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ORAL LESIONS IN PATIENTS WITH PEMPHIGUS VULGARIS AND BULLOUS PEMPHIGOID

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SUMMARY – Thirty three patients admitted to the University Department of Dermatology and Venereology, Sestre milosrdnice University Hospital, were included in the study. The purpose of the study was to compare data on age and gender, habits, lesion localization, onset of symptoms and therapy between patients with pemphigus vulgaris and those suffering from bullous pemphigoid. Based on clinical presentation, histopathologic analysis, direct and indirect immunofluorescence, Tzanck smear and desmogleins, 15 cases of pemphigus vulgaris and 18 cases of bullous pemphigoid were diagnosed. The results obtained indicated an increased prevalence of pemphigus vulgaris in middle-aged patients (46.6% of patients were aged between 50 and 70), while bullous pemphigoid predominantly affected elderly individuals (83.3% of patients were older than 70). Pemphigus vulgaris showed a female predominance (female 66.6% *vs*. male 33.4%), while no sex difference was recorded for bullous pemphigoid. Patients with both diseases presented with cutaneous and/or oral lesions. The majority of patients with pemphigus vulgaris had skin lesions with oral manifestations (86.6%), whereas in 40% of cases oral lesions were preceded by the cutaneous ones. Mucosal erosions were found in only 16.6% of patients with bullous pemphigoid. The majority of patients were administered systemic and topical corticosteroid therapy with adjuvant systemic immunosuppressant therapy. Timely recognition of pemphigus vulgaris and bullous pemphigoid and appropriate treatment are important for the prognosis of these autoimmune bullous disorders.

Key words: *Pemphigus – diagnosis; Pemphigus – therapy; Pemphigoid bullous – diagnosis; Pemphigoid bullous – therapy; Autoimmune diseases – drug therapy; Skin diseases, vesiculobullous – drug therapy; Skin – pathology*

Introduction

The pemphigus family comprises autoimmune bullous disorders characterized by the appearance of intraepidermal acantholytic blisters and erosions of the skin and/or mucous membranes. According to clinical features, histopathologic and immunologic analysis, there are several variants including pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, pemphigus brasiliensis, pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus. With respect to mucosal involvement, pemphigus vulgaris, vegetans, foliaceus, and erythematosus are distinguished[1,2]. A number of diagnostic procedures such as histopathologic analysis, direct and indirect immunofluorescence, Tzanck smear, desmogleins, etc. are frequently required for an accurate diagnosis to make[3,4].

Pemphigus vulgaris is the most common form of pemphigus (90%-95%)[2]. It is a chronic, recurrent, potentially life-threatening bullous dermatosis characterized by the appearance of intraepidermal blisters (bullae) and erosions on the skin and/or mucous membranes (Table 1). It is a rare disorder (the incidence is 0.5-3.2 cases

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Table 1. The major differences between pemphigus vulgaris and bullous pemphigoid (according to Braun-Falco)[1]

Characteristics	Pemphigus vulgaris	Bullous pemphigoid
Age	Middle-aged people	Elderly people
Clinical features	Monomorphic	Polymorphic
Blisters	Rupture easily, flaccid	Tense, firm
Content of blisters	Fluid-filled	Often hemorrhagic
Oral lesions	Common	Rare
Nikolsky's sign	Positive	Negative
Tzanck smear	Acantholysis	No acantholysis
Direct immunofluorescence	Intraepidermal deposits	Deposits at the epidermal basement membrane
zone	Target antigen	Desmoglein 1 and 3 BPAG2 (type 17 collagen)

per 100,000), and occurs mainly in adults, usually between the age of 30 and 60, most frequently in the fifth and sixth decade of life. It can affect both female and male patients.

Skin blisters in pemphigus vary in diameter, tension, fragility; they can be either filled with clear or hemorrhagic fluid, and rupture easily due to the thin cover and resulting erosions heal without scarring, through the process of epithelialization originating from the erosion margins (unless secondary infection ensues)[1].

Oral mucosal lesions in pemphigus are common (50%-70%) and predominantly appear as buccal erosions in the occlusal line, which is most exposed to trauma, and also on the palate, gingiva and tongue (Fig. 1). Other mucosal surfaces can be affected as well; lesions can be found on the conjunctivae, pharynx, larynx, esophagus, bronchi, stomach, genitalia and anal region in 13% of cases[2]. Crucial therapy for pemphigus includes systemic corticosteroids[5-8].

The pemphigoid family is comprised of relatively common chronic bullous disorders which manifest with the appearance of blisters on the erythematous surface[9]. There are several types including bullous pemphigoid and its variants (urticarial, vesicular, dyshidrosiform, seborrheic, vegetating, localized and prurigo nodularis-like bullous pemphigoid), herpes gestationis, cicatricial pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, linear IgA dermatosis and lichen planus pemphigoides[10].

Bullous pemphigoid is a chronic, autoimmune blistering disorder of the skin and mucous membranes, which shows lower morbidity and mortality rate than pemphigus vulgaris[9]. The disease predominantly occurs in patients older than 60 and usually lasts for 5 years; the average age at onset is 76 years[1]. Women are affected more often than men, at a 1.7 to 1 ratio[2]. Conversely, statistical data show the male to female predilection in Germany to be 1.8 to 1[1,11].

Oral manifestations in pemphigoid are presumed to be relatively common (40%); they follow cutaneous eruptions. Oral bullae rupture rapidly, thus forming erosions, predominantly affecting buccal mucosal surface, palate, gingiva, tongue and lower lip. Generally, bullous pemphigoid is characterized by slower-growing and smaller

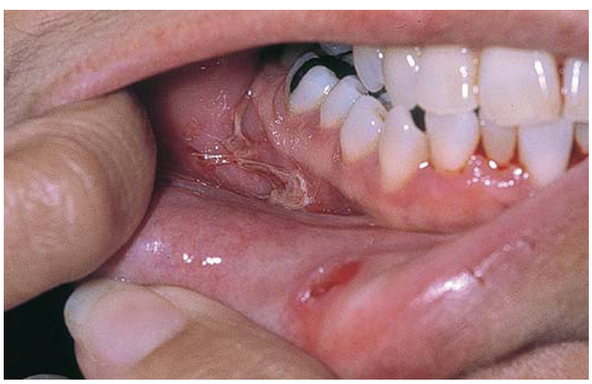

Fig. 1. Oral lesions in a patient with pemphigus vulgaris

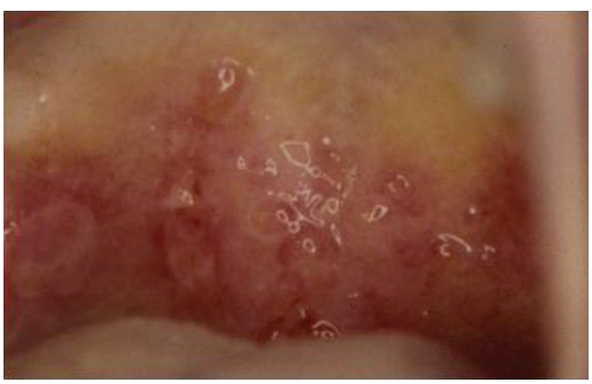

Fig. 2. Oral lesions in a patient with bullous pemphigoid

Table 2. The basic parameters of our patients with pemphigus and pemphigoid

	Pemphigus vulgaris	Bullous pemphigoid
Number of patients	15	18
Age	20-50 years 3/15 (29%) 50-70 years 7/15 (47%) 70-95 years 5/15 (33%)	20-50 years 0/18 (0%) 50-70 years 3/18 (17%) 70-95 years 15/18 (83%)
Gender	M 5/15 (33%) F 10/15 (67%)	M 9/18 (50%) F 9/18 (50%)
Habits	Smoking 4/15 (27%) Alcohol 0/15 (0%)	Smoking 4/18 (82%) Alcohol 4/18 (22%)
The most common localization	Trunk 9/15 (60%) Extremities 5/15 (33%)	Trunk 14/18 (82%) Extremities 18/18 (100%)
Oral lesions	13/15 (87%)	3/18 (17%)

oral lesions, which are less painful than lesions associated with pemphigus vulgaris[12,13] (Fig. 2). Gingiva can be affected in 16% of patients with bullous pemphigoid, resulting in desquamating gingivitis. Bullous pemphigoid has a chronic, recurrent course, but can be kept in remission with systemic glucocorticosteroid therapy.

The purpose of the study was to obtain data on the incidence of oral lesions and timing of their appearance in patients with pemphigus vulgaris and bullous pemphigoid admitted to our University Department of Dermatology and Venereology. The aim was to compare data on age and gender, habits, lesion localization, onset of symptoms and therapy between patients with pemphigus vulgaris and those with bullous pemphigoid.

Patients and Methods

This retrospective study included 33 patients, 19 female and 14 male, admitted to University Department of Dermatology and Venereology, Sestre milosrdnice University Hospital, due to pemphigus vulgaris and bullous pemphigoid from January 2000 to the and of 2006. Medical records from our Department were used in the study. Fifteen cases of pemphigus vulgaris and 18 cases of bullous pemphigoid were diagnosed based on clinical presentation, histopathologic analysis, direct and indirect immunofluorescence and desmogleins. Fifteen patients were hospitalized for pemphigus vulgaris (10 female and 5 male), and 18 patients for bullous pemphigoid (9 female and 9 male). Data on age and gender, habits, lesion localization, onset of symptoms and therapy for both diseases were analyzed.

Results

Thirty-three patients were included in our study, 15 with pemphigus vulgaris and 18 with bullous pemphigoid (Tables 2 and 3). Study results showed pemphigus

Table 3. The additional parameters in our patients with pemphigus and pemphigoid

	Pemphigus vulgaris	Bullous pemphigoid
Duration from diagnose to treatment	10 days to 2 years	3 days to 2 years
Primary localization	Oral cavity 6/15 (40%) Skin 4/15 (27%) Both 5/15 (33%)	Oral cavity 1/18 (5%) Skin 15/18 (83%) Both 2/18 (11%)
The most common comorbidities	Diabetes 4/15 (27%) Hypertension 2/15 (13%)	Diabetes 7/18 (39%) Hipertension 4/18 (22%)
Extensive skin lesions	6/15 (40%)	11/18 (61%)
Sistemic therapy	Corticosteroids 14/15 (93%) Immunosuppressants 10/15 (67%)	Corticosteroids 17/18 (94%) Immunosuppressants 8/18(44%)

vulgaris to predominantly occur between the age of 50 and 70 (46.6%), while bullous pemphigoid primarily affected elderly population, between the age of 70 and 95 (83.3%) (Table 2).

Pemphigus vulgaris predominantly affected women (66.6%), whereas no sex predilection was recorded in patients with bullous pemphigoid. Skin lesions were associated with oral lesions in the majority of patients with pemphigus vulgaris (86.6%).

Some patients with pemphigus and those with pemphigoid had exclusively cutaneous lesions, oral lesions or a combination of both. Oral lesions preceded the onset of skin lesions in 40% of our patients with pemphigus vulgaris, and only rarely in those with pemphigoid (1/18) (Table 3).

According to our results, oral erosions were rarely associated with bullous pemphigoid (16.6%). Almost all patients with either disease were treated with systemic corticosteroid therapy and about one half received immunosuppressive therapy in adjunct to the corresponding local management.

Discussion

The pemphigus family is comprised of autoimmune blistering disorders characterized by the appearance of intraepidermal acantholytic blisters and erosions on the skin and/or mucous membranes, while the pemphigoid family includes several bullous disorders characterized by subepidermal blisters and erosions on the erythematous surface, potentially associated with oral lesions[14,15].

Epidemiologically, pemphigus vulgaris is associated with a higher morbidity and mortality rate than bullous pemphigoid. It is a rare, potentially life-threatening disorder affecting mainly adults, predominantly in the fifth and the sixth decade. It affects both men and women, with a presumed female to male incidence ratio of 1.6 to 1[2]. There are contradictory data on gender predilection in pemphigus vulgaris; some authors claim an increased incidence in women (1.7 to 1 ratio)[2]. Other data support an inverse proportion (e.g., a male to female ratio of 1.8 to 1 in Germany)[1]. Similarly, in our study, pemphigus vulgaris predominantly affected females (a 2 to 1 ratio), while no sex predilection was observed in patients with bullous pemphigoid.

The clinical course of pemphigus vulgaris and bullous pemphigoid frequently shows characteristic transitions between disease stages or remissions and recurrences, predominantly with a chronic course[2,13,16]. Bullous pemphigoid usually affects somewhat older population than pemphigus vulgaris, predominantly over 60 years[2]. According to the literature, the average age at onset of bullous pemphigoid is 76 years[1].

According to the results obtained, pemphigus vulgaris predominantly affected individuals aged 50 to 70 (46.6%), while bullous pemphigoid primarily affected older people, aged 70 to 95 (83.3%), which is consistent with literature data.

Some patients with pemphigus and pemphigoid have oral mucosal lesions that accompany skin lesions, although isolated cutaneous or mucosal lesions are also possible. The diseases can commence with either oral or skin lesions. According to literature data, oral lesions usually precede the onset of skin lesions by four months in 68% of patients with pemphigus[2]. In our study, oral lesions preceded the onset of skin lesions in 40% of patients with pemphigus vulgaris. Literature reports describe a lower incidence of oral mucosa lesions, found in approximately 50% of patients[1].

Some authors found oral lesions in patients with bullous pemphigoid to be relatively common (40%), usually appearing after cutaneous eruptions[2]. Oral erosions usually affect buccal mucous membranes, as well as the palate, gingiva, tongue, and lower lip. Gingiva can be affected as well, resulting in erosions and/or desquamating gingivitis in 16% of patients with bullous pemphigoid[2]. Considering the incidence of mucosal lesions in bullous pemphigoid, it is significant that oral or conjunctival erosions occur in 20%-30% of the affected patients; according to some authors, oral lesions can appear in as many as 90% of patients[2].

The results obtained in the present study showed the cutaneous lesions to be associated with oral lesions in the majority of patients with pemphigus vulgaris (86.6%). Some patients presented with skin lesions only or oral lesions only, whereas some developed a combination of both. According to some authors, pemphigus commences with lesions in the oral cavity in 50% of patients[1], while others report on the oral origin of pemphigus in 68% of patients[2]**;** our study revealed a lower incidence of oral origin, recorded in 40% of patients. Literature reports describe oral manifestations in 40% of bullous pemphigoid patients[2]. Our results showed a lower incidence, as the manifestations involving oral mucosa were found in only 16.6% of patients with bullous pemphigoid.

Timely recognition of bullous diseases may occasionally pose a problem in clinical practice, thus the skin and oral lesions being diagnosed in an advanced stage

when they have already spread over. In our study, it took months to up to 2 years to recognize the disorder and make an accurate diagnosis in some patients, i.e. until they were admitted to our Department. This indicates the necessity of timely recognition as an imperative for appropriate treatment and future prognosis. The administration of appropriate therapy, predominantly systemic corticosteroids and immunosuppressants, is crucial considering the frequently affected mucosal surfaces, oral mucosa in particular. The majority of our patients were treated with topical and systemic corticosteroids and half of them by adjunct immunosuppressive therapy. Local therapy is especially important in the management of pemphigus, in order to control and prevent secondary infections and to stimulate epithelialization. Therefore, local corticosteroids are usually applied to smaller, non-eroded lesions. Eroded lesions are treated by antiseptics and antibiotics. Application of oral care products and local anesthetic solutions topically to oral cavity lesions is important to improve epithelialization.

The course and prognosis of pemphigus are unpredictable. Before the advent of systemic corticosteroid therapy, lethal outcome occurred 1-3 years of the diagnosis. Corticosteroid therapy has significantly prolonged life expectancy of these patients; lethal outcome occurs in only 5%-15% of cases[1,5-8]. However, the main cause of death in patients with bullous pemphigoid nowadays results from complications of corticosteroid or immunosuppressive therapy in addition to comorbidities (diabetes mellitus, osteoporosis, and hypertension)[12].

The management of patients with pemphigus and pemphigoid with oral lesions greatly relies on multidisciplinary care, including dermatologists and oral pathologists as well as internists, endocrinologists, ENT specialists, ophthalmologists, and others. This collaboration is often necessary for better prognosis of the disease.

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Sažetak

PROMJENE NA SLUZNICI USNE ŠUPLJINE U BOLESNIKA S VULGARNIM PEMFIGUSOM I BULOZNIM PEMFIGOIDOM

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Ova studija obuhvatila je 33 bolesnika hospitaliziranih u Klinici za kožne i spolne bolesti Kliničke bolnice "Sestre milosrdnice". Svrha ove studije bila je usporedba podataka o dobi i spolu, navikama, lokalizaciji kožnih promjena, pojavi simptoma i terapiji u bolesnika s vulgarnim pemfigusom i onih koji boluju od buloznog pemfigoida. Dijagnosticirano je 15 bolesnika s vulgarnim pemfigusom i 18 bolesnika s buloznim pemfigoidom temeljeno na kliničkoj slici, patohistološkoj analizi, direktnoj i indirektnoj imunofluorescenciji, Tzanckovom testu i dezmogleinima. Dobiveni rezultati upućuju na porast učestalosti vulgarnog pemfigusa u bolesnika srednje dobi (46,6% bolesniika između 50 i 70 godina), dok bulozni pemfigoid zahvaća bolesnike starije životne dobi (83,3% bolesnika bilo je starije od 70 godina). Vulgarni pemfigus zahvaća značajnije više žene (66,6%) nego muškarce (33,4%), dok je jednak broj žena i muškaraca bio zahvaćen buloznim pemfigoidom. Bolesnici s objema bolestima su imali promjene kože i/ili sluznice usne šupljine. Većina bolesnika s vulgarnim pemfigusom je imala promjene kože s promjenama na sluznici usne šupljine (86,6%), pri čemu su u 40% slučajeva promjene na sluznici usne šupljine prethodile kožnim promjenama. U samo 16,6% bolesnika s buloznim pemfigoidom su nađene erozije na sluznici usne šupljine. Većina bolesnika je dobivala sistemsku i lokalnu kortikosteroidnu terapiju uz dodatnu sistemsku imunosuprimirajuću terapiju. Pravodobno prepoznavanje vulgarnog pemfigusa i buloznog pemfigoida te odgovarajuća terapija važni su za ishod ovih autoimunih buloznih bolesti.

Ključne riječi: *Pemfigus – dijagnostika; Pemfigus – terapija; Pemfigoid bulozni – dijagnostika; Pemfigoid bulozni – terapija; Autoimune bolesti – terapija lijekovima; Kožne bolesti, vezikulobulozne – terapija lijekovima; Koža – patologija*