Dermatology Practical & Conceptual

Evaluation of the Quality of Life and the Demographic and Clinical Characteristics of Patients With Pemphigus With Oral Mucosal İnvolvement: A Multicenter Observational Study

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ABSTRACT **Introduction:** Pemphigus vulgaris (PV) is an autoimmune disease primarily affecting the oral mucosa.

Objectives: This study aimed to determine the demographic, clinical and treatment characteristics of PV patients with oral mucosal involvement and to assess the impact on their quality of life.

Methods: We conducted a prospective observational study among 106 patients diagnosed with PV and presenting oral mucosal involvement. Demographic data, clinical and treatment characteristics, and quality of life questionnaires were recorded.

Results: The study included 106 patients, 55 (51.89%) were male and there was a predominance of the mucocutaneous subtype in 83 individuals (78.38%). Oral mucosa was the initial site of manifestation in 44 patients (41.51%). Bilateral buccal mucosa was the most frequently affected site. The predominant symptom reported was a burning sensation, noted in 91 patients (85.85%). Oral mucosal examination revealed erosions in 85.85% of the patients. Systemic steroids were the most commonly administered treatment, and rituximab was used in 18 patients (16.98%). A positive and significant correlation was found between pemphigus severity and Oral Health Impact Profile-14, Dermatology Life Quality Index and Dermatological Quality of Life Scale scores ($P < 0.05$). The presence of superficial ulcers, flaccid bullae, lesion diameter ≥1 cm, and >10 lesions were factors that markedly diminished quality of life. Complete response to treatment was noted in all patients administered rituximab.

Conclusions: The most common area of involvement was bilateral buccal mucosa, and the severity of PV closely correlated with a decline in quality of life measures. These results highlight the need for careful clinical oversight of PV, taking into account its effects on patients quality of life.

Introduction

Pemphigus vulgaris (PV) is an autoimmune disease characterized by intraepithelial bullae and erosions in the skin and mucosa [1]. The disease is characterized by painful erosions, irregularly circumscribed ulcers, and small vesicles and flaccid bullae, especially in the buccal mucosa and gingiva [2]. Yaylı et al in a 1-year prospective study that evaluated patients with pemphigus in Turkey found that the annual incidence of pemphigus was 4.7/1 million, and PV was determined as the most common clinical subtype (87.3%) [3]. The presence of painful lesions disrupt oral intake depending on their location and markedly impairs the quality of life for patients. In the existing literature, research on the quality of life in individuals with pemphigus is scarce, and it often evaluate pemphigus with other diseases within the pemphigus spectrum [4-7]. Only Ghodsi et al. have specifically evaluated the quality of life of patients with PV [7]. However, in this study a specialized scale designed specifically for patients with oral manifestations of PV was not used [7]. In Turkey, two studies have evaluated the quality of life of patients with autoimmune bullous diseases in general but no study has specifically evaluated the quality of life of patients with PV [8,9].

Objectives

This multicenter study aimed to determine the demographic and clinical and treatment characteristics as well as the quality of life of patients with PV with oral mucosal involvement in Turkey and contribute to the epidemiological data with a large patient series.

Methods

In our prospective observational study, patients with PV with newly diagnosed oral mucosal involvement in Skin and Venereal Diseases clinics of 16 tertiary care institutions from different regions of Turkey were consecutively included between February 2020 and August 2021. The diagnosis of the patients was confirmed using clinical features, histopathology, direct immunofluorescence, and ELISA methods. Diagnostic criteria of the European Academy of Dermatology and Venereology guideline were applied in the diagnosis of PV [10]. The study was approved by the Ethics Committee of the University of Health Sciences, Istanbul Training and Research Hospital on 21/02/2020 (decision number: 2202). Sociodemographic and clinical and treatment characteristics of the patients were recorded and quality of life scales were applied. The following data were collected: (1) Demographic characteristics of the patients (age, gender, education level, income level, marital status, occupation, and body mass index), personal and family history, and personal history of illness, smoking, and alcohol use and (2) variables related to sociodemographic and clinical characteristics of the patients regarding pemphigus disease (age of onset of PV, duration of disease, delay in diagnosis, history of pemphigus in family and/or relatives, initial localization, clinical type, surface area involved, area of involvement in the oral mucosa, and

symptoms and findings in the oral mucosa), oral mucosal lesion type, number, diameter, disease severity, and disease activity and variables related to treatment and prognosis.

When assessing the severity of the disease, the Pemphigus Disease Severity Index (PDAI), a Pemphigus-Specific Severity Assessment scale developed in 2009 by Rosenbach et al, scored separately according to the number and diameter of lesions on the localized skin (12 anatomical regions), mucosal surface (12 anatomical regions), and scalp was used—250 points (120 points for the skin, 120 points for the mucosa, 10 points for the scalp) indicate disease activity and 13 points (12 points for the skin and 1 point for the scalp) indicate disease damage [11]. While evaluating the quality of life, the Oral Health Impact Profile-14 (OHIP14-TR) scale, Dermatology Life Quality Index (DLQI), and Dermatological Quality of Life Scale (DQLS) were used.

Oral Health Impact Profile Scale

The Oral Health Impact Profile (OHIP), which was first developed in Australia and consisted of 49 items, has been shortened due to its length, which made it time-consuming [12-14]. Basol et al, in 2014, developed and evaluated the Turkish OHIP14-TR, and its validity and reliability were demonstrated. The total scale score range is 0–56 [15].

Dermatology Life Quality Index

The DLQI scale, first created by Finlay and Khan in 1994, is an easy-to-use scale in practice and has been shown to be valid and reliable in Turkey [16,17].

Dermatological Quality of Life Scale

There are 11 questions in the DQLS developed by Gurel et al, and the total score range is 0–44 [18].

Statistical analyses were performed with the SPSS version 23.0 program. The conformity of the variables to the normal distribution was examined by histogram graphs and Kolmogorov-Smirnov/Shapiro-Wilk test. Mean, standard deviation, and median values were used when presenting descriptive analyses. The Mann–Whitney U test was used when evaluating non-normally distributed (nonparametric) variables between two groups, while the Kruskal–Wallis test was used when evaluating between more than two groups. The Bonferroni multiple comparison tests were used while investigating the reason for the significant difference between the groups. While presenting the categorical variables, the frequency and percentage values of the variables were used, and the analysis of the categorical variables was carried out with the chi-square (exact) test. The Spearman correlation test was used to evaluate the relationships between quantitative variables. Cases with a P value below 0.05 were considered statistically significant results.

Results

A total of 106 patients with PV with newly diagnosed oral mucosal involvement in 16 different dermatology clinics from different regions of Turkey were included in this study.

Demographic and Clinical Characteristics of the Patients

The mean age of all the patients was 50.06 ± 14.88 and 51.89% (N = 55) were males. While 34.91% were primary school graduates, 16.04% were university graduates. Body mass index was found to be 26.88 ± 4.04 (26.77). The most common personal disease history was diabetes (17.92%), followed by hypertension and coronary artery disease (Table 1). Of the patients, 19.81% were active smokers and 9.43% were regular alcohol users. Among the autoimmune diseases, Hashimoto thyroiditis was found in four patients, rheumatoid arthritis in two, Sjögren syndrome in one, and Graves in one.

Clinical Features of Pemphigus Disease

The mean age of pemphigus onset was 49.45 ± 14.98 years, the mean duration of illness was 7.59 ± 8.57 months, and the mean delay in diagnosis was 4.39 ± 5.26 months. There was no family history of pemphigus in 99.06% of the patients.

Mucocutaneous subtype was found in 78.38% of the patients. While the initial localization of 41.51% of the patients was only the oral mucosa, 7.55% had only the skin, 40.57% had the oral mucosa and skin simultaneously, and 7.55% had the first lesions on the skin. The body surface area involved was localized in 50.94% of the patients.

The involvement of the oral mucosa with PV in 63.21% of the patients was in the bilateral buccal mucosa, followed by the lower lip (46.23%) and the tongue (45.28%). In 98.11% of the patients, symptoms were present in the oral mucosa and most commonly (85.85%) accompanied by burning; 77.36% had pain and 0.94% had difficulty swallowing. Oral mucosal examination revealed erosions in 85.85% of the patients, superficial ulcers in the oral mucosa in 66.04%, small vesicles in 12.26%, and flaccid bullae in 10.38%. Of the patients, 57.55% had lesion(s) 1 cm or more in diameter. While the mean PDAI was 27.58 ± 21.28, the mean damage score was 0.89 ± 3.01 (Table 1). The mean PDAI mucosal score, which indicates the severity of the disease, was 15.19 ± 13.68 and the PDAI oral mucosa mean score was 13.85 ± 12.17.

Treatment Features

Systemic steroids were the most commonly administered treatment (N = 88, 83.02%). This was followed by topical steroid (N = 42, 39.62%) and rituximab (RTX) (N = 18, 16.98%) treatments. Other agents used in the treatment

Table 1. Sociodemographic characteristics and disease-related features of the patients.

Characteristics	Mean ± SD or N (%)
Age, $\bar{x}$ ± s.s. (median) (year)	50,06 ± 14.88 (52.00)
Gender	
Female	51 (48.11)
Male	55 (51.89)
Body mass index ($\bar{x}$ ± s.s. (median)	26.88 ± 4.04 (26.77)
Comorbidities	
Hypertension	17 (16.04)
Diabetes	19 (17.92)
Dyslipidemia	4 (3.77)
Thyroid dysfunction	6 (5.66)
Coronary artery disease	12 (11.32)
Liver diseases	2 (1.89)
Others (neurological, rheumatological, chronic obstructive pulmonary diseases)	6 (5.66)
Duration of disease (months)	7.59 ± 8.57 (4.00)
Delay in diagnosis (months)	4.39 ± 5.26 (3.00)
Age-onset of pemphigus $\bar{x}$ ± *s.s.* (median)	49.45 ± 14.98 (51.00)
Family history of pemphigus	1 (0.94)
Retained body surface area	
Localized	57 (53.77)
Generalized	49 (46.23)
Clinical subtype	
Mucocutaneous	83 (78.30)
Mucosal	23 (21.70)
Onset location	
Oral mucosa	44 (41.51)
Skin	8 (7.55)
Oral mucosa and skin (both)	43 (40.57)
Scalp	1 (0.94)
Nasal mucosa	2 (1.89)
Oral mucosa & skin & scalp	2 (1.89)
Oral nasal anogenital	5 (4.72)
Oral nasal skin	1 (0.94)
Involvement site in the oral mucosa	
Bilateral buccal mucosa	67 (63.21)
Hard palate	50 (47.17)
Lower lip	49 (46.23)
Tongue	48 (45.28)
Gingiva	43 (40.57)
Soft palate	40 (37.74)
Upper lip	33 (31.13)
Floor of mouth	29 (27.36)
Oropharynx	22 (20.75)
Unilateral buccal mucosa	18 (16.98)
Symptom in the oral mucosa	104 (98.11)
Burning	91 (85.85)
Pain	82 (77.36)
Dysphagia	1 (0.94)
Clinical findings in the oral mucosa	
Erosions	91 (85.85)
Superficial ulcer	70 (66.04)
Small vesicles	13 (12.26)
Flaccid bullae	11 (10.38)

Table 1. Sociodemographic characteristics and disease-related features of the patients. *(continued)*

Characteristics	Mean ± SD or N (%)
Diameter of the lesion in the oral mucosa	
< 1 cm	45 (42.45)
≥ 1 cm	61 (57.55)
PDAI, $\bar{x}$ ± s.s. (median)	27.58 ± 21.28 (20.50)
Damage score	0.89 ± 3.01

PDAI = Pemphigus disease area index.

Table 2. The relationship between pemphigus severity and quality of life scale scores.

		OHIP-14-TR	DLQI	DQLS
PDAI	r	0.193	0.494	0.232
	P	0.047	< 0.000	0.017
PDAI mucosa	r	0.207	0.208	0.016
	P	0.033	0.032	0.870
PDAI oral mucosa	r	0.194	0.184	0.016
	P	0.046	0.059	0.869

DLQI = Dermatology Life Quality Index; DQLS = Dermatological Quality of Life Scale; OHIP-14-TR: Oral Health Impact Profile-14-TR scale; PDAI = Pemphigus disease area index.

were azathioprine (N = 16, 15.09%), intravenous immunoglobulin (IVIG) (N = 5, 4.72%), and mycophenolate mofetil (N = 5, 4.72%). Of the patients, 78.3% received inpatient treatment.

Evaluation of Quality of Life Scales

The mean DLQI of the patients was 11.6 ± 9.01, the DQLS mean 19.98 ± 11.34, and the OHIP14-TR mean was 27.02 ± 13.21. A positive and significant correlation was found between pemphigus severity and OHIP14-TR, DLQI, and DQLS scores ($P < 0.05$). There was a positive and significant relationship between PDAI mucosa and OHIP14-TR and DLQI, as well as between PDAI oral mucosa and OHIP14-TR. While there was a moderately strong relationship between PDAI and DLQI, other significant relationships were of low strength (Table 2).

OHIP14-TR and DLQI scores were significantly higher in patients with superficial ulcers in the oral mucosa than those without, and this was statistically significant ($P < 0.05$). OHIP14-TR and DQLS scores were significantly higher in patients with flaccid bullae in the oral mucosa than those without and were statistically significant ($P < 0.05$). Those with more than 10 lesions in the oral mucosa had a significantly higher DQLS score. Again, the OHIP14-TR score was found to be significantly higher in patients with a lesion diameter of 1 cm and above in the oral mucosa (Table 3).

In the disease progressing with mucocutaneous involvement, the mean scores of DLQI and DQLS (13.24 ± 9.06 and 21.37 ± 11.30, respectively) were statistically significantly higher than those with only mucosal involvement ($P < 0.001$ and $P = 0.010$, respectively). No statistically significant difference was observed between the mean scores of OHIP14-TR (27.70 ± 13.53 and 24.57 ± 11.96, respectively) in the disease progressing with involvement ($P = 0.351$) (Table 4).

Conclusions

PV is an autoimmune disease characterized by the development of autoantibodies against intracellular adhesion proteins in the epidermis and progresses with intraepithelial bullae and erosions in the skin and mucous membranes [1]. Oral mucosal involvement is quite high in the disease [19-21], and has been reported as the most common initial localization in previous studies globally [22,23-25]. In our study, the most prevalent initial presentation was oral mucosal involvement, occurring in 41.51% of the patients, which is consistent with the literature. It is also noted that pemphigus vulgaris may manifest with concurrent cutaneous and oral mucosal involvement which was observed in 40.57% of our study participants [23-25]. Additionally, the onset of the disease can occur in other mucosal areas including nasal, anogenital, conjunctival, as well as the laryngeal and pharyngeal regions. Notably, in our study, nasal mucosal presentation was the initial sign in two individuals. Oral mucosal involvement typically manifests with symptoms such as pain, a burning sensation, and challenges in eating,

Table 3. Comparison of quality of life scale score levels according to oral mucosa.

		OHIP14-TR			P	DLQI			P	DQLS			P
		Mean	Std.	Median		Mean	Std.	Median		Mean	Std.	Median	
Superficial ulcer	Absent	22.53	±13.11	20.00	0.007	9.53	±9.32	7.50	0.035	17.61	±11.44	15.00	0.081
	Present	29.33	±12.75	30.50		12.67	±8.72	12.00		21.20	±11.17	21.00	
Erosions	Absent	27.00	±11.35	29.00	0.989	10.60	±8.10	8.00	0.768	19.87	±11.80	19.00	0.939
	Present	27.02	±13.55	27.00		11.77	±9.18	11.00		20.00	±11.33	19.00	
Small vesicles	Absent	26.42	±13.43	26.00	0.143	11.17	±9.07	10.00	0.113	19.77	±11.37	19.00	0.441
	Present	31.31	±11.05	33.00		14.69	±8.23	16.00		21.46	±11.43	26.00	
Flaccid bullae	Absent	26.07	±13.31	26.00	0.034	11.13	±8.98	10.00	0.077	19.25	±11.44	18.00	0.034
	Present	35.18	±9.33	35.00		15.73	±8.59	15.00		26.27	±8.49	28.00	
Number of lesions	< 3	19.94	±13.50	15.50	0.314	11.38	±10.64	9.00	0.515	18.81	±11.36	19.00	< 0.001
	3–5	28.29	±13.44	29.50		9.65	±7.52	9.00		18.12	±10.76	19.00	
	6–10	22.11	±12.16	20.00		11.37	±8.22	10.00		20.11	±10.33	18.00	
	> 10	34.00	±10.12	34.00		14.24	±10.11	14.00		22.69	±12.85	23.00	
Lesion diameter	< 1 cm	23.18	±12.56	23.00	0.013	11.24	±8.54	10.00	0.883	18.62	±9.82	19.00	0.360
	≥ 1 cm	29.85	±13.06	32.00		11.87	±9.40	11.00		20.98	±12.32	19.00	

DLQI = Dermatology Life Quality Index; DQLS = Dermatological Quality of Life Scale; OHIP-14-TR: Oral Health Impact Profile-14-TR scale.

Table 4. Comparison of quality of life scale score levels according to clinical type.

	Clinical type						P
	Mucocutaneous			Mucosal			
	Mean	Std.	Median	Mean	Std.	Median	
OHIP-14-TR	27.70	±13.53	28.00	24.57	±11.96	26.00	0.351
DLQI	13.24	±9.06	12.00	5.70	±5,89	4.00	< 0.001
DQLS	21.37	±11.30	21.00	14.96	±10.19	13.00	0.010

DLQI = Dermatology Life Quality Index; DQLS = Dermatological Quality of Life Scale; OHIP-14-TR: Oral Health Impact Profile-14-TR scale.

significantly impairing the patients quality of life. We found that OHIP14-TR was significantly affected in patients with superficial ulcers, loose bullae, and lesion diameter of 1 cm and above in the oral mucosa compared to those without. Again, the DYQS score was found to be significantly higher in patients with more than 10 lesions in the oral mucosa.

Godshi et al found burning sensations in 83.1% of patients and pain in 68.4% [7]. This is consistent with our findings in which the most common symptom was burning (n = 91, 85.85%), followed by pain (N = 82, 77.36%), while one patient had swallowing difficulties.

In the literature, several studies from various countries have evaluated the quality of life of patients with autoimmune bullous diseases. The number of patients with PV in these studies ranged from 32 to 43 [4-6]. Only Ghodsi et al have evaluated the quality of life in a study involving 61 patients with a diagnosis of PV [7]. In this context, various scales were used [9,11,26], as there are different quality-of-life scales for diseases with oral mucosal involvement [13,27,28]. In Godshi et al study, the most common clinical subtype was mucocutaneous (72%), followed by mucosal (20%) subtype. Similarly, the most frequently observed subtype in our study was mucocutaneous [7].

Oral mucosal lesions can be observed as painful erosions, irregularly circumscribed ulcers, small vesicles, and loose bullae and bulla residues anywhere in the oral mucosa, often in the buccal mucosa and gingiva [29]. Uzun et al reported that the disease started with persistent oral ulcers and erosion in 101 patients with PV [22]. In our study, 85.85% of the patients had erosions, 66.04% had superficial ulcers in the oral mucosa, 12.26% had small vesicles, and 10.38% had loose bullae. Suliman et al study, the most common site of involvement was found to be the buccal mucosa [2]. In our study, the most common site of oral involvement was the bilateral buccal mucosa with a rate of 63.21%. The severity of oral involvement is variable. Lesions may be localized or widespread. Symptoms may differ depending on the area of involvement and the number of lesions and their diameter, and the impact on quality of life may differ. The lesion diameter was 1 cm and above in 57.55% of the patients.

PV is observed more frequently in individuals aged 40–60 years. In the study conducted by Thansov et al[0] over a 16-year period, the onset of the disease was observed in the 5th or 6th decade of life. Bozdag et alreported the mean age of onset of the disease as 48.3 ± 12.6 years [30,31]. In our study, similar to the literature, the median age at onset was 49.45 ± 14.98 (51.00) years. Pemphigus is observed more frequently in women according to most of the literature [7,23,31]. In a retrospective study by Abdolsamadi et al in which they examined 20 years of data on patients with pemphigus in Tehran, 380 (56.9%) patients with PV with only oral mucosal involvement were females, while 288 (43.1%) were males [32]. In the same study, 146 (62.9%) of 232 patients with oral mucosa and skin involvement were females and 86 (37.1%) were males [32]. In the study conducted by Arduino et al with patients with OPV in Italy, 62.25% of the patients were females [20]. In contrast to the literature, most of the patients in our study were males (n = 55, 51.89%).

The association of pemphigus with various autoimmune diseases has been reported in the literature. In Taiwan, Chiu et al examined the co-existing autoimmune diseases in patients with pemphigus and observed that pemphigus was most commonly accompanied by Sjögren syndrome, psoriasis, systemic lupus erythematosus, and alopecia areata. [33] In our study, Sjögren syndrome accompanied PV in one patient, while four patients had Hashimoto thyroiditis, one had Graves, rheumatoid arthritis, and two had rheumatoid arthritis. Chiu et al found no statistically significant relationship between pemphigus and other diseases such as Graves disease, Hashimoto thyroiditis, pernicious anemia, rheumatoid arthritis, vitiligo, or ankylosing spondylitis [33].

Regarding treatment, systemic steroids, azathioprine, mycophenolate mofetil, methotrexate, chlorambucil, cyclophosphamide, cyclosporine, rituximab, and IVIG can be used for patients with PV. Again, intralesional corticosteroid injections, Orobase or inhaled steroids, and antiseptic mouthwashes are used to treat oral mucosal lesions [34]. In our study, the most frequently used treatment agent was a systemic steroid (N = 88, 83.02%). Fortuna et al used RTX as a combination therapy or alone in the treatment of 10 patients with oral PV and reported a positive response in all the patients [35]. We treated 18 patients with OPV in our study with RTX and obtained a successful response in all of them.

In our study, we determined the sociodemographic, clinical and treatment, and quality of life characteristics of PV disease with oral mucosal involvement were determined. The most common area of involvement was bilateral buccal mucosa, and the quality of life was affected in correlation with the severity of the disease. Notably, a marked decline in quality of life was noted among patients presenting with superficial ulcers, flaccid bullae, lesions measuring 1 cm or more in diameter, and those with more than ten lesions within the oral cavity. A successful response was observed in all the patients that used RTX as a treatment agent.

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