be developed due to primary diseases and/or their treatments.

Ethics

Ethics Committee Approval: The study were approved by the Uludağ University of Local Ethics Committee.
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Serkan Yazıcı, Emel Bülbül Başkan, Şükran Tunalı, Kenan Aydoğan, Hayriye Sarıcaoğlu, *Concept:* Serkan Yazıcı, Emel Bülbül Başkan, Şükran Tunalı, *Design:* Serkan Yazıcı, Kenan Aydoğan, Hayriye Sarıcaoğlu, *Data Collection or Processing:* Serkan Yazıcı, *Analysis or Interpretation:* Serkan Yazıcı, Emel Bülbül Başkan, Şükran Tunalı, Kenan Aydoğan, Hayriye Sarıcaoğlu, *Literature Search:* Serkan Yazıcı, *Writing:* Serkan Yazıcı.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Lo Schiavo A, Ruocco E, Brancaccio G, Caccavale S, Ruocco V, Wolf R: Bullous pemphigoid: etiology, pathogenesis, and inducing factors: facts and controversies. Clin Dermatol 2013;31:391-9.
2. Joly P, Baricault S, Sparsa A, et al: Incidence and mortality of bullous pemphigoid in France. J Invest Dermatol 2012;132:1998-2004.
3. Kasperkiewicz M, Zillikens D, Schmidt E: Pemphigoid diseases: pathogenesis, diagnosis, and treatment. Autoimmunity 2012;45:55-70.
4. Di Zenzo G, Della Torre R, Zambruno G, Borradori L: Bullous pemphigoid: from the clinic to the bench. Clin Dermatol 2012;30:3-16.
5. Ruocco E, Wolf R, Caccavale S, Brancaccio G, Ruocco V, Lo Schiavo A: Bullous pemphigoid: associations and management guidelines: facts and controversies. Clin Dermatol 2013;31:400-12.
6. Stavropoulos PG, Soura E, Antoniou C: Drug-induced pemphigoid: a review of the literature. J Eur Acad Dermatol Venereol 2014;28:1133-40.
7. Daniel BS, Borradori L, Hall RP, Murrell DF: Evidence-based management of bullous pemphigoid. Dermatol Clin 2011;29:613-20.
8. Feliciani C, Joly P, Jonkman MF, et al: Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. Br J Dermatol 2015;172:867-77.
9. Eming R, Sticherling M, Hofmann SC, et al: S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid. J Dtsch Dermatol Ges 2015;13:833-44.
10. Murrell DF, Marinovic B, Caux F, et al: Definitions and outcome measures for mucous membrane pemphigoid: recommendations of an international panel of experts. J Am Acad Dermatol 2015;72:168-74.
11. Parker SR, Dyson S, Brisman S, 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;59:582-8.
12. Lara-Corrales I, Pope E: Autoimmune blistering diseases in children. Semin Cutan Med Surg 2010;29:85-91.
13. 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.
14. Uzun S, Durdu M, Akman A, et al: Pemphigus in the Mediterranean region of Turkey: a study of 148 cases. Int J Dermatol 2006;45:523-8.
15. Nisa Akay B, Bodamyalı P, Şanlı H, Akyol A: Büllöz Pemfigoidli Hastalarda 10 Yıllık Gözlem. Turkderm 2010;44:61-4.
16. Ekiz Ö, Bülbül Şen B, Rifaioğlu EN, Şen T, Atik E, Doğramacı AÇ: Büllöz pemfigoidli hastalarda 3 yıllık gözlem: 29 olgu. Turkderm 2013;47:205-8.
17. Daye M, Mevlitoğlu İ, Esener S: Konya ilinde büllöz hastalıklar: 93 olgu üzerine bir çalışma. Turkderm 2013;47:200-4.
18. Marazza G, Pham HC, Scharer L, et al: Incidence of bullous pemphigoid and pemphigus in Switzerland: a 2-year prospective study. Br J Dermatol 2009;161:861-8.
19. Delgado JC, Turbay D, Yunis EJ, et al: A common major histocompatibility complex class II allele HLA-DQB1* 0301 is present in clinical variants of pemphigoid. Proc Natl Acad Sci U S A 1996;93:8569-71.
20. Sagi L, Baum S, Agmon-Levin N, et al: Autoimmune bullous diseases the spectrum of infectious agent antibodies and review of the literature. Autoimmun Rev 2011;10:527-35.
21. Stavropoulos PG, Soura E, Antoniou C: Drug-induced pemphigoid: a review of the literature. J Eur Acad Dermatol Venereol 2014;28:1133-40.
22. Chen J, Li L, Chen J, et al: Sera of elderly bullous pemphigoid patients with associated neurological diseases recognize bullous pemphigoid antigens in the human brain. Gerontology 2011;57:211-6.
23. Bastuji-Garin S, Joly P, Lemordant P, et al: Risk factors for bullous pemphigoid in the elderly: a prospective case-control study. J Invest Dermatol 2011;131:637-43.
24. Baum S, Sakka N, Artsi O, Trau H, Barzilai A: Diagnosis and classification of autoimmune blistering diseases. Autoimmun Rev 2014;13:482-9.
25. Ong E, Goldacre R, Hoang U, Sinclair R, Goldacre M: Associations between bullous pemphigoid and primary malignant cancers: an English national record linkage study, 1999-2011. Arch Dermatol Res 2014;306:75-80.