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Bullous pemphigoid in Dermatology Departments of Silesia in years 2001-2014

Pemfigoid pęcherzowy w oddziałach dermatologii województwa śląskiego w latach 2001-2014

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Key words

pemphigoid, paraneoplastic syndrome, treatment

Słowa kluczowe

pemfigoid, zespół paraneoplastyczny, leczenie

Summary

Introduction. Bullous pemphigoid (BP) is the most common disease from a group of bullous dermatoses. It affects mostly elderly people and the relative risk of disease development in people at the age 90 is 300-fold higher than in individuals who are 60 years old. It is supposed, that 15-20% of patients with BP may have malignant internal tumor and skin lesions can even precede the recognition of malignancy.

Aim. The aim of this retrospective study was to assess the occurrence of BP in relation to age of patients and concomitant systemic diseases, including neoplastic disorders. Further analysis gives a review of therapeutic options and the efficacy of these modalities.

Material and methods. A study group comprised of 120 patients who were diagnosed with BP: 74 female and 46 male patients. The mean age of patient was 71.13 ± 11.8.

Results. Co-existing of other disease was reported in 87.11% of patients and the history towards neoplastic disorder (active or previously treated) was positive in 19.8% of patients. In therapy of the disease, the drug of choice was Methylprednisolone. Other therapeutic options were also glucocorticoids (Dexamethasone, Prednisone, Triamcinolone), immunosuppressive agents (Cyclophosphamide, Chlorambucil or Azathioprine), antibiotics (Erythromycin, Doxycycline, Ceftriaxone), niacin and Dapsone.

Conclusions. Clinical presentation of BP is distinguished and the recognition of the disease should be always supplemented by diverse diagnostic tests towards potent and hidden tumor. Although, glucocorticoids have remained a first choice therapy with good effects, further studies are necessary to establish the efficacy of other therapeutic modalities.

Streszczenie

Wstęp. Pemfigoid pęcherzowy (*pemphigoid bullosus*) jest najczęściej występującym schorzeniem z grupy chorób pęcherzowych. Dotyczy zwykle osób starszych, ryzyko względne zachorowania w 90. r.ż. jest blisko 300-krotnie wyższe niż w 60. r.ż. W 15-20% przypadków pemfigoid pęcherzowy może być rewelatorem paraneoplastycznym – opisywano przypadki typowych pęcherzowych zmian skórnych zarówno poprzedzających rozwój, jak i współistniejących z nowotworami.

Cel pracy. Celem pracy była ocena częstości występowania pemfigoidu w różnych grupach wiekowych, metod i wyników leczenia, współistnienia z chorobami nowotworowymi i innymi schorzeniami dodatkowymi, wpływu leków stosowanych przez pacjentów na etiologię pemfigoidu.

Materiał i metody. Analizą objęto 120 pacjentów z rozpoznanym pemfigoidem pęcherzowym: 74 kobiety oraz 46 mężczyzn. Średnia wieku pacjenta wynosiła 71,13 ± 11,8 roku.

Wyniki. Współistnienie innych schorzeń układowych stwierdzono u 87,11% pacjentów, z czego u 19,8% wywiad w kierunku schorzeń nowotworowych był dodatni. Lekiem z wyboru w terapii pemfigoidu pozostawał Metyloprednizolon. Wśród innych opcji terapeutycznych stosowano również glikokortykosteroidy (Deksametazon, Prednizon, Triamcynolon), leki immunosupresyjne (Cyklofosfamid, Chlorambucil, Azatiopryna), antybiotyki (Erytromycyna, Doksycyklina, Ceftriakson) oraz witaminę PP i Dapson.

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Wnioski. Obraz kliniczny pemfigoidu pozostaje zróżnicowany, a rozpoznanie choroby powinno być zawsze uzupełnione o diagnostykę w kierunku ewentualnych, ukrytych schorzeń nowotworowych. Chociaż glikokortykosteroidy pozostają terapią z wyboru, to konieczne są dalsze badania, które pozwolą na lepsze poznanie i ugruntowanie skuteczności innych opcji terapeutycznych.

INTRODUCTION

Bullous pemphigoid (BP) is the most common disease from a group of bullous dermatoses and it affects mostly elderly people who are over 70 years old (1). An etiology of the disease has been still not fully elucidated, however some autoimmune antibodies against components of the basement membrane zone (BMZ) are suggested to be the main factors.

An onset of the disease can be non-specific and some urticarial-type or eryhematous lesions can occur on the skin. Following, bullae formation arise and may develop on previously unchanged skin or in area of preexisting, non-specific skin eruption. Typically, bullae are tense, firm-topped with epidermal layer and may contain serous or hemorrhagic fluid. The originally tense bullae rupture and transform into erosion which is covered with hemorrhage crusts. Some lesions can be accompanied by itching. The disease mostly spares mucosae membranes, however in 20-30% of patients some lesions occur also in oral cavity (fig. 1-5).

AIM

The aim of the analysis was to assess the occurrence of pemphigoid and its correlations to age of patients and association with systemic diseases, including neoplastic disorders.

MATERIAL AND METHODS

This is a retrospective study that encompasses the analysis of patients diagnosed with pemphigoid that were treated in years 2001-2014 in the Chair and Department of Dermatology at Medical University of Silesia or in other Dermatology Departments in Silesian Province.

RESULTS

A study group comprised of 120 patients who were diagnosed with BP: 74 female and 46 male patients. The mean age of patient was 71.13 ± 11.8 and in female group it was 72.7 ± 11.3, while in male group 62.43 ± 14.25. The mean time of latency from the occurrence of lesions to diagnosis of the disease was 27 months. The recognition of bullous pemphigoid was confirmed by skin biopsy in all patients. Direct immunofluorescence test in skin biopsy was performed in 74 patients (61.6%) and in 48 of them (65%) was positive. Indirect immunofluorescence test was made in all patients and was positive in 84 patients (70.0%).

In therapy of the disease, the drug of choice was Methylprednisolone, which was administered orally (Metypred) in 39 patients or as intravenous pulses (Solu-Medrol) in the next 6 patients. Other reported glucocorticoids were Prednisone (Encorton) in 21 patients, Triamcinolone (Polcortolon) in 7 patients, Dexamethasone orally (Pabi-Dexamethason) in 11 patients or intravenously (Dexaven) in 17 patients. Further modalities encompassed immunosuppressive drugs such as Cyclophosphamide (Endoxan) in 7 cases, Chlorambucil (Leukeran) in 8 cases or Azathioprine (Imuran) in 4 cases. Some of patients were administered with antibiotics and 27 of them were treated with Erythromycin coadministered with niacin. Doxycycline was reported in 18 cases, Ceftriaxone in 8 and Dapsone (Avlosulfon, Disulone) in 18 cases. A monotherapy was rare and 91% of patients received more than one of systemic therapeutic option. At the same time, all patients were treated externally with topical glucocorticoids or emollients.

Co-existing of other disease was reported in 87.11% of patients and encompassed mainly arterial hypertension, coronary heart disease, epilepsy, diabetes mellitus type 2 and hypothyroidism (with autoimmune thyroid disease reported in 1 case). The history towards neoplastic disorder (active or previously treated) was positive in 19.8% of patients. The breast cancer was the most common neoplastic disease and was reported in 9 patients. Some other malignancies were chronic leukocyte leukemia, lung cancer, colon cancer, gastric cancer, renal cancer or prostate cancer. In the study group, 41% of patients had been reported to receive a long-term systemic therapy of concomitant disorders and antihypertensive drugs (Enalapril, Captopril and Furosemide) were the most common pharmacological interventions in the study group.

DISCUSSION

Sub-epidermal bullae in BP are formed in just below the basal layer of keratinocytes and result from proteolysis and disjunction in the upper part of lamina lucida. In more than 95% of patients IgG antibodies occur and are aimed to components of BMZ. They are specific to BPAG2 (type XVII of collagen), which is a trans-membrane component of hemidesmosome, of 180 kDa weight and to BPAG1, protein of 230 kDa weight connected with internal hemidesmosome lamina. However, BPAG2 – an extracellular antigen is considered to be the starting point of the disease.

An initial diagnosis of BP can be based on four clinical criteria that encompass: age over 70 years, absence of cicatricial atrophic lesions, mucosa unaffected by the disease and lack or minor eruption within skin

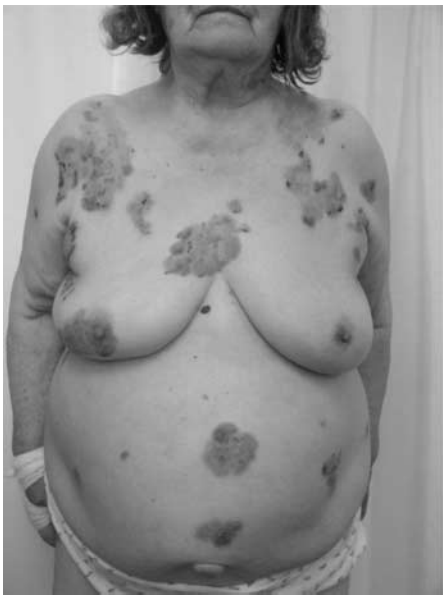

Fig. 1. 85-year-old patient, woman, eruptions numerous, well-tensed bullas on the erythematous area, edemic erythemas as well as erosions covered with hemorrhage crusts on the patient's torso, lower and upper extremities.

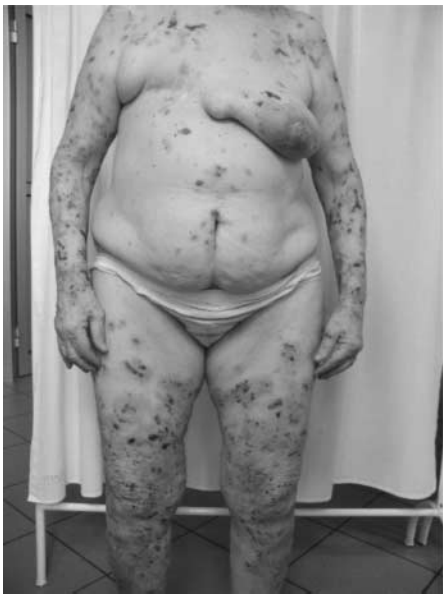

Fig. 2. 65-year-old patient, woman, erythema, bullas and blisters with a well-tensed surface, erosions, located near the scar after right mastectomy.

areas of face and neck. Indeed, a skin biopsy is recommended to diagnose BP. Typically, a sub-epidermal blister is visible in a specimen and the whole epidermis comprises its cover. However, the confirmation of the diagnosis should be based on some immunofluorescence technique. Indirect immunofluorescence (IIF) detects auto-antibodies BP 180 and BP 230 in blood serum with the ELISA or immunoblot tests, while direct immunofluorescence (DIF) reveals deposits of C3 constituent of complement and auto-antibodies IgG along cutaneous-epidermal junction in the skin specimen taken from the border line of lesion (2-4).

Essentially, BP can be a significant paraneoplastic revelator and several cases of a coexistence of BP and

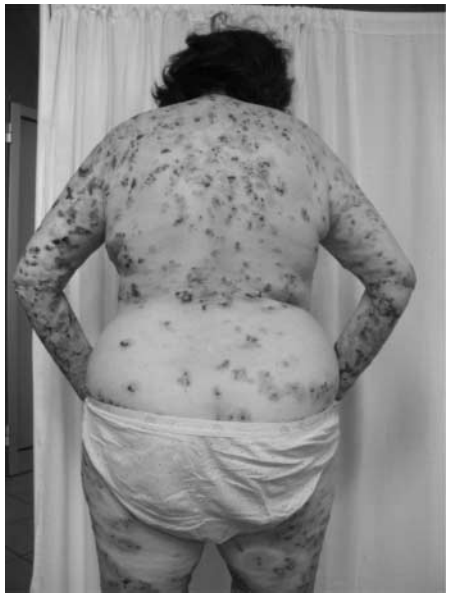

Fig. 3. 65-year-old patient, woman, erythema, bullas and blisters with a well-tensed surface, erosions, located on the back.

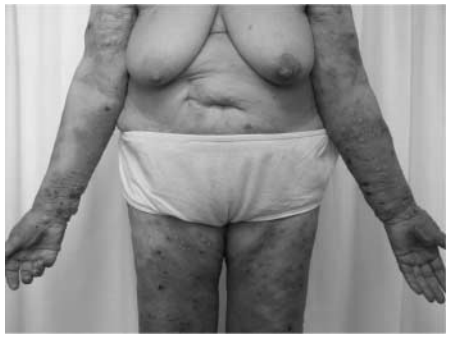

Fig. 4. 81-year-old patient, woman, numerous, well-tensed blisters on erythematous base, edemous erythemas and erosions covered with hemorrhagic eschars found on the patient's torso, upper and lower limbs.

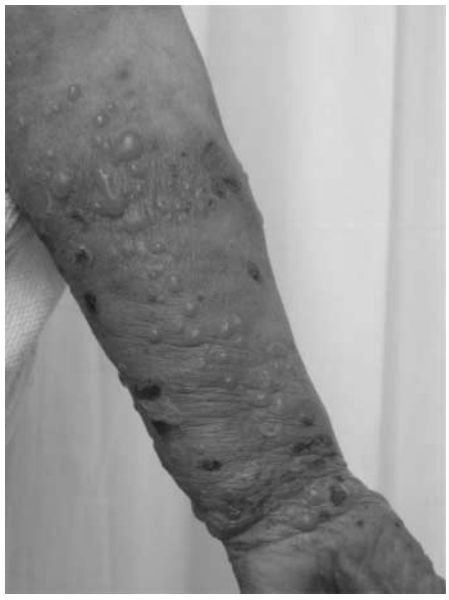

Fig. 5. 81-year-old patient, woman, well-tensed blisters on erythematous base, edemous erythemas and erosions covered with hemorrhagic eschars found on the patient's upper limb.

malignancy have been reported. It is supposed that 15-20% of patients with BP may have malignant internal tumor. Paraneoplastic pemphigoid most commonly coexists with adenocarcinomas of the gastrointestinal tract, predominantly in stomach and colon. Other malignancies may consider the skin, uterus mucous tunic, breast, lungs, salivary and prostate glands or Castelman disease, however they are less frequently diagnosed. Interestingly, the risk of neoplasia in patients with BP is disputable and some authors contest such correlations (5, 6).

Some cases of sudden onset of BP have been reported to be related to pharmacological interventions and considered mainly with the co-administration of antihypertensive- and diuretic-drugs (especially Furosemide) (3).

A prognosis in BP depends on the age, concomitant disorders as well as on Karnofsky score system, but the extension of skin lesions has the minor significance (7). A low albumin level in blood serum is known to be an additional factor which worsens the prognosis (8). Fairley et al. suggest that a level of eosinophils or immunoglobulin IgE concentration are important factors in the course of the disease (9).

Therapeutic complications related to glucocorticoids are considered to be the main cause of death among patients with BP, nevertheless, steroids have been still considered as pharmacological intervention of choice. The recommended dose related to Prednisone is 0.5-1.0 mg/kg per day. Further modalities encompass: Azathioprine, Chlorambucil, Mycophenolate Mofetil, Methotrexate, Dapsone, antibiotics (macrolides or tetracyclines) co-administered with nicotinic acid amide, intravenous immunoglobulin infusion or plasmapheresis. Interestingly, the strong glucocorticoids topically are considered to be the safest therapeutic option. Very promising seem to be clinical trials with the assessment of biologic agents such as Imatinib, Rituximab or Etanercept (3, 10-12). However, Monnier-Murina et al. reported a case of BP which occurred in patient with psoriasis during the therapy with Efalizumab (13).

In the period of time 2001-2014 there were 120 patients diagnosed with BP who were hospitalized in Dermatology Departments in Silesian Province. There were 74 female and 46 male patients. The mean age of patient was 71.13 ± 11.8, what stayed in consent to mean age reported by Braun-Falco (3). In 2008, Langan et al. analyzed the epidemiology of *bullosus dermatoses* such as *Pemphigus vulgaris* and BP in the Great Britain. In reviewed group of 869 patients who were diagnosed with BP, the mean age of patient was 80 years and the disease predominantly affected women – 534 patients (61%). The study revealed also that the risk factor of death in BP is increased twice than in general population (14).

There are several case reports which reveal a type of BP which is induced by drugs. The co-administration of antihypertensive agents and diuretics (especially Furosemide) seems to be associated with a significant increase in the risk of the development of such reactions (3). Popadic et al. reported a case of BP which developed during the therapy with Penicillamine in a patient with Wilson disease (15). In our study group, 41% of patients received treatment of coexisting systemic disease. The most common administered drugs were: enalapril (Enarenal), captopril (Captopril), furosemide (Furosemid). Patsatsi et al. reviewed a group of 34 patients with BP and following, they were divided in relation to other pharmacological interventions. The first group comprised of individuals who received treatment of concomitant systemic disorders before the development of BP, while the second group of patients were free of such pharmacological interventions. The analysis revealed, that specific antibodies against BMZ were detected more often in patients who concomitantly received other systemic drugs (16).

A characteristic for BP is a disjunction of the epidermis in the upper part of lamina lucida where are located target antigens such as BPAG2, BPAG1, laminine 5, antigen 105 kDa and antigen 200 kDa (3). Specific antibodies activate complement and induce inflammatory cascade what in following leads to chemotaxis of neutrophils and eosinophils and finally sub-epidermal blister formation. In our study group, the test towards detection of specific autoimmune antibodies – indirect immunofluorescence (IIF) – was performed in all patients and was positive in 84 of them (70.0%). A skin biopsy with direct immunofluorescence test was taken in 74 patients (61.6%) and characteristic deposits were detected in 48 of them (65.0%).

A review of medical literature, reveals numerous case reports of coexisting and correlations of BP with other systemic or skin diseases. There are several case reports of coexisting of BP with other dermatological states such as dermatomyositis, polymyositis, Pemphigus spectrum diseases, dermatitis herpetiformis, lichen planus, psoriasis vulgaris, systemic lupus erythematosus, rheumatoid arthritis or colitis ulcerosa and graft-vs-host disease (3, 17-19). In our study group, a concomitant systemic disorder was reported in 87.11% of patients. The most common reported abnormalities were arterial hypertension, coronary heart disease, epilepsy, diabetes mellitus type 2 and hypothyroidism (with autoimmune thyroid disease reported in 1 case).

BP can be also a significant cutaneous symptom which occurs in case of coexistence of neoplasm and is well known as paraneoplastic pemphigoid. It is supposed, that 15-20% of patients with BP may have malignant internal tumor (3, 14). Our review revealed, that the history towards neoplastic disorder (active or previously treated) was positive in 19.8% of patients. The breast cancer was the most common neoplastic disease and was reported in 9 patients. Some other malignancies were chronic leukocyte leukemia, lung cancer, colon cancer, gastric cancer, renal cancer or prostate cancer.

Mechanisms which lead to skin manifestations in patients with malignant tumor have stayed not elucidated.

Hall et al. claim that paraneoplastic syndrome is the kind of regular response of host to the occurrence of invalid neoplastic cells in human body. However, this response is excessive in some of patients with tumor, what leads to pathological bullae formation. What is more, it is supposed to be a residue reaction from the embryonic stage of human growth (20).

Hall suggests an involvement of following mechanisms in pathogenesis of paraneoplastic syndrome: 1) a necrosis of neoplastic cells and a release of autoantigens from tumor what induces paraneoplastic reactions; 2) some viral agents which lead to malignant transformation of cells can build-in own nucleic acids into genome of host what in following causes production of invalid superficial antigens and as a consequence, activates immune reactions of host lymphocytes; 3) a synthesis of diverse cytokines by neoplastic cells what activates autoimmune reactions; 4) a release of substances from tumor which destroy normal cells in milieu and therefore denude new autoantigens; 5) a production of paraproteins by tumor cells; 6) a cross reaction of host regular proteins with antibodies and cytokines which are generated in response of immune system to antigens of neoplastic cells (20).

A case of paraneoplastic mixed bullous skin disease in patient with B-cell-lymphoma was reported by Fernandes et al. The direct immunofluorescence test detected deposits of autoimmune antibodies in both class IgG and IgA which were bound to epidermal cover in skin split specimen, while immunoglobulins IgM were located along dermal bottom of the split. Additionally, there was positive direct immunofluorescence between cells of epidermis what correlated with the presence of autoantibodies IgM in blood serum which had an affinity to superficial antigens of keratinocytes. Authors, suggested an association of skin eruption with the presence of IgM monoclonal gammopathy which resulted from lymphoma (21). Wong et al. also reported a case of skin eruption with sub-epidermal bullae which developed in patient with IgA monoclonal gammopathy related to myeloma multiplex (22). Taniuchi et al. reported a case of sub-epidermal bullae disease and the presence of autoimmune antibodies IgG aimed to laminin-5 protein which occurred in patient with stomach cancer (23). Ahmed et al. described a 79-years-old female patient with lymphoma of gastrointestinal tract who presented bullae formation both on the skin and in oral cavity. Although mucosae are not common affected, the lesions clinically resembled BP (24). Another example of paraneoplastic pemphigoid was reported by Ameen et al. who presented the occurrence of BP in female patient with chronic myeloid leukemia (25). Blum et al. reported a case of a 74 year old female patient who was diagnosed with a renal cell carcinoma after admission to hospital because of BP (26). Another case of paraneoplastic BP was reported by Klein et al. who described a 52-year-old patient diagnosed with a partially sarcomatoid papillary renal cell carcinoma (27). Oztürkcan et al. reported a case of BP which occurred in male patient with prostate adenocarcinoma (28). A coexistence of several abnormalities such as BP, Sjöergen syndrome and polyneuropathy was reported by Calderoni et al. All disorders developed in a 51-years-old female patient with familiar breast carcinoma. A complete resolution of skin lesions and disappearance of autoimmune antibodies were achieved during the therapy of tumor (29). Hauschild et al. descibed a case of paraneoplastic pemphigoid which resembled erythema gyratum repens Gammel (30). Similarly, Gilmour et al. reported report a case of bullous pemphigoid with marked figurate erythema which arose shortly before the clinical presentation of colonic carcinoma and subsided a one week after its resection (31). Wong et al. described skin lesions which resembled BP clinically, however further immune diagnostic tests revealed paraneoplastic pemphigus that occurred in a patient with squamous-cell carcinoma of tongue (32). Reduta et al. suggested a necessity of extensive diagnostic tests towards malignancies of gastrointestinal tract in all patients with BP. This statement stay in agreement with other authors and observations of common development of BP in case of tumors of digestive system (33).

Glucocorticoids have still stayed as a treatment of choice for BP. Typical daily dose in relation to Prednisone ranges from 30 to 60 mg. In case of poor efficacy of steroids some therapeutic modalities encompass immunosuppressive drugs such as Azathioprine, Chlorambucil, Dapsone, Mycophenolate Mofetil or Cyclophosphamide. In some patients a good response is observed after the treatment with antibiotics (macrolides or tetracyclins), especially when are co-administered with niacin (3).

In our study group, the drug of choice in therapy of the disease was Methylprednisolone, which was administered orally (Metypred) in 39 patients or as intravenous pulses (Solumedrol) in the next 6 patients. Other reported glucocorticoids were Prednisone (Encorton) in 21 patients, Triamcinolone (Polcortolon) in 7 patients, Dexamethasone orally (Pabi-Dexamethason) in 11 patients or intravenously (Dexaven) in 17 patients. Further modalities encompassed immunosuppressive drugs such as Cyclophosphamide (Endoxan) in 7 cases, Chlorambucil (Leukeran) in 8 cases or Azathioprine (Imuran) in 4 cases. Some of patients were administered with antibiotics and 27 of them were treated with Erythromycin co-administered with niacin. Doxycycline was reported in 18 cases, Ceftriaxone in 8 and Dapsone (Avlosulfon, Disulone) in 18 cases. Monotherapy was rare and 91% of patients received more than one of systemic therapeutic option. At the same time, all patients were treated externally with topical glucocorticoids or emollients. Błaszczyk reports about good effects of topical therapy with glucocorticoids, however the most of cases consider 0.05% Clobetasol propionate. A prevalence

of topical steroids results from significantly fewer adverse effects than in systemic therapy with steroids. Interestingly, there is a better tolerance of topical steroids even though a daily application of 40 grams of steroidal cream may be an equivalent of 60 mg of Prednisone (11). Demitsu et al. described a good response to monotherapy with topical application of Tacrolimus which was applied in male-patient with Brunsting-Peery syndrome (localized cicatrical pemphigoid) (34). Kjellman et al. confirmed retrospectively a good response to treatment with Methotrexate orally in patient with BP which was administered after exclusion of malignancy (35). Carrozzo et al. reported a successful treatment with co-administration of Minocycline and Mycophenolate Mofetil in patient with lesions in oral cavity (36). An efficacy of Mycophenolate Mofetil and Methylprednisolone co-administered with Azathioprine was compared by Beissert et al. Both therapeutic modalities give comparable therapeutic effects, however more adverse events were reported in case of treatment with Mycophenolate Mofetil what was associated with a severe increase in the risk of hepatotoxicity (37). Mignogna et al. achieved a similar efficacy in a group of patients who had received intravenous immunoglobulin therapy (38). Schmidt et al. reported a successful treatment with Rituximab in patient with non-paraneoplastic BP which was resistant to other therapies (39).

BP even without therapy, may be a self-limited disease, but it may last from several months to many years. Approximately one-half of treated patients go into remission within approximately 2.5 to 6.0 years, however, in individual patients, the disease may continue for 10 years or more. Clinical remission with reversion of DIF or IIF to negative has been noted in patients, even those with severe generalized disease, treated with systemic corticosteroids alone or with Azathioprine. Despite of therapeutic modalities, the 1-year mortality of patients with BP has been reported to be between 19 and 40% in Europe. Old age and poor general health were associated with poor prognosis, as might be expected. As a result, BP is a potentially fatal disease mostly in the elderly, whose already may be fragile (40). Braun-Falco et al. suggest that the main cause of death in patients with BP results rather from complications of treatment than indeed from epidermolysis (3). Indeed, the most commonly administered glucocorticoids lead to significant metabolic abnormalities, which together with severe bacterial infections are the most common complications in patients with BP (10).

CONCLUSIONS

Clinical presentation of BP is distinguished and the recognition of the disease should be always supplemented by diverse diagnostic tests towards a hidden malignancy. A resistance to common therapeutic options should particularly indicate paraneoplastic character of the disease. Although, glucocorticoids have remained a first choice therapy with good effects, further studies are necessary to establish the efficacy of other therapeutic modalities.

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