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## Purpose

- Discuss the clinical presentation, epidemiology, diagnostic, and therapeutic options for mucous membrane pemphigoid.
- Emphasize the need to recognize a rare clinical entity during diagnostic workup in order to avoid a missed diagnosis.

## Background

Cicatrical pemphigoid, also known as mucosal membrane pemphigoid (MMP), is an autoimmune disease of the subepidermis that effects the mucous membranes, particularly of the aero-digestive and ocular mucosa<sup>2,3</sup>. Oral mucosa is most commonly involved, and can be used as to easily obtain biopsies for diagnosis<sup>1</sup>. Laryngeal involvement occurs in <10% of all mucous membrane pemphigoid cases and characteristically involves the supraglottic larynx<sup>1,6</sup>. Initial airway symptoms likely occur due to edema secondary to the underlying inflammatory process<sup>6</sup>. As the disease progresses, there is scarring of the airway which leads to stenosis, stridor, and possibly asphyxiation and death. As in this case, tracheostomy may be necessary to secure the airway secondary to impending airway compromise. Involvement of other sites can lead to scarring of the conjunctiva, esophagus, and nasal cavity/nasopharynx leading to blindness, dysphagia, and nasal airway obstruction respectively<sup>1</sup>.

## Case Report

A 66-year-old African American female presented to the emergency room three times over a six week period with exacerbation of recently diagnosed asthma refractory to medical management. During each episode, she initially improved with steroids but her symptoms returned. Furthermore, she was noted to have stridor on exam during her most recent episode. She denied dysphagia, pain, weight loss, and hemoptysis. Physical exam was notable for biphasic stridor, dysphonia, absent wheezing on exam, and 4mm area of superficial ulceration of the left buccal mucosa. Fiberoptic endoscopy revealed supraglottic stenosis, most prominently at the infrahyoid epiglottis and ventricular folds.

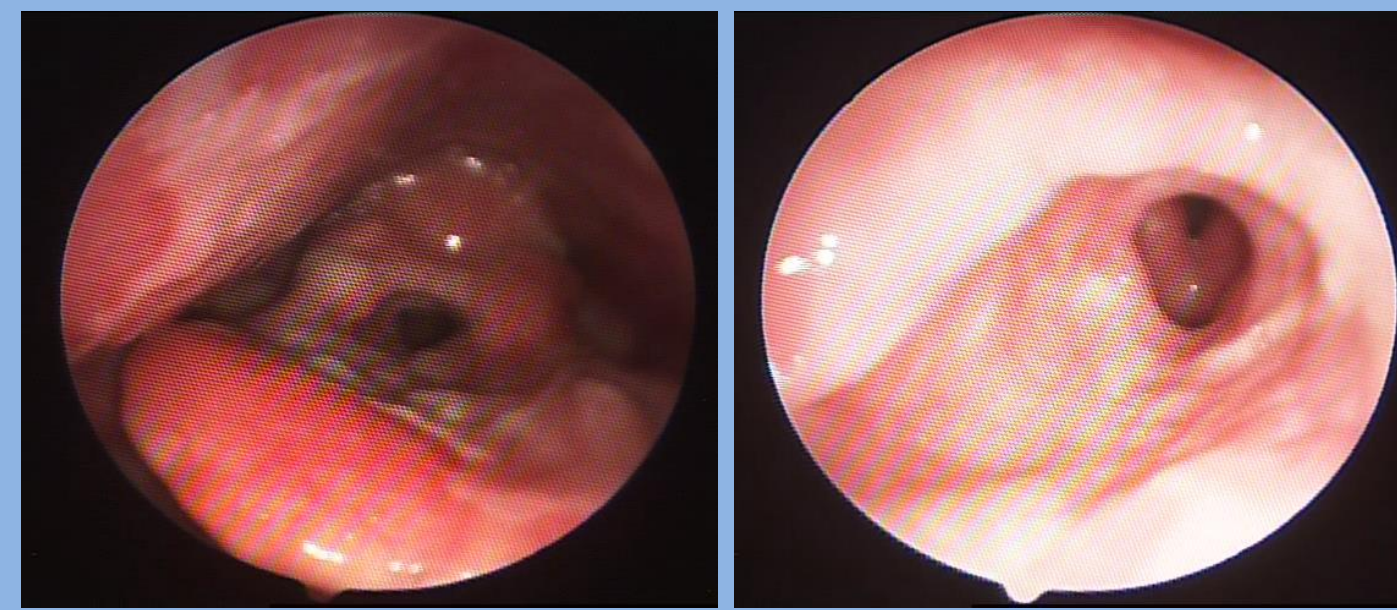


Figure 1. Indirect Laryngoscopy. Indirect laryngoscopy revealed supraglottic stenosis with a severely narrowed airway and mobile vocal cords.

The patient underwent awake tracheostomy, direct laryngoscopy, and biopsies of the oral and supraglottic lesions. During her procedure, she was noted to have laryngeal mucosa that very easily separated from underlying structures.

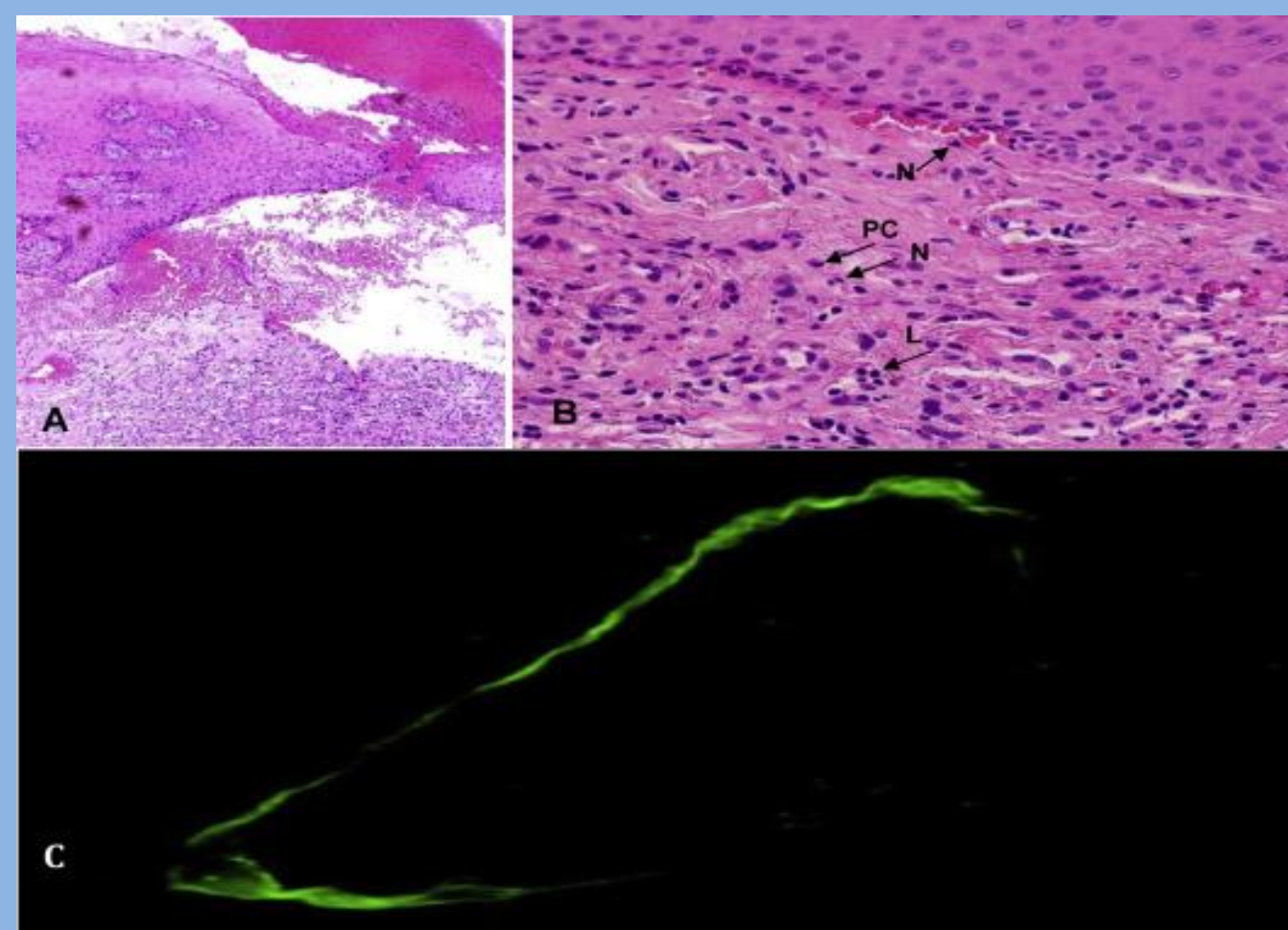


Figure 2. A, B – H&E stain demonstrating subepithelial bullae and a mixed inflammatory cell infiltrate. C. Direct Immunofluorescent staining revealing linear IgG and C3 deposits along the basement membrane.

Histopathology and immunostaining were suggestive of MMP. Laboratory testing revealed increased serum IgG<sub>1</sub>, as well as increased anti-nuclear antibodies in a speckled pattern. The patient was referred for further care and medical management and patient started steroids and a trial of cyclophosphamide with consideration given to IVIG therapy. Once her disease process stabilized, attention would then be turned towards surgical options to improve the caliber of her airway.

## Review

### Diagnosis

Presence of sub-epithelial blisters with a mixed inflammatory cell infiltrate suggests diagnosis, but is only confirmed by direct immunofluorescence demonstrating immunoglobulin or complement deposits in the epithelial basement membrane<sup>3</sup>. Many target antigens have been identified including BPAg<sub>2</sub> (BP180), BPAg<sub>1</sub> (BP230), integrin subunits  $\alpha 6/\beta 4$ , laminin-5 (laminin-332/epiligrin,  $\alpha 3$ ,  $\beta 3$ ,  $\gamma 2$  chains), laminin-6, and type VII collagen<sup>3</sup>. Furthermore, salt split skin tests may demonstrate DIF staining on the dermal side of the split rather than the epidermal side, helping to distinguish MMP from other similar blistering entities such as bullous pemphigoid and epidermolysis bullosa<sup>3</sup>.

### Therapy

Patients with MMP can be stratified based on involved sites into “high risk” (pharynx, larynx, esophagus, conjunctiva, genitourinary mucosa) and “low risk” (oral mucosa, skin) categories which help determine medical management<sup>2</sup>. Medical therapy for laryngeal (“high risk”) patients includes systemic and topical immunosuppressants, systemic steroids, and consideration for intravenous immunoglobulin therapy particularly in patients who fail to respond to a trial of Dapsone<sup>2,5,6</sup>. One case report suggests resolution of laryngeal MMP following 2 years of IVIG therapy, with 5 years of follow up from the end of therapy without evidence of relapse<sup>7</sup>. Consideration for interventions can be done to augment the airway should patients either remain symptomatic or required surgical tracheostomy initially. Interventions may include dilations, laser-assisted laryngeal surgery, or partial open laryngeal surgery<sup>1,4,6,7</sup>.

### Prognosis

High risk patients have increased probability of scarring or stenosis. A multidisciplinary prospective study of 110 patients diagnosed with MMP by Alexandre and colleagues demonstrated that severe ocular lesions or involvement of 3 or more sites other than the nose or throat were predictive of laryngeal involvement. Amongst patients in the overall group followed for greater than 6 months, 34% developed stenosis in the upper aero-digestive tract, with frequent relapses despite initial improvement on therapy dermatology, and immunology.

## Conclusions

A multi-disciplinary team is needed for disease management and surveillance for disease progression. Our patient’s manifestations were predominately of the skin, supraglottic larynx, and conjunctiva requiring management and surveillance by otolaryngology, ophthalmology, Immunosuppressants remain the mainstay of medical therapy, with some evidence for IVIG therapy. However, laryngeal disease represents “high-risk” MMP and is often recalcitrant to management with frequent relapses.

## References

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