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Endoscopic Findings of Mucosal Pemphigus Vulgaris: Clinical Correlation and Diagnostic Value

Zeynep Karaca Ural[1], Merva Hatun Erkayman[1], Zeynep Utlu[1], Handan Bilen[1], Özgür Yörük[2]

1 Ataturk University, School of Medicine, Department of Dermatology, Erzurum, Turkey
2 Atatürk University, Faculty of Medicine, Department of Ear Nose and Throat, Erzurum, Turkey

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Corresponding Author: Dr. Zeynep Karaca Ural, MD, Ataturk University, School of Medicine, Department of Dermatology, Erzurum, Turkey. ORCID ID: 0000-0002-3333-7027. E-mail: zeynepkaraca.zk90@gmail.com

ABSTRACT

Background: Pemphigus vulgaris (PV) is an autoimmune bullous disease that usually starts on the oral mucosa, but it can affect all mucosal surfaces. There are limited data about endoscopic otorhinolaryngological examination of patients with PV.

Objective: To assess the prevalence of nasal, pharyngeal, and laryngeal involvement in patients with PV and to determine its correlation with clinical symptoms.

Methods: Thirty-four patients with pemphigus vulgaris were questioned for rhinorrhea, epistaxis, hoarseness, and throat pain. All patients' nasal, oral, hypopharyngeal, and laryngeal mucosa were then examined endoscopically by the same otolaryngologist, and mucosal lesion localizations were noted. The association between symptoms and lesion localization was assessed using the chi-squared test.

Results: The study included 34 patients, 14 (41.2%) males and 20 (58.8%) females; 32 (94.1%) patients had oral mucosal involvement. Nasal, hypopharyngeal, and laryngeal involvement were detected in 52.9%, 58.8%, and 55.9% of cases, respectively. Endoscopic examination revealed lesions in areas other than the oral mucosa in 30 patients, with 24 (70.6%) exhibiting symptoms related to these regions. Nasal bleeding was a significant symptom of nasal involvement (P=0.006), whereas nasal obstruction was not (P=0.388). Throat pain was significantly associated with hypopharyngeal involvement (P=0.003), while hoarseness showed marginal significance (P=0.05). No significant association was found between laryngeal or tonsillar involvement and any symptom.

Conclusion: The study demonstrates that a significant proportion of pemphigus vulgaris patients have silent mucosal involvement. This suggests that symptom-based evaluations may be insufficient and that systematic endoscopic screening could play a critical role in PV management.

Introduction

Pemphigus comprises a group of potentially life-threatening autoimmune blistering diseases primarily affecting the skin and mucous membranes [1-3]. The pathogenesis involves IgG autoantibodies targeting desmoglein 3 and/or desmoglein 1, essential desmosomal adhesion proteins in epidermal keratinocytes, leading to intraepithelial blister formation [4]. While pemphigus is a rare disorder, its estimated prevalence is approximately two cases per 1 million individuals annually in Central Europe. Pemphigus vulgaris and pemphigus foliaceus are the two main types, with mucosal involvement typically expected in pemphigus vulgaris but not in pemphigus foliaceus. The oral cavity is the most common site of mucosal lesions and often serves as the initial site of pemphigus vulgaris [5]. However, a simple dermatological examination cannot accurately detect the presence of lesions in the nasal and pharyngolaryngeal cavities. Endoscopic examination is usually performed in patients with symptoms suggestive of nasopharyngolaryngeal lesions. There are limited data on endoscopic otorhinolaryngological examination of patients with pemphigus.

This study aimed to determine the frequency of nasal, pharyngeal, and laryngeal mucosal involvement on endoscopic otorhinolaryngological examination and to investigate the relationship between nasal, oropharyngeal, and laryngeal mucosal involvement and symptoms.

Methods

This cross-sectional study was conducted in the Departments of Dermatology and Otorhinolaryngology at a tertiary university hospital. Ethics committee approval (B.30.2.ATA.0.01.00/717) was obtained before the study's initiation, and all participants provided written informed consent before enrollment.

Study Population

The study included patients diagnosed with pemphigus vulgaris (PV) at the outpatient clinic for autoimmune bullous diseases. The diagnosis of PV was confirmed through histopathological examination and direct immunofluorescence (DIF) microscopy, which demonstrated intraepidermal intercellular deposits of IgG ±C3 antibodies in perilesional skin or mucosa [6]. The exclusion criteria included a history of another autoimmune or mucocutaneous disease, prior head and neck surgery or radiotherapy, and a current upper respiratory tract infection.

Clinical and Endoscopic Examination

All participants underwent a thorough dermatological examination to evaluate mucocutaneous involvement and systemic disease manifestations. Additionally, specific symptoms associated with mucosal involvement beyond the oral cavity were systematically assessed, including: nasal obstruction, nasal bleeding, hoarseness, and chronic sore throat.

Following the symptom assessment, all patients underwent an endoscopic examination of the oral, nasal, hypopharyngeal, and laryngeal mucosa performed by the same otolaryngologist to ensure consistency. Mucous membranes were divided into areas such as the palate, lips, gingiva, buccal mucosa, tonsils, tongue, nose, hypopharynx, and larynx. Each region was independently examined for the presence of pemphigus-related lesions.

Statistical Analysis

Descriptive statistics are presented as frequency (n), percentage (%), median, and interquartile range (25^{th}–75^{th} percentile). The normality of continuous variables was tested using the Kolmogorov-Smirnov test. Normally distributed continuous variables were compared using the independent samples t-test, whereas non-normally distributed data were analyzed using the Mann-Whitney U test.

For categorical variables, associations between mucosal involvement and symptoms were analyzed using the chi-squared test (χ^2 test) or Fisher's exact test, depending on sample size. A p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Power Analysis: A post-hoc power analysis was conducted using a chi-squared test with an assumed medium effect size (Cohen's w = 0.5), an alpha level of 0.05, and a power of 0.8. The minimum required sample size to detect statistically significant differences was 32 patients. Since our study included 34 patients, the sample size was sufficient to detect medium or larger effect sizes.

Results

A total of 34 patients with pemphigus vulgaris, including 14 (41.1%) males and 20 (58.9%) females, were enrolled in the study. The mean age was 52.79 (±17.236), the median disease duration was 5.5 (1.00–12.50) months, and the median time to diagnosis from the onset of symptoms was two (1.00–6.25) months.

Findings of Dermatological Examination

A complete dermatological examination was performed at the time of enrollment, which revealed oral mucosal involvement in 32 (94.1%) patients and cutaneous involvement in 25 (73.5%) patients. Mucocutaneous lesions were found in 23 (67.6%) participants. Nine patients had isolated oral mucosal disease.

Findings of Endoscopic Examination

Nasal, hypopharyngeal, and laryngeal involvement were observed in 52.9%, 58.8%, and 55.9% of the patients, respectively. Three (8.8%) patients showed concurrent involvement of eight mucosal sites, whereas eight (23.6%) patients showed concurrent involvement of six mucosal sites. One patient (2.9%) showed no disease in any area of the mucous membranes. Endoscopic examination revealed mucosal involvement in one of the two patients in whom no mucosal involvement was detected during dermatological examination.

Association between Symptoms and Affected Mucosal Areas

Mucosal involvement in at least one site beyond the oral mucosa was observed in 30 patients (88.2%); among these, 24 patients (70.6%) exhibited at least one symptom associated with this involvement. Table 1 presents the frequency of mucosal symptoms and the distribution of the affected mucosal sites.

The study found that the nasal mucosa was affected in 18 (52.9%) patients, including seven of the 11 patients with nasal obstruction and 13 of the 17 patients with nasal bleeding. All patients with nasal involvement reported at least one symptom of nasal bleeding and/or nasal obstruction. Although no significant association was found with nasal obstruction, a substantial increase in nasal involvement was found among individuals reporting nasal bleeding (P=0.388 and P=0.006, respectively). The nasal mucosa was involved in seven of the 10 patients who described nasal obstruction and bleeding, but this was statistically insignificant (P=0.198).

Fourteen (41.2%) patients reported hoarseness. Four patients had erosions in the tonsils, nine in the larynx, and 11 in the hypopharynx. No association was observed between hoarseness and the involvement of the tonsillar area and larynx (P=0.928, P=0.409, respectively). Nevertheless, hoarseness was found to be marginally significant in cases with hypopharynx involvement (P=0.05).

The tonsils, hypopharynx, and larynx were involved in six, 17, and 14 of the 22 (64.7%) patients with throat pain, respectively. The throat pain was statistically significant regarding hypopharyngeal involvement (P=0.711, P=0.003, P=0.218, respectively). None of the symptoms was associated with involvement of the larynx and tonsils. The correlation between symptoms and the affected mucosal areas is summarized in Table 2.

Table.1 Mucosa-related Symptoms and Localization of Lesions.

	Frequency	Percent %
Symptoms		
Nasal congestion	11	32.4
Epistaxis	17	50
Hoarseness	14	41.2
Throat pain	22	64.7
Localization		
Palate	22	64.7
Lips	20	58.8
Gingiva	19	55.9
Buccal mucosa	23	67.6
Tonsils	10	29.4
Tongue	13	38.2
Nose	18	52.9
Hypopharynx	20	58.8
Larynx	19	55.9
Total (mucosal involvement in at least one area)	33	97.1

Absence of Symptoms despite Mucosal Involvement

Epistaxis was a statistically significant predictor of nasal involvement, while hoarseness and throat pain were significant predictors of hypopharyngeal involvement. However, among the five patients (14.7%) with nasal involvement, epistaxis was not reported. Similarly, among those with hypopharyngeal involvement, nine patients (26.5%) did not report hoarseness, and three patients (8.8%) did not report throat pain. These patients were asymptomatic in terms of symptoms that could be associated with lesion localization. Although 33 (97.1%) patients had mucosal participation in at least one area on endoscopic examination, nine (26.5%) had no symptoms.

Discussion

Pemphigus vulgaris (PV) was a fatal disease before the use of corticosteroids and adjuvant immunosuppressive agents [7]. The involvement of the ear, nose, and throat (ENT) mucosa in PV not only increases the severity of the disease but also raises morbidity, thereby affecting the treatment process [8]. The involvement of multiple mucosal areas is a determining factor in classifying the disease as mild, moderate, or severe. This classification directly influences the treatment plan. In mild cases, 0.5 mg/kg of prednisolone per day may be required, whereas in severe cases, up to 1.5 mg/kg of prednisolone may be necessary. Additionally, adjuvant immunosuppressants or rituximab may be added to the treatment based on clinical severity [7]. Therefore, accurate assessment of mucosal involvement at the initial evaluation and during follow-ups is of critical importance. In our study,

Table 2. Correlation between Symptoms and Lesion Location.

Endoscopic findings		Symptoms (+) n (%)	Symptoms (-) n (%)	p	Symptom type
nasal mucosa	(+)	7(20.6)	11(32.4)	0.388	nasal obstruction
	(-)	4(11.8)	12(35.3)		
	(+)	13(38.2)	5(14.7)	**0.006**	nasal bleeding
	(-)	4(11.8)	12(35.3)		
palatine tonsil	(+)	6(17.6)	4(11.8)	0.711	throat pain
	(-)	16(47.1)	8(23.5)		
	(+)	4(11.8)	6(17.6)	0.928	hoarseness
	(-)	10(29.4)	14(41.2)		
hypopharynx	(+)	17(50.0)	3(8.8)	**0.003**	throat pain
	(-)	5(14.7)	9(26.5)		
	(+)	11(32.4)	9(26.5)	**0.050**	hoarseness
	(-)	3(8.8)	11(32.4)		
larynx	(+)	14(41.2)	5(14.7)	0.218	throat pain
	(-)	8(23.5)	7(20.6)		
	(+)	9(26.5)	10(29.4)	0.409	hoarseness

mucosal involvement was present in 97.1% of PV patients. Various studies in the literature have investigated the prevalence of ENT involvement, and their primary findings indicate that the frequency of ENT involvement is higher than previously estimated [9-15].

Studies have reported that oral cavity involvement in pemphigus vulgaris ranges between 97.4% and 100%, and in our patient series, this rate was found to be 94.1%. Additionally, research has shown that the gingiva and buccal mucosa are more frequently affected [17,18]. Our results are consistent with these findings, demonstrating a higher rate of involvement in the buccal and palatal mucosa [16].

While the involvement of the oral mucosa in pemphigus can be assessed during routine dermatological examination, the involvement of other mucosal sites is typically evaluated by questioning patients about symptoms that may be associated with the affected areas. Patients' symptoms may relate to the oral cavity (68-100%), pharynx (68-82%), larynx (36-42%), nasal cavity (29-82%), and ear (3-27%) [9,11-13,15]. Mouth pain, throat pain, dysphagia, bleeding gingiva, hoarseness, epistaxis, nasal congestion, earache, hearing loss, and odynophagia are symptoms that may be asked about when examining a pemphigus vulgaris patient [9,11,16]. However, asking about symptoms may not always provide definitive information about the involvement of mucosal areas. As we found in our study, a subset of patients may present with mucosal involvement despite being asymptomatic, posing a challenge for clinical diagnosis [12,13].

A landmark study by Hale et al. [15] underscored the necessity of endoscopic evaluation in PV, revealing that only 49% of patients with endoscopically-confirmed mucosal lesions exhibited symptoms. This highlights the potential limitations of symptom-based assessment in routine dermatological practice. In our study, 88.2% of patients had at least one lesion in mucosal areas outside the oral cavity, and 70.6% of patients had at least one symptom that could be related to these areas. A comparable rate was also reported by Mahmoud et al. [10].

In our patient group, throat pain and hoarseness were associated with hypopharyngeal involvement; however, no significant symptom was identified for tonsillar or laryngeal involvement. While nasal bleeding was associated with nasal involvement, nasal congestion was not found to be statistically significant. There are varying results in the literature regarding the relationship between involvement of a mucosal area and the presence of symptoms. While some researchers have reported that laryngeal involvement is mostly asymptomatic [9,12,16], one study associated laryngeal involvement with throat discomfort or tenderness, difficulty swallowing, or hoarseness [15]. Similarly, in another study, hoarseness was found in 44% of patients, whereas active laryngeal involvement was detected in 75% of cases [10,13]. In our study, no statistically significant symptom was found to be associated with laryngeal involvement.

A recent study reported that nasal involvement could be associated with nasal congestion, crusting, bleeding, or bloody mucous discharge [15], whereas Espana et al. [13] found that nasal mucosal involvement is generally asymptomatic. In the study by Mahmoud et al. [10], endoscopic examination revealed active laryngeal lesions in 95% of patients , but only half of them reported pharyngeal or laryngeal symptoms.

Our results in the present study suggest that nasal congestion as a symptom of nasal involvement has no statistical significance. This indicates that nasal congestion may be associated with common conditions such as septal deviation or allergic rhinitis. Although our study did not specifically investigate ear involvement in PV, a previous study found an association between ear and pharyngeal and laryngeal involvement [12].

This study has some limitations that should be considered when interpreting the results. First, as a single-center study, the findings may not be fully generalizable to broader populations. A multicenter study could provide a more diverse and representative dataset. Second, although the sample size (n=34) was statistically sufficient based on power analysis, a larger patient cohort would strengthen the robustness of the findings, particularly in subgroup analyses.

Third, this was a cross-sectional study, meaning it provides only a snapshot of mucosal involvement in pemphigus vulgaris (PV). Longitudinal studies are needed to evaluate asymptomatic mucosal lesions' progression, resolution, or persistence over time.

Fourth, although patients with significant comorbidities were excluded, potential confounding factors such as mild allergic rhinitis or minor vocal cord pathology could have influenced symptom reporting and lesion severity.

Fifth, a significant limitation of our study is the lack of histopathological or immunofluorescence confirmation from nasal mucosa. Although oral mucosal biopsies were performed during the diagnostic process, nasal biopsies were not obtained due to ethical and practical considerations. The nasal cavity is anatomically delicate and highly sensitive, and in the absence of overt ulcerative or erosive lesions, invasive biopsy was not deemed justifiable in clinical practice. Future prospective studies should consider performing targeted nasal biopsies in symptomatic patients to validate endoscopic findings and strengthen diagnostic accuracy.

Another limitation is the absence of standardized olfactory testing. Olfactory dysfunction may serve as a subtle clinical marker of nasal mucosal involvement in PV. Although our protocol did not include objective smell testing, we acknowledge that it is a simple and non-invasive tool that could provide additional insights. We recommend that future studies incorporate validated smell tests in the evaluation of nasal mucosal involvement.

Lastly, this study categorized mucosal involvement in a binary manner (present/absent) rather than using a quantitative severity scoring system. Future studies could benefit from a standardized grading system for lesion severity to allow better assessment and treatment planning.

In conclusion, this study found that hoarseness and throat pain were significantly associated with hypopharyngeal involvement, while nasal bleeding was correlated with nasal mucosal involvement. One of the most significant findings of this study is that a substantial proportion of patients with pemphigus vulgaris (PV) exhibit asymptomatic mucosal involvement, particularly in the nasal, pharyngeal, and laryngeal regions. This finding suggests that a symptom-based assessment alone may be insufficient to detect mucosal lesions, as endoscopic examination can reveal disease manifestations even in asymptomatic patients.

However, the single-center design and relatively small sample size of our study limit the generalizability of the findings. Therefore, multicenter prospective studies with larger patient cohorts are necessary to gain a more comprehensive understanding of the clinical significance of asymptomatic mucosal involvement in PV. While our study underscores the potential benefits of endoscopic evaluation, it does not provide sufficient evidence to support routine screening for all PV patients. Future research should focus on identifying high-risk patient subgroups who would derive the greatest benefit from endoscopic assessment and developing more effective strategies for optimizing disease management.

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