Evaluation of Ear, Nose, and Throat Involvement in Pemphigus Vulgaris in Comparison with Pemphigus Severity Scoring Systems: A Cross-sectional Study

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ABSTRACT Pemphigus vulgaris (PV) frequently affects the mucous membranes of the ear, nose, and throat (ENT). Since ENT examination is not a routinely performed procedure, the exact involvement of PV remains unrecognized. The available severity scoring systems (Pemphigus Disease Area Index (PDAI) and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)) for PV do not include a full ENT examination. This study was designed to evaluate the real extent of PV in ENT areas and to find out the specific scores which indicate the need for ENT examination. The patients were evaluated for ENT manifestations by endoscopic examination whether or not they exhibited symptoms. PDAI, ABSIS, and ENT scores were calculated, and the results were compared for correlation and significance. The mucosal involvement was more severe when scored by ENT examination than when assessed by PDAI or ABSIS. The ENT score was significantly associated with symptoms and endoscopic findings, especially when PDAI ≥15 and/or ABSIS ≥17. ENT endoscopic examination could result in more accurate grading in PV. In particular, performing such an examination should be considered in patients, especially when PDAI ≥15 and/or ABSIS ≥17, regardless of ENT symptoms.

KEY WORDS: pemphigus vulgaris, ear, nose, and throat, mucosa, disease severity, PDAI (Pemphigus Disease Area Index), ABSIS (Autoimmune Bullous Skin Disorder Intensity Score)

INTRODUCTION

Pemphigus is a potentially life-threatening, autoimmune blistering disease of the skin and mucous membranes. It is mediated by autoantibodies which target the transmembranous adhesion glycoproteins desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3). Pemphigus vulgaris (PV) is the major subtype of pemphi-

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gus, characterized as having a progressive course which may lead to death if not treated. Involvement of mucosal areas in PV significantly increases patient morbidity and mortality. Since endoscopic ear, nose, and throat (ENT) examination is not a routinely performed procedure, ENT involvement of pemphigus generally remains unrecognized. The ENT mucosa are well-known involvement areas for PV; its frequency, however, has been investigated only in a limited number of studies (1-6). Moreover, the relationship between ENT involvement and pemphigus scoring systems, i.e. Pemphigus Disease Area Index (PDAI) and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), has not yet been investigated.

This study was designed to evaluate the real extent of PV involvement, the effect of routine ENT examination on pemphigus scoring systems, and to find out the optimal scores which indicate the need for ENT examination.

PATIENTS AND METHODS

Patients with PV attending the Dermatology Outpatient Clinic during the period between December 2015 and June 2016 were included in the current cross-sectional study, after approval of the Research Ethics Committee Office (70904504/66). Those patients with clinical conditions described below were selected to participate in the study:

i) Patients with a new diagnosis of PV who were not treated previously.

ii) Patients with clinical exacerbation.

iii) Patients in clinical remission (7).

A full detailed written consent for participation and endoscopic examinations was retrieved before inclusion in the study. Diagnosis of PV was based on a combination of clinical and histopathological examination, as well as direct immunofluorescence findings for skin or oral lesions. The subtypes of PV were identified as mucosal PV (MPV) and mucocutaneous PV (MCPV) according to clinical and immunological features. The patients were asked whether they had oral, ear, nose, and throat symptoms, and all of them were evaluated for ENT manifestations by direct and endoscopic examination. ENT examinations were carried out by one fixed otolaryngologist (from among the researchers).

Patients with a new diagnosis or exacerbation were accepted as active disease participants; patients on remission were accepted as control subjects. The clinical activity of the PV was evaluated by PDAI and ABSIS (8). The activity scores of the ENT involvement were calculated by a method adapted from the mucosal scoring method in PDAI (Table 1). To evaluate the relationship between ENT scores and disease severity, cut-off values for PDAI and ABSIS were accepted as those defined in the recent study of Boulard *et al.* (9). The cut-off values distinguishing moderate, significant, and extensive pemphigus suggested were 15 and 45 for PDAI and 17 and 53 for ABSIS. Since extensive disease was so limited, we only used cut-off values of 15 for PDAI and 17 for ABSIS.

The results were expressed as mean± SD or median (min-max) for quantitative data and as frequencies (number and percent) for categorical findings. Statistical analysis of clinical data between the two groups consisted of unpaired t-tests for parametric data and Mann Whitney U-test analysis for nonparametric data. These were used to determine the strength of correlation between the ENT, PDAI, and ABSIS scores. In addition, proportions were compared according to either the Chi-square or Fisher exact test. Results were considered significant at 5% critical values ($P<0.05$). All data were analysed using the statistical program SPSS 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

RESULTS

In total, 50 patients (20 men and 30 women) were enrolled in this study. The mean age was 48.0±11.21 (mean ± Standard Deviation; range: 26-76) years and the mean duration of disease was 32.66±36.66 months, with a range of 1 to 144 months. Thirty-eight patients had active disease and 12 patients were in remission. Of the 38 active patients, 20 were newly diagnosed, while 18 were experiencing disease exacerbation. Of the 50 patients, 20 (12 active disease, 8 patients in remission) had MPV and 30 (26 active disease, 4 patients in remission) had MCPV. The mean PDAI, ABSIS, and ENT scores were 18.82±23.71, 20.13±20.87, and 9.97±11.10 in patients with MCPV and 7.56±15.18, 7.30±14.80, 11.44±17.94 in patients with MPV respectively.

Symptoms of ENT involvement were most commonly described as oral pain (or discomfort) (68%), dysphonia (58%), or dysphagia (54%) (Table 2). Although it was not the case for all patients, there was a significant correlation between clinical symptomatology and endoscopic findings (Figure 1). Endoscopic findings were significantly associated and highly correlated with oral pain, dysphagia, and nasal obstruction ($P<0.05$). Oral symptomatology and findings were significantly more frequent in patients with MCPV than with MPV ($P<0.05$).

ENT scores were found to be highly correlated with PDAI total activity scores ($r=0.716$, $P<0.05$), PDAI mucosal scores ($r=0.918$, $P<0.05$) and ABSIS mucosal

Table 1. Ear, nose and throat (ENT) scoring system

Anatomical location	*Erosion/Blisters:*	
	0: absent *1: 1 lesion* *2: 2-3 lesions* *5: >3 lesions or 2 lesions>2 cm* *10: entire area*	*If number of the lesions<3 or none of them> 2cm* *1 lesion:1* *2 lesions:1.3* *3 lesions:1.6*
Nose		
Ear		
Oropharynx		
Nasopharynx		
Larynx		

scores (r=0.869, P<0.05), but only moderately correlated with ABSIS total scores (r=0.660, P<0.05). The severity of the mucosal involvement obtained by PDAI and / or ABSIS was not an exact indicator of disease severity. The mean ENT scores were 3.86±5.62 and 4.68±8.28 in patients with PDAI <15 and ABSIS <17, respectively. The mean ENT score was 22.46±16.73 and 20.14±16.41 in patients with PDAI ≥15 and ABSIS ≥17, respectively (P<0.05) (Figure 2, Figure 3).

There was no correlation between the duration of disease and the severity of involvement in terms of PDAI, ABSIS, and ENT scores (P>0.05) regardless of the subtype of pemphigus (MPV or MCPV) or the type of patient (newly diagnosed or in exacerbation).

Table 2. Frequency of ear, nose, and throat symptoms in patients with pemphigus vulgaris

Symptoms	**Frequency, n (%)**
Oral	
Oral pain and burning	34 (68)
Laryngeal	
Dysphonia	29(58)
Pharyngeal	
Dysphagia	27 (54)
Odynophagia	22 (44)
Nasal	
Epistaxis	8 (16)
Nose obstruction	19 (38)
Bloody mucus	15 (30)
Nasal stuffiness	14 (28)
Hyposmia / dysosmia	2 (4)
Ear	
Otalgia	0
Ear blockage	5 (10)
Hypoacusi	0

DISCUSSION

Our study found that the severity of ENT involvement in PV was significantly associated with ENT endoscopic findings and symptoms, especially for PDAI ≥15 and / or ABSIS ≥17. This is the first report to identify the correlation between internationally accepted pemphigus scoring tools (PDAI and ABSIS) and severity of ENT involvement. Involvement of ENT mucosa in PV significantly increases patient morbidity. Several studies in the literature have attempted to define the frequency of ENT involvement (1-6), the main outcome being that the frequency of ENT involvement was higher than expected in these studies. Similarly, all the studies agree that endoscopic ENT findings show a greater frequency of clinically active PV lesions than the symptoms reported for each mucosa individually (1-6).

All reports, including our study, identified that oral, pharyngeal, and laryngeal symptoms were the most common symptoms respectively (Table 3) (1-6).

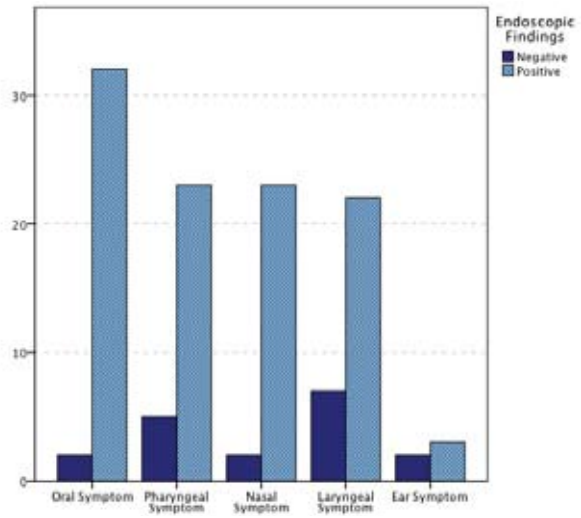

Figure 1. Clinical symptomatology and endoscopic findings of the patients.

Table 3. Oral mucosa and ear, nose, and throat manifestations in published series

Published series	Symptoms / Endoscopic findings (%)				
	Oral mucosa	**Pharynx**	**Larynx**	**Nasal mucosa**	**Ear**
Hale and Bystryn (6) (n=50/11*)	-/-	-/-	39.6/57.0	22.6/75.0	-/-
Espana *et al.* (5) (n=16)	93.7/93.7	75/62.5	44.0/75.0	38.0/75.0	18.7/18.7
Kavala *et al.* (4) (n=38)	100.0/97.4	81.6/65.8	38.7/55.3	81.6/76.3	2.6/10.5
Fernandez *et al.* (3) (n=40)	92.5/92.5	75/85	42.5/85.0	47.5/70.0	7.5/7.5
Robati *et al.* (2) (n=41)	75.6/90.2	70.7/61	39.0/58.5	-/36.6	26.8/26.8
Fawzy *et al.* (1) (n=34)	67.6/100.0	56/76.5	14.7/76.5	29.4/32.4	26.5/26.5
Current study (n=50)	68.0/64.0	56/48	58.0/46.0	50.0/48.0	10.0/10.0

**This series includes 53 patients but only 11 were studied by laryngeal and nasal endoscopy.*

Conversely, the least frequent symptoms were related to the ear. There are only two prospective studies in which the relationship between the severity of PV and ENT mucosa involvement had been investigated in the literature (1,4). ENT involvement was not associated with the severity and clinical improvement of the disease in the study of Kavala *et al.* in their evaluation of 38 patients with active PV (4). In this study, a severity scoring system was used to evaluate eight body surface areas for disease severity. The severity was scored as mild, moderate, or severe, according to the number of involved areas (mild ≤3, moderate 4-6, and severe ≥7). No relation between disease severity and ENT involvement was found. However, since the scoring system used in this study was not a validated tool for the determination of disease severity, such as PDAI, the value of the results of this study is somewhat debatable. Fawzy *et al.* used a different scoring system to calculate disease severity: the pemphigus area and activity score (PAAS) (1,10). They also added a grading of free, mild, moderate, and severe in terms of the number of involved body sites. According to their results, there was no correlation between mucosal involvement and disease severity. However, they also concluded that the disease duration is the main determiner for the severity of mucosal involvement in patients with PV, because they showed a positive correlation between the duration of the disease and the severity of the involvement with no relevance to the type of pemphigus (MPV or MCPV) or the type of patient (newly diagnosed or in exacerbation) (1). In contrast, our study did not demonstrate a

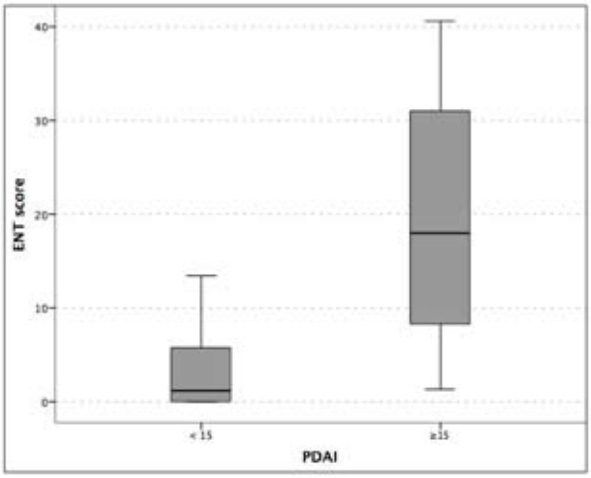

Figure 2. Correlation between ear, nose, and throat (ENT) score and disease severity detected by Pemphigus Disease Area Index (PDAI).

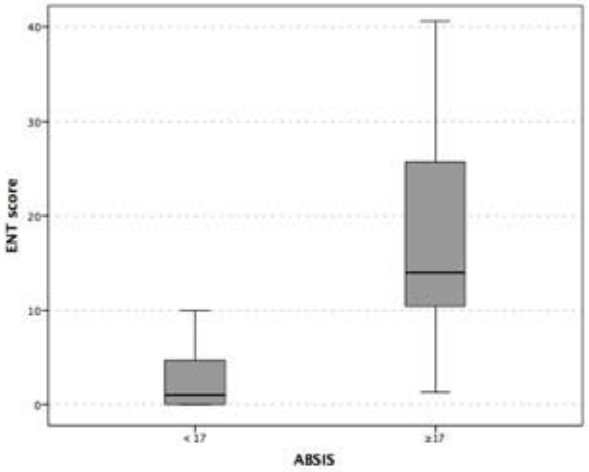

Figure 3. Correlation between ear, nose, and throat (ENT) score and disease severity detected by Autoimmune Bullous Skin Disorder Intensity Score (ABSIS).

statistically significant correlation between the duration of the disease and the severity of the involvement. This discrepancy could be explained by the individual differences in clinical courses of the disease between the patients in the study groups. It is probable that the previous two studies mostly consisted of patients with progressive disease; conversely, ours consisted of patients who had mostly stable and clinically persistent disease. In the study by Espana *et al.* 10 patients with the mucosal form of PV (MPV) and 6 with the mucocutaneous form of PV (MCPV) were evaluated by endoscopic examination and reported more frequent laryngeal involvement in the mucosal form than in the mucocutaneous form of patients with PV (5). However, in our study, oral pain and oral endoscopic findings were reported as being more frequent in patients with MCPV than with MPV. Also, all the other ENT symptoms were reported as being more frequent in patients with MCPV, although the result was not statistically significant. This could be related to the result that the mean PDAI and ABSIS scores of patients with MCPV were significantly higher than in patients with MPV among our subjects. However, there was no significant difference between the mean ENT scores of patients with MCPV and MPV. Fernandez *et al.* investigated the relation between anatomical locations and trauma for the development of mucosal lesions in patients with PV (3). They suggested keeping in mind that trauma produced by the very dynamic of the anatomical structures involved in the functions of the upper aero digestive tract may exert an influence on the severity of PV lesions. The results of current and previous studies have indicated that the probable cause of the development of more frequent oropharyngeal lesions than lesions in other anatomical sites such as ear and nose is the effect of physiological trauma in oropharyngeal region. Therefore, patients should be informed about the role of traumatic physiological mechanisms to avoid the appearance of new mucosal lesions (3). Robati *et al.* evaluated new patients with PV before and after treatment by endoscopic examination (2). This study demonstrated that endoscopic ENT examination is useful not only in finding out the extent of the disease and its severity, but also for evaluation of the effectiveness of the treatment.

As a result of these studies, full ENT examination leads to a more accurate diagnosis of the severity and extent of the disease. However, our study has additionally uncovered the specific scores which indicate the ENT involvement, obtained via the recently validated and accepted scoring systems.

Limitations

The primary limitation of our study would be the lack of endoscopic biopsies, although we demonstrated acantholytic cells by cytology which was performed in the course of endoscopic examination.

CONCLUSIONS

Identification of the exact severity of ENT involvement in patients with PV plays a role in the prediction of prognosis and may serve as a guide for its management. However, as endoscopic ENT examination cannot become a routinely performed procedure because of time and economic issues, performing such an examination should nonetheless be considered in patients, especially for PDAI ≥15 and / or ABSIS ≥17, regardless of ENT symptoms.

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