Mucous Membrane Pemphigoid Causing Central Airway Obstruction

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Summary: Mucous membrane pemphigoid (MMP) is a rare variant of the skin disease pemphigoid, which predominantly involves the mucous membranes. This rare autoimmune disease that infrequently affects the respiratory tract is characterized by subepithelial blister formation that may result in scarring. Immunopathologic examination of mucous membranes reveals the deposition of immunoglobulins and complement within the subepithelial basement membrane. We describe a patient with undiagnosed MMP, with a near-fatal presentation of central airway obstruction causing acute respiratory distress. The patient was successfully treated with emergent rigid bronchoscopic resection of a ball valve-like endotracheal mass, and diagnosed with a rare variant of pemphigoid disease, MMP. The patient was treated with mycophenolate and was clinically in remission, with bronchoscopically stable lesions at 1 year of follow-up.

Key Words: mucous membrane pemphigoid, tracheobronchial obstruction, rigid bronchoscopy, mycophenolate

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Mucous membrane pemphigoid (MMP) is a rare, chronic autoimmune disease that involves various mucous membranes, most commonly the eyes and mouth.¹ It is characterized by subepithelial blistering lesions with linear deposition of immunoglobulins (IgG and IgA) and complement (C3) seen on immunofluorescence

microscopy. Central airway involvement is exceptionally rare, with just 7 previous reports.^{2–8} Although airway compromise associated with central MMP is very rare and associated with mortality, neither emergent treatment, nor follow-up have been discussed in previous reports. We describe a case with central airway obstruction due to a severe case of MMP and the emergent treatment of acute airway compromise with rigid bronchoscopy, utilizing LASER and mechanical resection.

CASE REPORT

A 24-year-old woman with a chronic tracheostomy performed 4 years ago, presented to the emergency department with acute respiratory distress. Erythematous plaques and areas of scarring were noted on the upper extremities but no bullae on the skin were visualized (Fig. 1). A chest x-ray showed bibasilar atelectasis without other acute findings.

Four years before presentation, the patient was extensively worked up for oropharyngeal ulcers and

FIGURE 1. Left upper extremity erythematous plaques and scarring.

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hoarseness. A laryngeal mass at the level of the cricoid cartilage was found that encased the glottic and supraglottic spaces, requiring a tracheostomy to relieve upper airway obstruction. A biopsy of the mass showed nonspecific, chronic, ulcerative inflammation, and laboratory testing for tuberculosis, and connective tissue disease was negative. A diagnosis could not be reached and the patient subsequently suffered recurrent pulmonary infections requiring several courses of antibiotics.

In the emergency department, a bedside fiberoptic bronchoscopy through the patient's tracheostomy revealed a near-total occlusion of the trachea approximately 4 cm proximal to the carina by a pedunculated, inflamed mass with extensive fibrous tissue, that moved with respirations causing a ball valve-like obstruction (Fig. 2A). The patient was taken emergently to the operating room for rigid bronchoscopy with intent of restoring airway patency.

Rigid bronchoscopy performed via the oropharynx revealed complete destruction of the vocal cords; therefore, the rigid bronchoscope was advanced through the tracheostomy stoma after removal of the tracheostomy tube. The discolored, highly inflamed, abnormal mucosa of trachea, and the obstructing endotracheal mass were visualized. LASER was performed to coagulate the mobile endotracheal mass, followed by mechanical resection (Fig. 2B). A stenotic left main stem lesion was also seen on airway inspection (Fig. 3A) but due to the friable nature of the lesion, further interventions were deferred. The tracheostomy tube was replaced after resection of the central airway mass and the patient was admitted to the intensive care unit for supportive

care. Pathology of the central airway mass revealed ulcerated squamous mucosa (Fig. 4A) with methicillin-sensitive *Staphylococcus aureus* (MSSA) growth on bacterial culture. Immunofluorescence showed linear IgG and C3 deposition along the basement membrane.

Skin lesions were also biopsied and sent for direct immunofluorescence, also revealing linear deposition of IgG and C3 along the basement membrane (Fig. 4B). Tuberculosis, connective tissue disease, and vasculitides were ruled out by repeat testing and the patient was diagnosed with a variant of pemphigoid disease termed MMP. Intravenous antibiotics for MSSA and a prolonged prednisone (0.75 mg/kg) taper over 3 months were initiated. Because of deficiency of thiopurine-methyltransferase activity (below 0.11 nmol/mL) posing an increased risk of side effects from azathioprine, the patient was started on immunosuppression with mycophenolate.

One month following intensive care unit discharge, a rigid bronchoscopy was repeated to treat the left main stem bronchial stenosis. Holmium LASER was used in contact mode to cut the circumferential web-like stenosis followed by sequential mechanical dilatations with the small rigid bronchial tubes (8 mm to a maximum of 11 mm). Several small pemphigoid-related lesions were observed during the bronchoscopy at different levels in the tracheobronchial tree (Fig. 3B). Successful restoration of airway patency was accomplished.

Oral mycophenolate mofetil was prescribed in increasing doses up to 1000 mg twice a day, with appropriate monitoring of complete blood count and complete metabolic panel for the next year.

FIGURE 2. A, Pedunculated, inflamed mass with extensive fibrous tissue, that moved with respirations causing a ball valve-like obstruction. B, Patent trachea after LASER and mechanical resection of the obstructing mass.

FIGURE 3. A, Left main stem stenosis. B, Several small mucous membrane pemphigoid lesions observed during the bronchoscopy.

Surveillance bronchoscopy was performed every 3 months for the first 6 months, then at 1-year post-treatment initiation showing stable disease. The patient suffered a single mild bacterial infection of the tracheobronchial tree, treated as an outpatient with oral doxycycline. No further pulmonary infections or exacerbations of her MMP were detected on surveillance bronchoscopy during the 1-year follow-up period. Pulmonary function tests could not be performed due to patient's tracheostomy and

supraglottic scarring failing to detect a quantitative improvement.

Mycophenolate was well tolerated, no adverse events were seen and no disease progression was observed. The patient also reported a decrease in the frequency of skin and oropharyngeal lesions.

DISCUSSION

MMP is a rare autoimmune disease that infrequently affects the respiratory tract. It is

FIGURE 4. A, Endotracheal biopsy showing ulceration and bacterial colonization. B, Skin lesion showing direct immunofluorescence with linear deposition of IgG and C3 along the basement membrane.

TABLE 1. A Summary of the Prior Reports on MMP With Tracheobronchial Involvement

References	Age (Y)	Sex	Bronchoscopic Description	Coexistent Lesions	Treatment	Outcome
Derbes et al ²	20	Male	Tracheal stenosis starting 2 cm proximal to carina	Ocular, larynx and tracheobronchial lesions	None	Death
Müller and Salzer ³	22	Male	Left main stem bronchial stenosis	Skin, oral lesions, and laryngeal stricture	Sleeve resection and end-to-end anastomosis	Relief of the stenosis with 8 wk follow-up
De Carvalho et al ⁴	20	Female	Tracheal ulcers surrounded by scarring	Cornea, oral cavity, esophagus, vulva, bullous skin lesions	Triamcinolone, dapsone, cyclophosphamide, azathioprine	Death
Gamm et al ⁵	17	Female	Subglottic, tracheal, and severe left main stem bronchial stenosis	Skin, conjunctiva, and oral cavity	Left main stem bronchus stent placement, dapsone, and prednisone	Death
Bonifazi et al ⁶	73	Female	Extensive ulcerative tracheitis/bronchitis with fibrinous exudates	Bullous skin lesions	High-dose prednisone, antibiotic not specified	Death at 1 y from ischemic heart disease
Kato et al ⁷	76	Female	Scarred mucosa in the trachea and left bronchus, severe airway edema	Conjunctiva, oral mucosa, bullous skin lesions	Prednisone, cyclophosphamide	Death
Minaie and Surani ⁸	34	Female	Entire tracheal mucosa replaced by thick whitish-gray mucosa, abruptly stops at the carina	Cornea, oropharynx	Prednisone, methotrexate, rituximab, vancomycin	Responded to therapy, no follow-up mentioned

characterized by mucosal, subepithelial blister formation that may result in scarring with immunopathologic findings defined by the deposition of immunoglobulins and complement within the subepithelial basement membrane. The usual course is benign with chronic lesions that cause scarring, hence also known as “cicatricial” pemphigus.¹

MMP lesions are prone to infection causing fibrosis and granulation tissue formation. Coinfection with MSSA was witnessed in our case as well as in a previous report.⁶ Scarring involving the upper and lower airways may lead to acute respiratory compromise and fatal sequelae similar to this case.

Reports of MMP with tracheobronchial involvement are very rare. It is worth mentioning that a majority of cases reported, including our case, involved younger adults. This is in contrast to MMP as a whole, which commonly arises in older adults between 60 and 80 years of age.¹ This suggests that age may be a possible predictor of airway involvement, perhaps warranting screening bronchoscopies in that population of patients to prevent high-risk consequences. Furthermore, sex may also play a role in

predicting lower airway involvement, noting that most cases reported with tracheobronchial involvement have been in female patients.

To our knowledge, only 7 cases of MMP with tracheobronchial involvement have been reported. All cases showed a tendency of central airway involvement and some with left main stem stenosis as in our case. Four cases presented with respiratory failure that resulted in mortality.^{2,4,5,7} Our patient had near-fatal respiratory failure from the valve-like pedunculated mass that may have resulted in mortality without emergent resection. Table 1 summarizes the findings of prior reports of respiratory tract MMP.

MMP is generally diagnosed with a combination of clinical findings characterized by subepithelial blister formation, and immunopathologic findings of immunoglobulins and complement within the subepithelial basement membrane. Direct immunofluorescence is considered the gold standard for diagnosis.

Immunosuppression with azathioprine and a prolonged prednisone taper has been the mainstay of therapy for many years^{9,10} with no reports on managing tracheobronchial MMP with mycophenolate.¹¹

Our patient could not be treated with azathioprine due to deficiency of thiopurine-methyltransferase activity posing an increased risk of side effects from azathioprine, thus mycophenolate proved to be an effective treatment for our patient.

CONCLUSIONS

The possibility of tracheobronchial MMP should be considered in young women with skin lesions and blister-like lesions of the tracheobronchial tree. Submission of fresh tissue by the bronchoscopist for immunofluorescence can be vital in confirming this diagnosis. Noting that most reported cases of tracheobronchial MMP were in young females, they may benefit from closer follow-up to prevent complications and mortality.

REFERENCES

1. Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol*. 2002;138:370–379.
2. Derbes VJ, Pitot HC, Chernosky ME. Fatal cicatricial mucous membrane pemphigoid of the trachea. *Dermatol Trop Ecol Geogr*. 1962;1:114–117.
3. Müller LC, Salzer GM. Stenosis of left mainstem bronchus in a case of cicatricial pemphigoid. *Eur J Cardiothorac Surg*. 1988;2:284–286.
4. de Carvalho CR, Amato MB, Da Silva LM, et al. Obstructive respiratory failure in cicatricial pemphigoid. *Thorax*. 1989;44:601–602.
5. Gamm DM, Harris A, Mehran RJ, et al. Mucous membrane pemphigoid with fatal bronchial involvement in a seventeen-year-old girl. *Cornea*. 2006;25:474–478.
6. Bonifazi M, Zuccatosta L, Poidomani G, et al. Bullous pemphigoid with the unusual complication of tracheobronchial involvement. *Chest*. 2013;143:236–238.
7. Kato K, Moriyama Y, Saito H, et al. A case of mucous membrane pemphigoid involving the trachea and bronchus with autoantibodies to beta3 subunit of laminin-332. *Acta Derm Venereol*. 2014;94:237–238.
8. Minaie A, Surani SR. Mucous membrane pemphigoid with tracheal involvement. *Case Rep Pulmonol*. 2016;2016:5749784.
9. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol*. 2005;6:93–103.
10. Nguyen QD, Foster CS. Cicatricial pemphigoid: diagnosis and treatment. *Int Ophthalmol Clin*. 1996;36:41–60.
11. Trebing D, Ziemer A. Acquired epidermolysis bullosa with a highly varied clinical picture and successful treatment with mycophenolate mofetil. *Hautarzt*. 2001;52:717–721.

ERRATUM

Erratum: Cynthia Diane Ray, MD, August 28, 1970—April 5, 2017

In the July 2017 issue, the name of the author of the In Memoriam article entitled “Cynthia Diane Ray, MD, August 28, 1970—April 5, 2017” (*J Bronchol Intervent Pulmonol* 2017;24(3):186–187) was misspelled. The author’s name should have appeared as Michael J. Simoff, MD. The publisher sincerely regrets this error.

REFERENCE

- Simo MJ. Cynthia Diane Ray, MD, August 28, 1970—April 5, 2017. *J Bronchol Intervent Pulmonol*. 2017;24:186–187.