

Evaluation of Pemphigus Cases Involving Oral Mucosa

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Abstract

Purpose: Pemphigus, defines a group of disorders in autoimmune etiology which could be life-threatening and clinical manifestations are mainly epithelial blistering affecting cutaneous and/or mucosal surfaces including oral mucosa. The aim of our study is to evaluate the clinical appearance of pemphigus with oral involvement by reported 15 pemphigus cases.

Material and Methods: This retrospective study of 15 cases of pemphigus obtained over a period of 7 years from 2006 to 2013 in Istanbul University, Dentistry Faculty, Oral Medicine and Surgery Department was designed.

Results: Age distribution of pemphigus was from 15 to 59 years with an average age of 41.3 years. Of the 15 patients, the male:female ratio was 1:2.75 (4 male, 11 female). The most common clinical various of pemphigus was pemphigus vulgaris, diagnosed in all patients. The buccal mucosa (34.3%) was the most commonly affected site followed by tongue (20%), gingiva (17.1%), palate (11.4%), lips (11.4%) and floor of mouth (5.7%).

Conclusion: Our explanation of this conclusion, while speculative, is that socioeconomic situation related stress in males and hormonal changes like pregnancy and menostasis in females; systemic disease and using drugs; dental trauma and bruxism could be responsible for flare up in the disease.

Key words: Pemphigus, Oral lesions, Diagnosis, Dental trauma

Introduction

Pemphigus, defines a group of disorders in autoimmune etiology which could be life-threatening and clinical manifestations are mainly epithelial blistering affecting cutaneous and/or mucosal surfaces including mucosa of the mouth, nose, conjunctiva, genitals, esophagus, pharynx and larynx [1-3].

The disease shows variable incidence, prevalence, sex and age distributions and season of onset [2]. Pemphigus affects 0.1-0.5/ 100.000 patients per year [1-4]. It is insignificantly predominant in women and generally appears in adults during the fiftieth and sixtieth years of life. Juvenile cases have also been rarely reported [3,5,6]. Although the certain pathogenesis of pemphigus is not totally understood, high frequency of pemphigus in some races, especially Ashkenazi Jews and Mediterranean and South Asian origin, has been shown to be actually related to HLA- II genes [2,3,7].

Additionally the genetic background, environmental factors, such as drugs, foods, chemicals, viruses, physical agents and stress, have been admitted as triggers of pemphigus [2,3,7]. In skin lesions and peripheral blood mononuclear cells of patients with pemphigus, Herpes virus DNA has been detected by PCR. A higher number of pregnant patients developed pemphigus, suggesting that estrogens precipitate the disease process [3].

In some cases, pemphigus can be caused by certain drugs. A wide variety of drugs have been involved in the inception of drug-induced pemphigus, such as thiol drugs (captopril, penicillamine, enalapril) and non-thiol drugs (cephalosporins, penicillins, piroxicam). The clinical, histological and immunofluorescence findings are same as idiopathic pemphigus [3].

Pemphigus may be companion to other autoimmune disorders such as rheumatoid arthritis, lupus erythematosus,

myasthenia gravis or pernicious anemia [7].

A few variants of pemphigus defined with different autoantibody profiles and clinical presentations. The most common form is Pemphigus Vulgaris (PV) and frequently involves the mouth which approximately 75 % of pemphigus cases [4,8,9]. Pemphigus vegetans, pemphigus foliaceus/seborrhoicus (pemphigus superficialis), pemphigus erythematosus, pemphigus paraneoplasticus and pemphigus juvenilis are the other variants of pemphigus [4].

The critical importance of PV is typically running a chronic course, nearly constantly causing blisters, ulcers and erosions on the oral mucosa and skin. PV, the most common variant, shows oral lesions as an initial symptom in 50 % of cases. Blisters, which speedily lead to painful chronic erosions and ulcers, are usually seen in the buccal mucosa, palate, ventrum of tongue and lips [10]. The cutaneous lesions begin as flabby blisters on skin [7]. In PV, Ig G serum antibodies are directed against a cadherin-type cell adhesion molecule which is called desmoglein 3 (Dsg 3) and located in stratified squamous epithelium that binds keratinocytes to each other. The oral mucosa expresses high concentration of the antigens affected PV-oral keratinocytes express primarily Dsg 3, and thus oral lesions are occurred at an early stage but once Dsg 1 antibodies are evident, the lesions spread to involve other mucosa and skin [7,11].

Addition to PV, the other important variant involving the mouth is Paraneoplastic Pemphigus (PNP), commonly associated with lymphoproliferative disease, though one case with oral squamous cell carcinoma has been reported [1,3]. Pemphigus vegetans (P veg) is rarely seen clinical variant accounting for 1-2 % of all pemphigus cases. Vegetating plaques especially localized to the flexural areas are characterized in P veg. [12].

Diagnosis of pemphigus is depended on clinical features,

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histologic findings and immunologic tests. An intraepidermal blister is seen in the histopathology examination of the lesions, loss of intercellular attachments resulting in acantholysis, and also a dermal inflammatory infiltration in a mild manner could be detected. Direct Immunofluorescence (DIF) on perilesional skin biopsy reveals antibody (Ig G) deposition in the intercellular spaces of the keratinocytes [3,4]. In all forms of pemphigus, cytological smears obtained by scraping the base and the roof of a blister reveal the presence of acantholytic epidermal cells, i.e., Tzanck cells [3,7,10].

The current treatment for pemphigus is topical and systemic corticosteroids, immunosuppressive drugs, anti-inflammatory drugs, immunomodulatory procedure and biological therapy [3,13-15].

Actually blisters on the oral mucosa in 87 % of cases are the initial symptoms of the disease and dental professionals may play a critical role in diagnosing of this disease. The aim of our study is to evaluate the clinical appearance of pemphigus with oral involvement by reported 15 pemphigus cases.

Material and Methods

This retrospective study of 15 cases of pemphigus obtained over a period of 7 years from 2006 to 2013 in Istanbul University, Dentistry Faculty, Oral Medicine and Surgery Department was designed.

Patients' age and sex data, the clinical and pharmacological treatment history, the clinical presentation (presence or absence of ulceration), symptoms, location of lesions within the oral cavity, duration and their extent within the mouth were documented in all cases. The involvement of other mucosal membranes and/or skin was also documented.

Histopathology examination with or without direct immunofluorescence was the method of diagnosis in all cases. The specimen sections were stained with hematoxylin-eosin, and the histological characteristics were evaluated. Direct Immunofluorescence (DIF) studies were carried out in nine cases.

Finally, the treatment provided in each patient was recorded, along with its effect in reducing the lesions.

Results

During the study period (2006-2013), totally, 15 just diagnosed cases of pemphigus were evaluated.

Age distribution of pemphigus was from 15 to 59 years with an average age of 41.3 years. Mean age of presentation in male was 42.7 years and in female was 40.81 years. The majority of the cases were in the 31-50 year-age group (66.6 %). Of the 15 patients, the male:female ratio was 1:2.75 (4 male, 11 female). Pemphigus vulgaris, which is the most common variant of disease, was diagnosed in all patients.

The duration of oral lesions was taken as the period between the time when patient had first noticed lesion and attended to our clinic. The mean duration of pemphigus was 5.83 (range between 10 days-36 months) months. In our case series, pemphigus began with generalized lesions (73.3 %) rather than localized lesions (26.7 %). As the first onset of the disease, in about 86.6 % of cases, the oral cavity was the primary site involvement. Two of the cases presented skin

lesions initially. All cases presented as ulcers or erosions with pain and burning sensation as the presenting oral symptoms (Table 1).

The most commonly affected site was buccal mucosa (34.3 %), followed by tongue (20 %), gingiva (17.1 %) (Figure 1), palate (11.4 %), lips (11.4 %) (Figure 2) and floor of mouth (5.7 %) (Figure 3).

Histopathology examination with or without direct immunofluorescence was the method of diagnosis in all cases. DIF was performed in 9 cases which were not diagnosed definitely by histopathology examination. All DIF cases showed fluorescence with Ig G and C₃.

Our patients were received a detailed medical history and systemic diseases, used drugs were noted. In all patients, oral hygiene instructions were given and the situations creating local trauma (pointed tubercle, sharp-edged dentures, fillings etc.) have been eliminated and checked in every recall. All patients were prescribed clobetasol propionate % 0.05, dexpantenol % 5 and antifungal rinse solution for topical use against fungal infections as prophylaxis. All patients were referred to Istanbul University, Medical Faculty, Department of Dermatology for dermatological consultation and 4 hospitalized patients and 11 outpatients had been treated with systemic corticosteroids.

Discussion

This paper reports the clinical course of 15 pemphigus vulgaris patients who complained oral lesions and discomfort. The results of this study showed that, in Turkey, there is a moderately high incidence of pemphigus compared with in other countries. The mean annual incidence of pemphigus 100.000 inhabitants ranges from 0.08 to 1.62 in earlier epidemiologic reports from Turkey that comply with the present series [16].

In the literature of last ten years, there was a slightly female preponderance observed in most of the large series around different parts of the world like North Africa, Europe,

Table 1. Gender, age distribution and clinical features of pemphigus.

	Gender	Age	Localization	Dermal involvement	Duration	Dental trauma
1	M	41	B	+ *	4 m	+
2	F	35	T	-	7 d	+
3	F	31	B,T	-	2 y	+
4	M	42	B,G,L	-	1 m	+
5	F	48	B,T,L	-	4 m	+
6	F	41	B,T,G	+ *	1 m	+
7	F	57	F	+	10 d	-
8	F	59	B,T,P	-	4 m	+
9	M	33	B,T,G,P	-	2.5 m	+
10	F	43	B,T,F	-	3 m	+
11	F	53	B	-	3 y	+
12	F	35	B,G,L	-	1 m	+
13	F	32	B,G,P	-	4 m	+
14	F	15	G,P	+	3 m	-
15	M	55	B,L	-	6 m	+

B: Buccal mucosa, T: Tongue, G: Gingiva, L: Lips, P: Palate, F: Floor of mouth

*Presented skin lesions initially
d: days, m: months, y: years

and in some East Asian countries [2,4,17-21]. In none of these series the female/male ratio was over 2.25. The ratio was calculated as 2.75/1 in this paper which is slightly higher from the previous works around the world and from the Turkish study by Uzun et al. [16] since limited numbers of patients were evaluated the results may not be compared with the epidemiologic data. We suggest that the incidence of the disease to be higher in women occurs because of hormonal differences as suggested by previous studies [2,4,17-21].

The majority of affected patients were aged between 40

and 60 years at the inception, and the condition has been infrequently recorded in individuals younger than 30 or after 60 years [2,10,16,18,22]. The average age of onset was 41.3 years in our patient group. Among 15 pemphigus cases, 6 (40 %) were younger than 40 years. Although only 15 patients were included in this study, our group seems younger than epidemiologic study results. There are some reports in younger populations similar with our group [2,9] and especially a Turkish study including 148 patients indicated mean age as 43 [16], whereas reports from Kuwait [23] and Pakistan [24] does not support this findings.

It was noteworthy that the number of female patients younger than 40 years had been five. Two of these patients reported that initial lesions had appeared during their pregnancy. This supports literature about initiating or aggravation of pemphigus lesions by pregnancy [25-27]. Other gingival lesions seen in pregnancy is also known and related hormonal changes.

PV is the most prevalent subtype as confirmed by the previous reports [4,8,9,28]. Also P. erythematosus and P.foliaceus was found in higher incidences in a group of studies with limited number of patients [17,29-32]. Our group was consisting of only PV patients. It is associated that pemphigus vulgaris is the most common variant of pemphigus and symptoms are usually seen in oral mucosa.

Histopathologically, the lesions showed intraepidermal blister, loss of intercellular attachments resulting in acantholysis, and dermal inflammatory infiltrate. Direct Immunofluorescence (DIF) on the patient's oral mucosa reveals antibody (Ig G) deposition in the intercellular spaces of the keratinocytes. These results are consistent with the literature [5,6,17,19].

The oral lesions are generally multiple, as in the present study. The most commonly affected site was buccal mucosa (34.3%) followed by tongue (20%), gingiva (17.1%), palate (11.4%), lips (11.4%) and floor of mouth (5.7%). Any localization of oral mucosa may be affected, however, sites of trauma such as buccal mucosa, gingiva and palate are especially affected [22,33,34]. In the present series, lesions in buccal mucosa were usually on the line of linea alba which is the most frequent area where dental traumas are detected. Dental trauma induced lesions were detected in 13 patients and localized either in buccal mucosa and/or in tongue.



Figure 1. Pemphigus lesions widespread in gingiva.



Figure 2. Pemphigus in labial mucosa.

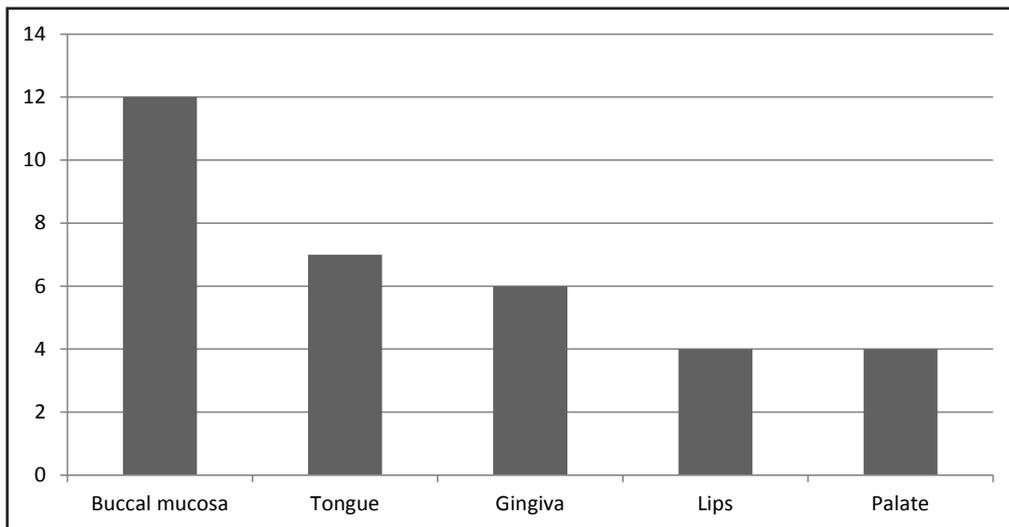


Figure 3. Affected sites of oral mucosa.

Oral lesions of pemphigus are initially vesiculobullous, but they readily rupture to form ulcers, new bullae developing as the older ones rupture and ulcerate. Ulcers are initially red with a whitish surround but, as infection supervenes, they develop a yellowish, slough and heal slowly but rarely with scarring. Gingival lesions usually comprise severe desquamative or erosive gingivitis [22].

In summary, in previous studies etiologic factors were mainly attributed to hormonal disturbances and in conjunction with this view effects of hot weather in Thailand, and

menostasis period of women and in some genetic effects were suggested [1,7,19,22,27].

Turkey is of particular importance for further epidemiological investigations, including HLA analysis, because of its heterogeneous population composed of different ethnic groups. Our explanation of this conclusion, while speculative, is that socioeconomic situation related stress in males and hormonal changes like pregnancy and menostasis in females; systemic disease and using drugs; dental trauma and bruxism could be responsible for flare up in the disease.

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