Ear, nose and throat manifestations in pemphigus vulgaris

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SUMMARY

Background: Pemphigus vulgaris (PV) is an autoimmune disease characterized by mucocutaneous intraepithelial blisters and pathogenic autoantibodies against desmoglein 3. There are two clinical forms: mucosal (MPV) and mucocutaneous (MCPV). The frequency of ear, nose and throat (ENT) involvement in PV is not clearly defined. Only a few isolated individual cases have been reported.

Objectives: The objective of our study was to determine the incidence of ENT involvement in patients with PV.

Patients: We studied prospectively all 16 patients diagnosed with PV and treated in the Department of Dermatology of the University Clinic of Navarra between 2001 and 2005. They were 10 cases of MPV and six cases of MCPV. All patients were evaluated for ENT manifestations by endoscopic examination.

Results: Of the 16 patients, 13 presented with throat symptoms (81%), 12 pharyngeal (75%) and seven laryngeal symptoms (44%). Fourteen patients (88%) had active PV lesions on endoscopic evaluation (eight patients had active lesions on both pharyngeal and laryngeal mucosa, four had PV lesions only on laryngeal mucosa and two had PV lesions on pharyngeal mucosa). Laryngeal lesions were most commonly present in MPV patients. The frequency of nasal symptoms (38%) was lower than active PV lesions (62%) found on ENT examination. Oral symptoms and oral active PV lesions were the most frequent findings (94%). Only three patients with MCPV showed erosions on the external auditory canal. Conclusions As ENT endoscopy allows more extensive areas of mucosa to be examined than simple visual inspection, we recommend that it be included in the examination of all patients with PV. By obtaining more complete information concerning the extent of the disease, a more accurate diagnosis can be made, better choice of drug and dose may be decided and, ultimately, response to treatment may be improved.

Key words: ear nose and throat manifestations, mucosal manifestations, pemphigus vulgaris

Conflicts of interest: None declared.

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Pemphigus vulgaris (PV) is an autoimmune bullous disease, characterized by the development of acantholysis on the skin and/or mucosa secondary to IgG antibody synthesis against a desmosomal glycoprotein, desmoglein (Dsg), present in keratinocytes.[1] Two clinical subtypes of PV have been defined. The mucosal form of PV (MPV) is characterized by a predominant anti-Dsg3 autoimmune response. In contrast, the mucocutaneous form (MCPV) shows a combined anti-Dsg3 and anti-Dsg1 autoantibody response, the patients' mucosa is affected and over five skin lesions are present.[2] The frequency of ear, nose and throat (ENT) involvement in PV is not known. Only a few isolated individual cases have been reported,[3–17] most published in ENT journals. Recently, Hale and Bystryn[18] described laryngeal and nasal findings in 53 patients with PV, although only 11 underwent ENT examination. In the present report, ENT manifestations in 16 patients with PV, examined by ENT endoscopy, are presented.

PATIENTS AND METHODS

This prospective study includes 16 sequential patients with PV, 10 cases of MPV and six of MCPV. All attended the Department of Dermatology of the University Clinic of Navarra between 2001 and 2005. Criteria used for diagnosis of PV are described elsewhere.[2] Briefly, patients with MPV showed predominant oral erosions with limited skin involvement, fewer than five or six scattered or isolated erosions or blisters, and each <5 cm in diameter. Patients with MCPV showed extensive skin involvement in addition to oral involvement. If more than six erosions or blisters >5 cm in diameter were present on the skin, the patient was considered to have the mucocutaneous type of PV.[2] If patients meeting the mucosaltype criteria had positive anti-Dsg1 and anti-Dsg3 antibodies, these cases were considered to have mucosal-dominant PV, as has been established by other authors.[19] Initial symptoms and clinical lesions in our patients had been observed for between 1 and 60 months before the patient came to our department for the first medical visit (Table 1). In all patients the treatment consisted of high doses of corticosteroids (0.3–1 mg kg^{-1} daily), together with immunosuppressive drugs (azathioprine 1–1.5 mg kg-1 daily or mycophenolate mofetil 3 g daily). Only patient 1 had not been treated before coming to our department. The dose of corticosteroids and immunosuppressive treatment was adjusted at each follow-up visit based on the cutaneous and mucosal manifestations of PV, and the mucosal involvement observed by ENT endoscopy.

All patients were evaluated for ENT manifestations by endoscopic examination at the first medical visit to our hospital, whether or not they had symptoms. All ENT examinations were carried out by one of the authors (S.F.). After the first ENT examination, each patient was evaluated by endoscopic examination at subsequent follow-up visits only when ENT symptoms were persistent or active PV lesions had been observed in the previous ENT examination. ENT examination was also carried out when a patient had a new flare of PV lesions. As a result, the number of ENT examinations was different for each patient. Mucosal cultures were taken in those patients in whom a bacterial, viral or fungal mucosal infection was suspected. If patients had previously been evaluated in other hospitals, and had already presented with ENT symptoms or clinical lesions related to PV, or had undergone previous ENT endoscopy, that information was always included in their medical records. Table 1 includes

complete clinical and serological information for each patient. Table 2 shows the complete symptomatology presented by our 16 patients from the beginning of their mucosal and skin manifestations.

RESULTS

Oral symptoms and active oral PV lesions were the most frequent findings in our study. The oral symptoms reported were pain or stinging in the oral cavity (94% of all the patients with PV) (Table 2). To date, only one patient with MCPV has not had active oral mucosal lesions at some time during the course of the disease (Table 1). Oral symptoms appeared at the beginning of the clinical manifestations of PV.

Of the 16 patients with PV, 13 presented with throat symptoms (81%) (either pharyngeal or laryngeal symptoms, or both), but 14 (88%) had active PV lesions as determined by endoscopic evaluation (Table 1). Symptoms affecting the pharyngeal mucosa most often manifested as tenderness in the throat or pain on swallowing; these symptoms occurred in 12 patients (75% of all the patients with PV, both symptoms) (Table 2). Symptoms related to the laryngeal mucosa were reported by seven patients (44%), including hoarseness and/or dysphonia (31% and 44%, respectively) (Table 2). These symptoms appeared when PV first occurred, and when some patients experienced a flare of their symptoms including new blisters and erosions on skin and/or mucosa. Overall, 12 patients presented with active lesions on the laryngeal mucosa (75% of the patients with PV) and 10 patients presented with active lesions on the pharyngeal mucosa (62% of PV patients); eight patients had active PV lesions on both pharyngeal and laryngeal mucosa, four had PV lesions only on the laryngeal mucosa, and two patients had erosions only on the pharyngeal mucosa (Table 1). Surprisingly, while all patients with MPV presented with laryngeal lesions (100% of patients with MPV), this was the case with only two of the patients with MCPV (33% of patients with MCPV) (Table 1). However, the frequency of active erosions on pharyngeal mucosa was similar in patients with either MCPV or MPV (60% and 67%, respectively) (Table 1).

Of all the 16 patients with PV, only six had nasal symptoms (38%). However, 10 cases (62%) presented with active mucosal PV lesions, such as crusting and erosions, on ENT examination (Table 1). Six of these 10 cases had MPV (60% of the patients with MPV) and four had MCPV (67% of patients with MCPV). Nasal symptoms appeared at the beginning of the mucocutaneous disease, or with flares of PV. The symptoms reported were epistaxis (38%), presence of a blood-tinged mucus (19%) or stuffiness (25%) (Table 2).

Ear symptoms were the least frequent symptom and clinical finding in the 16 patients with PV. All three patients with ear symptoms presented with pain and ear canal obstruction (Table 2). Ear symptoms appeared when the patients had a flare of PV lesions. These symptoms followed an evolution similar to that of skin lesions after administration of corticosteroids and immunosuppressive drugs. These three patients had MCPV. No ear lesions were observed in patients with MPV.

In some patients, active lesions were found on mucosae other than those of the ear, nose or throat. These included anal (patients 3 and 13), genital (patients 1, 3, 5 and 7) and conjunctival mucosae (patients 5, 7 and 13).

Some patients were asymptomatic for pharyngeal, laryngeal or nasal symptoms despite active lesions demonstrated by endoscopy (e.g. patients 4, 5, 7, 8 and 10). Those patients with more extensive mucosal active PV lesions received higher doses of corticosteroids and were treated for longer than those patients with fewer mucosal PV manifestations.

In several patients ENT symptoms could have been due to mucosal inflammation, as six cases had cultures positive for Staphylococcus aureus on nasal mucosa, and five patients had cultures positive for Candida spp. (Table 1). These patients were treated with antibiotics and anticandidal therapy, along with corticosteroids and immunosuppressive drugs.

DISCUSSION

This study reveals that a high number of patients with PV may present with active ENT lesions. Therefore, all dermatologists should be aware of which ENT manifestations might be present in patients with PV at some time during the course of this disease. Most of the data related to ENT manifestations in PV have been in reports of individual cases.[3–17] However, Hale and Bystryn[18] described laryngeal and/or nasal findings in 53 patients with PV, although only 11 underwent ENT examination. Our study underlines the importance of exploring ENT mucosa by endoscopic techniques in all patients with PV, in order to determine the real extent of active PV lesions. Overall, all of our patients except one (patient 16) had some active erosions on ENT mucosa together with one or more symptoms. However, individual symptoms were missing in some patients where erosions were found (Table 1). Also, our findings show that ENT manifestations in patients with PV are not in fact associated with a more aggressive form of PV. Indeed, most of our patients presented a mucosal form with active lesions apparently localized only on the oral mucosa (Table 1).

Although many patients may experience ENT symptoms during their disease, our study shows that the presence of active lesions on mucosal surfaces may be more extensive than was originally thought. This difference between symptoms and clinical findings by ENT examinations was most striking in the nasal cavity. Nasal symptoms were reported in 38% of patients (mainly epistaxis and stuffiness) (Table 2), but erosions and crusting on nasal mucosa were detected in 62% of cases. Patients with MPV usually reported no discomfort in the nasal fossa, but ENT examination frequently revealed erosions and crusting (Table 1). In contrast, all the patients with MCPV with nasal symptoms also presented active PV lesions on the nasal mucosa by ENT examination (Table 1). Hale and Bystryn reported nasal symptoms in 23% of their patients, but ENT evaluation was recommended only in four, and active nasal PV lesions were found in only three.[18] These authors noted, as was also the case in our study, that these symptoms were usually related to a flare of PV. Of the six patients with cultures positive for S. aureus on nasal mucosa in our study, only three had some discomfort in the nasal fossa.

Perhaps the role of these bacteria in the presentation of nasal symptoms was minor in our patients.

The most surprising findings in this study were related to laryngeal manifestations. Only 44% of patients presented with symptoms associated with the larynx, mainly hoarseness and dysphonia (Table 2). However, 75% had active PV lesions on the laryngeal mucosa on ENT examination. Even more interesting is the fact that these lesions were found mostly in patients with MPV. Only two patients with MCPV had lesions on this mucosa (Table 1). Hale and Bystryn[18] found laryngeal symptoms in 40% of patients with PV. Only seven of these patients had an ENT evaluation, and active laryngeal lesions were found in four of them. The difference between laryngeal symptoms and the findings of active PV lesions may be related to the area of larynx affected. Only erosions on the vocal folds produced dysphonia or hoarseness, while active lesions on the epiglottis produced tenderness in the throat or pain on swallowing. We do not know the reason for the high frequency of active laryngeal lesions almost exclusively in patients with MPV. In general, this kind of PV symptom is associated with a flare of PV lesions. On the other hand, Candida spp. infection on the laryngeal mucosa could contribute to hoarseness in our patients, as has been established by other authors.[7] Both symptoms and infection of Candida spp. were more prevalent in patients with MPV. As yet, we can offer no reason for these findings.

There are some data in the dermatological literature related to ear involvement in PV.[13] Our study found only three patients showing erosions in the auricle and auditory canal of the ear. All three patients presented with MCPV. These findings may reflect one more characteristic clinical manifestation of MCPV.

Our findings show that the management of PV must be an interdisciplinary process. ENT manifestations should be examined by an ENT specialist with experience of PV patients, and endoscopic techniques should be used. Other diagnoses to be considered when using direct fibroendoscopy are Wegener's granulomatosis, blistering mucosal disease, such as cicatricial pemphigoid, or nonspecific membranous mucositis. Furthermore, ENT endoscopy may be useful for obtaining additional information related to the viral, bacterial or fungal agents causing the infection on the inflamed mucosa in patients with PV.

In summary, ENT endoscopy allows more extensive areas of mucosa to be examined than simple visual inspection. Consequently, we recommend that it be included in the examination of all patients with PV. By obtaining more complete information concerning the extent of the disease, a more accurate diagnosis can be made, a better choice of drug and dose may be decided and, ultimately, response to treatment may be improved.

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Table 1. Clinical and ear, nose and throat (ENT) manifestations in 16 patients with pemphigus vulgaris (PV)

Patient number	Type of PV	Time from the beginning of PV (months)	Throat symptoms pharynx/larynx	Pharyngeal endoscopy findings	Laryngeal endoscopy findings	Nasal symptoms	Nasal endoscopy findings	Oral symptoms	Oral endoscopy findings	Ear symptoms	Ear clinical findings	ICS	ELISA Dsg1/Dsg3	Bacterial-positive culture of mucosa	Candida-positive culture of mucosa
1	MPV	1	+/+	+	+	−	−	+	+	−	−	1 : 80	−/48	−	+
2	MPV	30	+/+	+	+	+	+	+	+	−	−	1 : 640	−/244	+	+
3	MPV	2	+/−	+	+	−	−	+	+	−	−	1 : 80	53/163	+	+
4	MPV	6	+/+	+	+	−	+	+	+	−	−	1 : 20	−/42	−	−
5	MPV	7	+/+	+	+	−	+	+	+	−	−	1 : 10	−/26	−	−
6	MPV	36	+/+	−	+	+	+	+	+	−	−	Neg	191/200	−	−
7	MPV	24	+/−	+	+	−	+	+	+	−	−	1 : 320	−/175	+	+
8	MPV	9	+/−	−	+	−	+	+	+	−	−	Neg	−/142	+	−
9	MPV	35	−/+	−	+	−	−	+	+	−	−	1 : 80	−/104	−	−
10	MPV	4	−/−	−	+	−	−	+	+	−	−	Neg	41/173	−	−
11	MCPV	10	+/−	+	+	−	−	+	+	−	−	1 : 640	182/253	−	−
12	MCPV	11	+/+	+	+	+	+	+	+	+	+	1 : 20	55/215	−	−
13	MCPV	60	+/−	+	−	+	+	+	+	+	+	1 : 80	99/160	+	−
14	MCPV	10	+/−	+	−	+	+	+	+	−	−	1 : 640	185/184	−	−
15	MCPV	36	−/−	−	−	+	+	+	+	+	+	1 : 640	222/259	+	+
16	MCPV	3	−/−	−	−	−	−	−	−	−	−	1 : 20	188/90	−	−
Total	16		12/7	10	12	6	10	15	15	3	3			6	5

MPV, Mucosal pemphigus vulgaris; MCPV, mucocutaneous pemphigus vulgaris; ICS, intercellular substance antibodies; Neg, negative; Dsg, desmoglein.

Table 2. Frequency of ear, nose and throat symptoms in 16 patients with pemphigus vulgaris

	Frequency of symptoms	
Symptoms	**Number of patients**	**%**
Throat	13	81
Pharyngeal mucosa	12	75
Tenderness	12	75
Pain on swallowing	12	75
Laryngeal mucosa	7	44
Hoarseness	5	31
Dysphonia	7	44
Nasal mucosa	6	38
Epistaxis	6	38
Blood-tinged mucus	3	19
Stuffiness	4	25
Ear	3	19
Pain	3	19
Ear canal obstruction	3	19
Oral	15	94
Pain	15	94
Stinging	15	94