

Review Article

Is laryngeal involvement in pemphigus vulgaris rare? A review

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ABSTRACT

The lesions of pemphigus in the larynx have been reported as case reports. However, the frequency with which it occurs is not known. The purpose of this study was to investigate the incidence of laryngeal involvement in pemphigus vulgaris and to examine the laryngeal lesions and the treatment in detail. The databases searched were PubMed, EMBASE, Cochrane Library and Google scholar. The involvement of larynx in patients with pemphigus vulgaris is common. The most common parts involved are epiglottis and arytenoids. This study indicates that laryngeal symptoms are common in pemphigus vulgaris. Laryngeal findings must be considered at the beginning of diagnosis for the better management and to prevent life threatening complications.

Keywords: Larynx, Pemphigus, Oral ulcer

INTRODUCTION

Acute oral ulcers can be caused by aphthous ulcers, trauma, microbial infections, fungi, allergies, chemotherapy, radiotherapy, acute necrotizing gingivostomatitis, erythema multiforme, herpangina, herpetic infections. Chronic oral ulcers include allergies, pemphigus, bullous pemphigoid, lichen planus, chronic trauma, chronic invasive infections, cancer, syphilis, HIV, necrotizing sialometaplasia.¹ Pemphigus is a chronic autoimmune bullous disease with dermatologic and mucosal manifestations. It is characterized by the development of intraepithelial blisters secondary to IgG antibody synthesis against desmoglein (desmosomal glycoprotein) present in keratinocytes.² Endemic pemphigus foliaceus has familial cases and has no involvement of the oral and upper airway mucosa, whereas pemphigus vulgaris involves upper airway mucosa.³

Two clinical subtypes of pemphigus vulgaris have been reported. The mucosal form has predominant anti-desmoglein 3 autoimmune responses while

mucocutaneous form shows a combined antidesmoglein 3 and anti-desmoglein 1 autoantibody response.²

Pemphigus vulgaris is a chronic, potentially fatal and autoimmune disease that represents the most common subtype of the bullous diseases of the group of pemphigus. Antibodies against the desmosomes, mainly desmoglein-3 cause intradermal separation due to the loss of integrity of the epidermal cells, called acantholysis.⁴ The incidence of the pemphigus disease is about 0.1-1.5 cases/100 population/year and is more frequent in Jews and in Mediterranean populations and the average age of the appearance of the disease is 60 years. Early diagnosis and prompt treatment with corticosteroids significantly reduces the mortality of the disease.^{5,6}

The lesions of pemphigus in the larynx have been mostly reported as case reports. However, the frequency with which it occurs is not known. The objective of this study was to investigate the incidence of laryngeal involvement in pemphigus vulgaris and to examine the laryngeal lesions and their treatment in detail.

METHODS

This review included studies that examined the laryngeal involvement in pemphigus vulgaris. The databases searched were PubMed, EMBASE, Cochrane Library and Google scholar. All searches were completed by November 2015. These were augmented by references from these articles. Author evaluated the titles and abstracts of all the studies identified in the initial search to locate any potentially relevant studies. The full texts of studies identified as potentially relevant were then evaluated. Studies were eligible if they examined the laryngeal involvement in patients with pemphigus vulgaris. The following types of studies were also included excluded: reviews, commentaries, case reports and letters. No limits were applied to year of study; however author did exclude publications that were not in English and did not have abstracts. Relevant articles were also sought by a hand search review of reference books. Data from the articles were extracted using a pre-defined data-extraction form.

RESULTS

The majority of the studies' patients 67%, 72.5% had the mucocutaneous form of pemphigus vulgaris.^{2,7} In Mahmoud study almost 50% of the patients had experienced pharyngeal or laryngeal symptoms; however, upon endoscopic laryngeal evaluation the proportion of these patients with active laryngeal lesions was found approximately 95%.⁷ In España and colleagues' study of 16 pemphigus vulgaris patients, active laryngeal lesions were found in 88%.² Females predominated over males, with respective proportions of 80% and 20%. Patient age varied from 13 to 78 years, with a mean age of 46.35 years. 73% patients had the mucocutaneous form of pemphigus vulgaris and twenty seven had the mucosal form.⁷

Laryngeal and nasal symptoms are common in pemphigus vulgaris and in the majority of cases; it is with the disease or with candidiasis.⁸ The erosive and bullous lesions located in the larynx of patients with pemphigus vulgaris are characteristic. Laryngeal lesions were classified as grade I, II, III or IV, according to the sites (epiglottis, supraglottis, pyriform sinuses, ventricular folds or vocal folds) involved.⁷

Hale, Bystryn (2001) investigated the incidence of laryngeal and nasal disease involvement in patients with pemphigus vulgaris. In their retrospective analysis, 53 sequential patients with pemphigus vulgaris diagnosed by clinical, histologic, and immunofluorescence criteria were selected. 49% of the patients (26) complained of laryngeal or nasal symptoms at some time during the course of their disease. 21 patients had laryngeal symptoms and 12 had nasal symptoms.⁸

Mahmoud et al (2012) proposed a graded classification of laryngeal involvement according to the location of the

lesions. In their prospective study (Mahmoud et al 2012), 40 sequentially treated pemphigus vulgaris patients, diagnosed using clinical, histological and immunofluorescence criteria, were evaluated for laryngeal manifestations using endoscopic examination. Active laryngeal lesions (ulcers or blisters) were found in 16 patients (40 per cent).⁷ Supraglottic lesions are usually ulcers while intact blisters are seen on the vocal folds.

The diagnosis of pemphigus is based on immunohistopathology and the clinical examination.⁹ Biopsy demonstrates detachment of the epidermis above the level of the basal membrane and lesions of chronic inflammation in the subepithelial connective tissue.⁴ More than 80% of patients with laryngeal or nasal symptoms had evidence of pemphigus or rapid response to increased doses of corticosteroids, and 2 patients had candidiasis confirmed by fungal culture.⁸

Elderly man with primary pemphigus presents with hoarseness, haemoptysis and dysphagia. An erythematous patch on oral mucosa without ulcerations is usually seen. Supraglottic ulcerations are mainly in the laryngeal surface of the epiglottis and in the arytenoids with gray color membranes. Microlaryngoscopy biopsies in this primary pemphigus of larynx reveal inflammatory and granular lesions with necrosis.⁹ Patient with primary pemphigus of larynx has dysphagia at the level of larynx which aggravates on coughing. There is no hoarseness if the vocal cords are spared. CBC, Wasserman reaction, cultures from nose and throat reveal nothing (Murphy 1929). The pain increases when mucosal bleb in the supraglottic part of larynx develops and ruptures. The denuded surface shows hyperemic base. Patient's inability to take solid food can lead to loss of weight. When lesions appear somewhere else the diagnosis of pemphigus becomes obvious.¹⁰

Treatment includes intravenous high doses of corticosteroids (prednisolone 75 mg/24h) for 10 days and gradually reduced to 10 mg/24h. After a week approximately 80% of the lesions disappear. However, the dose of 10 mg prednisolone per day is continued for 3 months as prednisolone discontinuation is related with reappearance of the disease. Patient should remain under long-term follow-up.⁹

Corticosteroid treatment can be combined with other immunosuppressive agents like azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate, cyclosporine to reduce the dose and the side-effects of corticosteroids. Refractory cases can be treated with the intravenous administration of immunoglobulin, plasmapheresis, and extracorporeal photopheresis. Rituximab (an anti-CD20 monoclonal antibody) has been introduced to the treatment of pemphigus with encouraging results. The prophylactic administration of antibiotics for protection against staphylococcal infections is important.¹¹⁻¹³

DISCUSSION

Pemphigus vulgaris is an autoimmune mucocutaneous life threatening disorder that is characterized by intraepithelial cleavage and affects older age group of 50-70 years.¹⁴ Primary laryngeal involvement without skin lesions is extremely rare.⁹ Besides the oral cavity pemphigus can manifest with nasal and laryngeal lesions in approximately 50% of the cases.^{2,8} Pemphigus involving the mucous membrane of the pharynx and mouth primarily or secondarily to its manifestation on the skin is not infrequently seen.¹⁰

The patients with secondary laryngeal pemphigus do not need laryngeal biopsy as the diagnosis can be confirmed from a biopsy of skin or oral mucosa and the laryngeal lesions are similar to oral cavity lesions. Biopsy from the oral mucosa can be taken under local anaesthesia for histological examination and direct immunofluorescence analysis.

Direct immunofluorescence of intercellular space regions with anti-IgG antibody is diagnostic of pemphigus vulgaris.¹⁵ The supraglottic region is the most commonly involved and involvement of vocal folds is uncommon. Endoscopic examination is important in patients both with and without laryngeal symptoms, in order to enable examination of a greater area of mucosa and to guide therapy.⁷

The oral mucosa can be the first and only site of pemphigus vulgaris manifestation, long before it appears on the skin. The places of increased friction are common sites and the reason why intact blisters are difficult to find. White-grey patches could be removed easily and leaving red raw area behind. The nikolsky sign (gentle rubbing of adjacent mucosa easily causes stripping of this mucosa) and asboe-Hansen sign (pressure over an intact bulla results in the expansion of the bulla) are usually seen but nonspecific for pemphigus. Patients with pemphigus vulgaris are diagnosed on the basis of characteristics clinical, histological and immunofluorescence findings.

The involvement of the larynx in the case of pemphigus vulgaris can vary in severity from hoarseness to the airway impairment that may require tracheostomy. Intubation is avoided because the laryngeal mucosa becomes fragile and could be seriously injured.⁹

All patients with pemphigus need either a flexible nasopharyngo-laryngeal endoscope or a rigid 90°/70° laryngeal telescope examination under local anaesthesia with topical application of local anesthetic.

Physicians should be aware of pemphigus as primary laryngeal manifestation in order to investigate and manage patients accordingly.⁹ Patients are usually elderly people in their eighth decade.^{9,10} Pemphigus involving the larynx primarily and remaining restricted to larynx for a

period of three months before lesions appear on the skin and mucous membrane elsewhere is a condition that has not been included in the differential diagnosis of obscure laryngeal lesions.¹⁰ Initial treatment includes prednisone 1 mg/kg supplemented by azathioprine or mycophenolate mofetil. Severe cases need cyclophosphamide in conjunction with plasmapheresis. Intravenous IgG is employed in recalcitrant cases.¹⁵ The presence of lesions in the larynx, for example, requires the use of more aggressive therapy because of the risk of acute respiratory failure.⁷

CONCLUSION

The majority of the patients have the mucocutaneous form of pemphigus vulgaris. This study indicates that laryngeal symptoms are common in patient with pemphigus vulgaris. Pemphigus involving the larynx primarily though rare should be included in the differential diagnosis of obscure laryngeal lesions. Laryngeal findings must be considered at the beginning of diagnosis of pemphigus vulgaris. Supraglottic lesions are usually ulcers while intact blisters are seen on the vocal folds. Patients with pemphigus need endoscopic laryngeal examination whether they have laryngeal symptoms or not because laryngeal involvement warrants aggressive treatment to prevent life-threatening complications.

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