Epiglottitis as the Presenting Sign of Mucous Membranous Pemphigoid: A Case Report

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Summary: Mucous membranous pemphigoid (MMP) is an autoimmune disease of the mucous membranes characterized by formation of subepithelial blisters. MMP commonly involves the ocular and oral mucosa. Laryngeal MMP is very rare, estimated as occurring in 1 of 10 million persons in the general population. It mostly affects the supraglottis, but may also involve other laryngeal sites as well as extralaryngeal areas. This report describes the clinical picture, workup to diagnosis, and differential diagnosis of an isolated epiglottic process in an elderly female who presented with isolated, long-standing, nonresolving epiglottitis, later diagnosed as MMP with epiglottal and oral involvement.
Key Words: Larynx–Mucous membrane pemphigoid–Epiglottitis–Chronic–Non-infectious.

INTRODUCTION

Mucous membranous pemphigoid (MMP) is an autoimmune disease of the mucosal membranes characterized clinically by formation of subepithelial blisters. The blisters are caused by separation of the epithelium from the basal membrane due to interference to attachment by autoantibodies against molecules in the hemidesmosome and basement membrane.[1] Unlike bullous pemphigoid, which affects the skin and spares the mucous membranes, MMP predominantly affects the mucous membranes. The disease most commonly involves the ocular and oral mucous membranes, but there may also be involvement of the skin, nose, pharynx, larynx, esophagus, trachea, genitalia, and perianal area.[1]

Laryngeal MMP (LMMP) is very rare, occurring in only 12.2% of all MMP cases, or in 1 of 10 million persons in the general population.[1] LMMP usually presents in the fifth to sixth decades of life and has equal gender distribution. The supraglottis is the most affected laryngeal site (84%),[2] although other laryngeal sites may be involved as well. The chronic ongoing supraglottic inflammatory process may lead to cicatricial supraglottic narrowing and respiratory distress.[3]

In this report, we describe a rare case of MMP that initially presented as isolated, long-standing, unresolving epiglottitis. The clinical picture, workup to diagnosis, and differential diagnosis of an isolated chronic epiglottic process and treatment are discussed.

CASE

An 85-year-old female presented at the otolaryngology clinic due to intermittent hemoptysis for 2 weeks accompanied by mild discomfort during swallowing. There was no dyspnea, and the patient denied recent upper respiratory tract infection, oral burn due to hot food ingestion, foreign body ingestion, skin rash, joint pain, new drug intake, or heartburn. Her medical history was significant for essential hypertension, hyperlipidemia, and prior radiotherapy to facial skin due to dermal malignancies. There was no history of smoking or of a familial autoimmune disease. Her head and neck examination was significant for a thickened epiglottis with multiple white plaque-like lesions over an erythematous base with occasional detachment of the epiglottic mucosa (Figure 1). No oral or skin lesions were noted.

The initial diagnosis was an infectious process of the epiglottis, and the patient was prescribed antibiotics (amoxicillin-clavulanic acid) and a proton pump inhibitor (omeprazole). She was re-examined 2 weeks later, and no change in her symptoms or in the laryngeal findings were noted. The patient underwent direct laryngoscopy in the operating theater, and epiglottic cultures and biopsies were obtained. The microbiology culture showed normal flora and the Ziehl-Neelsen stain for acid-fast bacilli was negative. Pathology demonstrated fibropurulent exudate, granulation tissue, and separate fragments of squamous epithelium and cartilage, which were considered as being nonspecific. There was no evidence of tumor. Direct immunofluorescence (DIF) was positive for immunoglobulin M in the basement membrane zone, suggestive of, but not conclusive of, pemphigoid. As the microbiology, histology, and immunohistochemistry workup were nonspecific, and the laryngeal findings persisted, the patient was referred for further workup. She was examined by a dermatologist who ruled out dermal and other mucosal lesions. A computed tomographic study of the chest and neck was obtained to rule out a laryngeal mass or a granulomatous lung process, and there was no evidence of pathology. At that time, 4 months after the initial presentation, with no improvement in her laryngeal findings, and repeated reports of sloughing of tissue from the oral mucosa, the patient was sent for consultation with an oral pathologist. Oral examination revealed erythematous and desquamated gingival lesions (desquamative gingivitis), in both the maxilla and the mandible, which were consistent with MMP (Figure 2). The gingival lesions were biopsied and sent for histology. Hematoxylin-eosin staining showed ulcerated tissue with remnants of connective tissue infiltrated by a dense chronic inflammatory infiltrate, with no basal cells. DIF demonstrated a positive immunoglobulin M stain in colloid bodies (Figure 3). Based on the clinical, histologic, and immunostaining findings, bullous pemphigoid emerged as the most likely diagnosis. The patient was prescribed oral gel containing 0.025% clobetasol, to be applied topically on the affected oral mucosa three times daily. The gingival lesions had

Accepted for publication March 16, 2017.
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Journal of Voice, Vol. ■■, No. ■■, pp. ■■-■■
0892-1997

http://dx.doi.org/10.1016/j.jvoice.2017.03.025

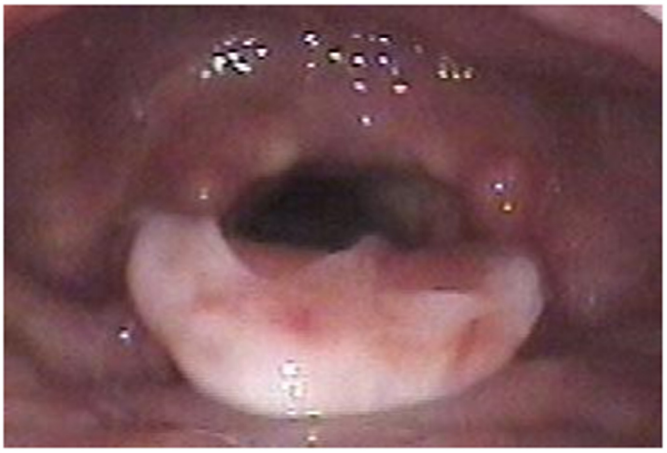

FIGURE 1. Fiberoptic image of the larynx. The epiglottis is thickened and has white plaque-like lesions over an erythematous base with occasional detachment of the epiglottic mucosa.

improved considerably at 1-month follow-up examination. At 2-month follow-up, the laryngeal discomfort was ameliorated, and the epiglottic lesions had receded only to recur after cessation of the steroid treatment.

DISCUSSION

This paper describes a rare case of MMP initially presenting as isolated epiglottitis, eventually diagnosed as MMP confined to the larynx and oral cavity. Isolated epiglottic lesions are infrequent, and they usually suggest acute inflammatory conditions such as acute epiglottitis (viral or bacterial), laryngopharyngeal reflux, or traumatic injury (thermal or caustic ingestion). In the setting of chronic, nonresolving epiglottic lesions, malignancy of the epiglottis (eg, squamous cell carcinoma), chronic infections (eg, fungal, mycobacterial, syphilitic), vasculitis (eg, Wegener granulomatosis, systemic lupus erythematosus), or immunologic conditions (eg, sarcoidosis, chronic relapsing polychondritis) and autoimmune bullous diseases (eg, pemphigus and pemphigoid diseases) are included in the differential diagnosis.[4] Chronic nongranulomatous epiglottitis is another extremely rare entity.[4,5]

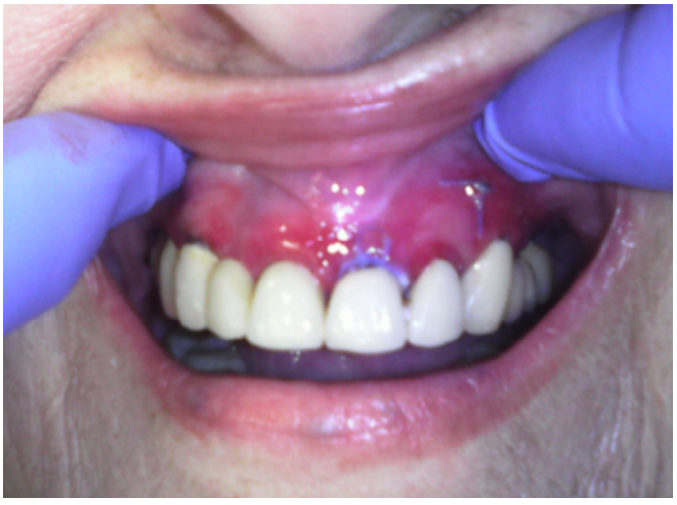

FIGURE 2. Image of the gingiva displaying erythematous and desquamated gingival lesions.

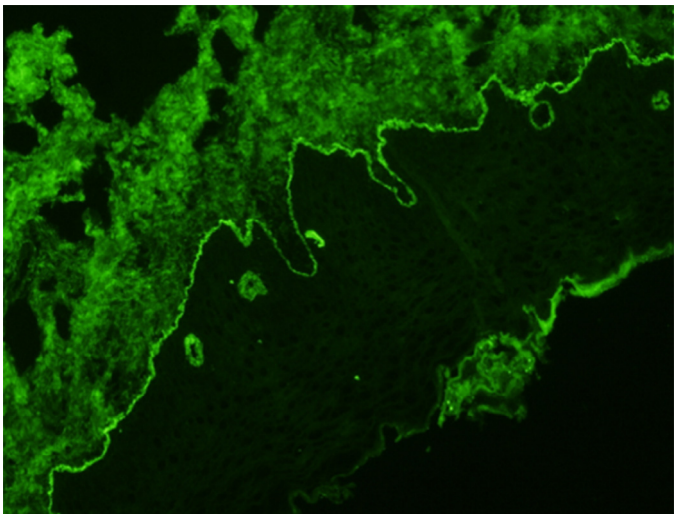

FIGURE 3. Direct immunofluorescence staining of the gingival biopsy specimen showing a positive (*green*) immunoglobulin M stain in colloid bodies. (For interpretation of the reference to color in this figure legend, the reader is referred to the Web version of this article.)

The diagnosis of MMP should be considered in all cases of chronic erosions or blistering of mucosal surfaces, especially when associated with scarring and progressive function loss.[6] MPP is one of the pemphigoid autoimmune bullous diseases that also include bullosa pemphigoid, pemphigoid gestationis, linear IgA disease, anti-p200 pemphigoid, epidermolysis bullosa acquisita, and dermatitis herpetiformis.[6] They are all characterized by subepithelial blisters (in contrast to the epidermal blisters characteristic of pemphigus vulgaris), erosions, and scarring of the mucous membranes, skin, or both. Autoantibodies targeting structural components of the basement membrane that maintain cell-matrix adhesion are present in this group of pemphigoid diseases, and they are mainly directed against the α3 chain of laminin 332 in MMP.[6] In two case series of MMP with α6β4 integrin reactivity, autoantibodies to α6 integrin were found in patients with mainly oral involvement, whereas ocular pemphigoid was associated with reactivity to β4 integrin.[6] The histopathologic examination of MMP patients' lesions reveals subepidermal blisters and a mixed inflammatory infiltrate.[6]

The diagnosis of MMP is confirmed by the demonstration by DIF of IgG and C3 deposits at the basement membrane.[5,7] Characterization of the molecular specificity of autoantibodies has important clinical consequences and may be performed by enzyme-linked immunosorbent assay (ELISA) or immunoblotting. Because of the high rate of negative immunofluorescence results (approximately 50% of the patients' sera show negative indirect immunofluorescence), techniques such as separated human skin immunoprecipitation and immunoblotting of extracellular matrix for laminin-322 and ELISA are important assays in the diagnosis of MMP.[7]

Tissue biopsy is required in cases of nonresolving epiglottic lesions, and a systemic workup is needed to rule out systemic diseases with laryngeal manifestations. Adequate biopsy is

difficult to achieve in case of LMMP due to the tendency of the mucosa to separate or split under local pressure, during the procedure, resulting in a nondiagnostic specimen for either histopathology or DIF. When there is a high index of suspicion of an immunobullous disease, careful examination of the skin and mucous membranes is mandated and immunostaining should be ordered in addition to the histologic examination. The final diagnosis of an immunobullous disease is based on the immunohistopathology test results and the clinical manifestations (skin, mucous membrane involvement, or both). In our case, the initial laryngeal biopsy was insufficient to determine an immunobullous disease, but it was able to rule out a laryngeal malignancy. Only when gingival lesions were noted and biopsied was the diagnosis of MMP with laryngeal involvement confirmed.

The overall 5-year relative survival rate of patients with LMMP is excellent (92.4%). Steroids usually comprise the initial treatment,[1,8] which may also include a helium and oxygen mixture in cases of severe narrowing of the airways.[2] Relapses are frequent despite the efficacy of a steroidal regimen, and up to 10.5% of patients with LMMP will eventually require a tracheostomy due to supraglottic narrowing and upper airway obstruction. Our patient did not receive systemic steroids. However, orally applied clobetasol gel may have had a systemic effect due to absorption through oral mucous membranes and possibly swallowing and ingestion of some of the drug with saliva, as well as a topical effect on the laryngeal mucosa while swallowing.[9] These may explain the resolution of laryngeal lesions with the orally applied clobetasol gel. Laryngeal surgical interventions, such as epiglottectomy, may be effective in severe cases with supraglottic narrowing and obstruction.[1]

CONCLUSION

Laryngeal involvement in MMP is very rare. The differential diagnosis of isolated epiglottic processes is wide, and the workup to diagnosis may involve a multidisciplinary team approach. A chronic nonresolving epiglottic process should raise a high index of suspicion of the possibility of an autoimmune disease. Laryngeal biopsy may not be sufficient for diagnosis, but the progressive involvement of extralaryngeal sites may facilitate it.

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