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Pemphigoid of the pulmonary system (POPS): A review of a less recognized feature

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ABSTRACT

This review of Pemphigoid of the Pulmonary System (POPS) is a comprehensive description of pulmonary involvement in patients with mucous membrane pemphigoid (MMP), which is an orphan autoimmune blistering disease. The objective of the review was to analyze clinical features of pulmonary involvement in MMP. This POPS review is a case series in which multiple search engines were utilized from inception to June 2022 for cases of MMP with biopsy and immunopathology proven tracheal and bronchial pemphigoid. Clinical profiles prior to pulmonary involvement, bronchoscopy findings, clinical course and therapy were recorded and cause of death was analyzed.

Patients with documented MMP who developed tracheal, bronchial and pulmonary involvement were included in the POPS review. Histology and immunopathology documentation were essential diagnostic criteria. Comparison groups were not possible. Patients were treated with immunosuppressive therapy. Some required surgical interventions. Six of the 11 patients attained complete or partial remission on or off therapy. Five patients died from pulmonary complications.

The POPS review had six females and five males. The mean age at onset was 20 years (range 4–76), while 80% of the patients were under 40 years. All had severe widespread MMP involving three to five mucosal tissues. 100% had oral, 82% had ocular and cutaneous involvement. Pulmonary involvement occurred at 24 mo (range 2–372) after the onset of MMP. Bronchoscopy revealed acute inflammation during active disease and scarring of the trachea and bronchi in the later stages. Systemic infections occurred in 45%, while pulmonary infection occurred in 36%. Mortality due to respiratory failure, at the median age of 20 years (range 18–76), occurred in 45% of the patients, and was considered disease related.

In spite of the young age, while there are some similarities in the clinical profile and response to systemic therapy, there are definitive differences from other patients with MMP. Early diagnosis with appropriate management could produce better clinical outcomes and prevent mortality in this orphan disease. Consequently, there is a critical need for early identification and diagnosis of POPS.

1. Introduction

Mucous membrane Pemphigoid (MMP) is an orphan autoimmune mucocutaneous blistering disease, which may be potentially fatal [1]. It is exceedingly rare. The reported incidence is one to two patients per million population per year [2]. It is predominantly a mucosal disease affecting the ocular, nasal, oral, oropharyngeal, pharyngeal, laryngeal, tracheal, upper third of the esophagus, genital, and anal canal mucosa and the skin [1–4]. The distribution reported was oral mucosa (80–90%), ocular mucosa (50%), the skin (20%), genitalia (15%), anal mucosae (10%), pharynx (<10%), larynx (<10%) and esophagus (<10%), described in several reviews, [5–10]. Neither of them mention lower airway or pulmonary involvement.

The disease presents as intact bullae, vesicles, or erosions. A distinctive feature of this orphan disease is that, as the blisters or erosions heal, they result in scarring, except in the oral cavity [1]. The sequelae of this scarring process are consequential and devastating [1]. Ocular involvement can cause visual impairment in 30% and lead to bilateral blindness in 20–25% [11]. Nasal scarring reduces airway access [12]. Laryngeal involvement causes laryngeal stenosis, sudden

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asphyxiation, and death [12]. Esophageal stenosis causes dysphagia and, when severe, may require gastric tube feeding. Esophageal rupture causes fatal mediastinitis [13]. Vaginal stenosis excludes sexual activity and Pap smears are no longer possible [14]. Anal stenosis results in constant fecal leakage and a lifelong need for adult diapers [15].

The objective of this review of POPS was to examine clinical features, diagnosis, treatment, consequences and sequelae of such involvement, and associated high mortality rate. In so doing, the clinical entity of "pulmonary pemphigoid" (PPg) or POPS was described. There are many distinguishing features of POPS. Therefore, it may be considered an important late subset of MMP.

2. Methods

Several databases were searched for studies between their inception to June 2022. Keywords used were pulmonary, respiratory, bronchial, tracheal, bronchioles, and mucous membrane pemphigoid. Eleven cases were reported [16–26].

The following inclusion criteria were used (i) Diagnosis of MMP based on histology and immunopathology (ii) Involvement of upper airway confirmed by an ENT specialist, esophageal involvement by endoscopy confirmed by a gastroenterologist or ocular involvement confirmed by an ophthalmologist. (iii) Pulmonary involvement documented from physical examination and preferentially by bronchoscopy and biopsies. Exclusion criteria: lack of clinical features, lack of documentation of pulmonary disease by bronchoscopy, and absence of pulmonary histology or immunopathology.

On each of the 11 patients, the following information was collected: sex, age of onset of MMP, sites of involvement, pulmonary symptoms, the time between the initial symptoms of MMP and pulmonary symptoms, biopsy information, direct immunofluorescence studies, autoantibody studies, infection rate, observations on bronchoscopy, medical treatments, surgical interventions, clinical outcome, mortality rate, cause of death, the time interval between bronchoscopy and time of death and the time interval between the onset of initial symptoms and time of death in patients.

Study data were analyzed with MedCalc. Numerical data were presented as median and interquartile range (IQR) and frequency data as rates. Two group comparisons were carried for a number of parameters with Chi-square test. All hypotheses were constructed as two-tailed and an alpha-critical value of 0.05 was accepted as significant.

3. Observations

3.1. Pathogenesis

To describe the entire pathway for pathogenesis is beyond the scope of this review. Only significant issues relevant to POPS are included. Mucous membrane Pemphigoid (MMP) results from the production of autoantibodies targeting molecules (antigens) such as BP180, BP230, α6 integrin, β4 integrin, laminin-332, and possibly other molecules in the basement membrane zone (BMZ). Binding of the autoantibodies to these molecules results in blister formation [27]. Cells of the inflammatory and immune system participate in the pathophysiology of blister formation.

Presence of β4 integrin has been described in the lung epithelium [28]. This would provide a target antigen for anti-BMZ autoantibodies. In addition, investigators using immunohistochemical techniques and electron microscopy, have demonstrated that some of the molecules, in the hemidesmosomes, that bind bronchial epithelial cells to the extracellular matrix, are present in the lung [29]. These include BPAG 1 (BP230), BPAG 2 (BP180), α6β4 integrin and laminin-5 (laminin-332) [29].

Earlier studies have demonstrated that the epitopes involved in ocular pemphigoid are different from epitopes in other mucosae in MMP [30]. Most recently, using a computer based model, it has been demonstrated that BP180, BP230, α6 and β4 integrin contain multiple epitopes that bind to MHC Class II gene products, which are present in most MMP patients worldwide. This may partially account for involvement of different mucosae in the same or different patients [31]. İt is entirley possible that one of these epitopes could be involved in pulmonary pemphigoid. Nonetheless, the experiments to prove this possibility have not been reported.

3.2. Clinical presentation

The frequency of involvement of various mucosal sites and baseline characteristics are presented in Table 1. There was a slight female preponderance (6:5). One hundred percent of patients had oral disease, 82% had ocular and skin, 64% laryngeal, 36% esophageal and pharyngeal, 18% vulvar/cervix, and 36% had anal or penile involvement. All 11 patients had tracheal and bronchial involvement. All the patients had at least three additional mucosae involved. Four had involvement of five mucosal tissues. This indicated that MMP was widespread and severe. Neither author of the 11 case reports described their patients as having pulmonary pemphigoid or POPS.

The age distribution at the time of disease onset was particularly noteworthy. The median age of onset was 20 years (range 4–76). At the age of disease onset, six patients were under 20, seven under 25, nine under 40 and 10 were under 65. Only one patient was 76 years old. Hence, 82% of the patients were under 40 years of age at the time of the onset of disease. One of these patients had the first ocular symptoms of MMP at the age of 4 [24].

The patients experienced symptoms based on the sites of involvement. These were similar to those reported in previous studies and reviews [4]. These 11 patients had pulmonary symptoms, indicating lower airway involvement, that are presented in Table 2. Shortness of breath was reported in all the patients but persistent cough and bloody sputum were less frequently reported.

Table 1
Comparison of MMP and PPg baseline characteristics, clinical features and outcomes.

	Total number and percentages of patients with MMP [24]' (N = 162)[a]	Total number and percentages of patients with PPg in POPS study (N = 11)	Difference (95% Confidence Interval)	P value
Age of onset (yrs)	Mean 65 Range 27–103	Median 20 Range 4–76	NA[b]	NA[c]
Sex (F:M)	92:70	6:5	NA	0.88
Sites of involvement (N)(%)				
Oral mucosa	121 (75%)	11 (100%)	26% (−1% to 33%)	0.055[e]
Ocular mucosa	109 (67%)	9 (82%)	15% (−15% to 30%)	0.30
Skin	45(34%)	9 (82%)	48% (18% to 63%)	0.001[d]
Esophageal	15(12%)	4 (36%)	24% (2% to 53%)	0.02[d]
Anogenital	15 (12%)	4 (36%)	24% (2% to 53%)	0.02[d]

[a] 24 Hong GH, Khan IR, Shifera AS, et al. Incidence and Clinical Characteristics of Ocular Involvement in Mucous Membrane Pemphigoid. Ocul Immunol Inflamm 2019;27:821–825. doi:https://doi.org/10.1080/09273948.2018.1455879. PMID: 29672212

[b] NA: Non-applicable.

[c] P value cannot be calculated, standard deviation information is not available.

[d] P value <0.05 difference statistically significant.

[e] A borderline statistically significant difference.

Table 2
Clinical symptoms, sites of involvement and treatments.

	Total number of patients ($N = 11$)	Percentage of patients (%)
Symptoms related to the lower airway involvement		
Difficulty breathing often at rest	11	100%
Hoarseness / aphonia	5	45%
Persistant cough	3	27%
Bloody sputum	3	27%
Sputum with mucousal tissue present	1	9%
Bronchoscopic Findings		
Bronchial inflammation but no active ulceration or	2	18%
Bronchial mucosa fragile, easily peeling off, thick white gray overlay	2	18%
Multiple erosions with thick bloody lesions from trachea to bronchi	3	27%
Bronchial inflammation, erythema, active ulceration and sloughing	5	45%
Subglottic tracheal and bronchial stenosis	7	64%
Occlussion of trachea with extensive fibrosis extending to bronchi	5	45%
Systemic Medications		
Systemic corticosteroid as prednisone or prednisolone (1–1.5 mg/kg/day)	10	91%
Cyclophosphamide (200 mg/day)	6	54%
Rituximab	4	36%
Azathioprine after TMPT levels (150–200 mg/day)	3	27%
Methotrexate (20–25 mg/week)	3	27%
Dapsone (100–200 mg/day)	3	27%
Mycophenolate Mofetil (3 g/day)	2	18%
Doxycycline (100 mg/BID) +/− NAD	2	18%
Plasmapharesis	2	18%
IVIg	1	9%
Bortezomib	1	9%

3.3. Assessment and diagnosis

Among the 11 patients, the diagnosis of MMP was confirmed by skin biopsy in five cases [17,18,21,23,26], conjunctival biopsy in one case [20], vulva biopsy in one case [22], tracheal biopsy in two cases [18,22], pharyngeal biopsy in one case [19] and oral cavity biopsy in three cases [22,25,26]. Some patients had biopsies from multiple sites [18,22,23,26]. In one patient, a biopsy was not done and the diagnosis was made at autopsy [24]. The histology showed subepidermal or submucosal bulla with a mixed cell infiltrate in the dermis or submucosa in all 11 patients.

Results of direct immunofluorescence (DIF) studies were presented in ten of the 11 patients [16–23,25,26]. It was unavailable from a case that was described in 1962 [24]. In these, deposition of IgG and C3 was observed in a smooth linear pattern on the basement membrane zone (BMZ) (Fig. 1A). In these 10 patients, DIF staining pattern was positive and similar when biopsies were done from different sites, including the skin, [17,18,21,23,25,26] pharynx, [19] oral cavity, [25,26] conjunctiva, [20,21] and trachea [16,18].

DIF staining of respiratory tract biopsies showed deposition of immunoreactants at the BMZ in four out of six patients [16,18,19,21] (Fig. 1B). The lack of DIF in some patients was primarily due to the inability of the endoscopist to identify perilesional normal mucosa in the midst of acute inflammation and desquamation. Serological studies were available in only three cases [16,21,26]. Its lack in others may be due to lack of access or unavailability of a testing laboratory. Autoantibodies to laminin-332 were present in the sera of two patients. These patients did not have a detectable malignancy at the time of reporting [16,26]. Autoantibodies to BP180 were reported in one patient [16], and anti-BMZ antibodies detected by indirect immunofluorescence were recorded in one patient [21].

The time interval between the initial onset of symptoms of MMP and the confirmation of tracheal and/or pulmonary involvement by bronchoscopy was a median of 24 months (range 2–372). In one patient, the pulmonary involvement was confirmed at autopsy [24].

The details of observations on bronchoscopy are presented in Table 2. A spectrum of lesions were observed, which were progressive in nature. During the active stage, severe inflammation, erythema, blisters, erosions and tissue sloughing were observed (Fig. 2A and B). During the healing process, fibrosis occurred. The simultaneous presence of established fibrosis and active disease with erosions and mucosal sloughing were observed in some patients (Fig. 2C and D). Disease progression resulted in scarring in the trachea and bronchi. The timing of the bronchoscopy and the stage(s) of disease usually determined the spectrum of morphology observed.

4. Treatment

Cumulative data on systemic therapy of the 11 patients are presented in Table 2. There were no significant differences in the drug therapies

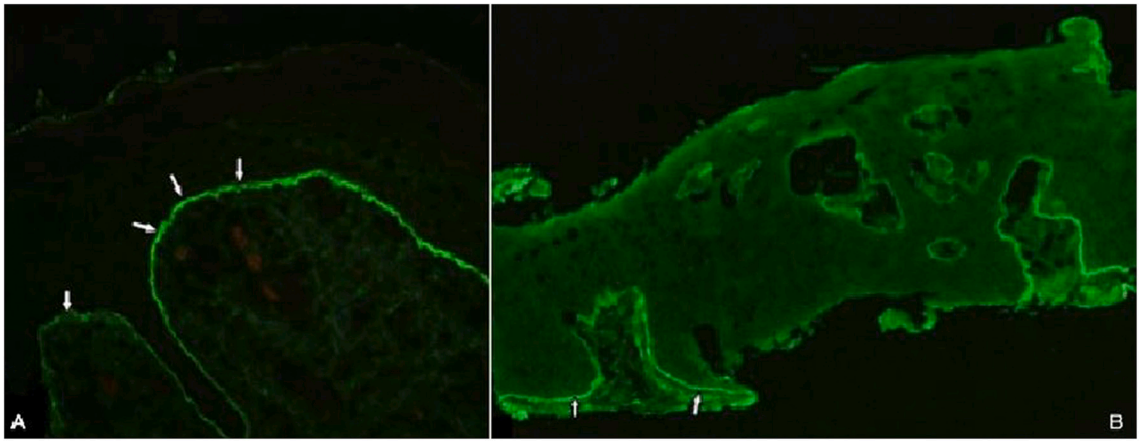

Fig. 1. Direct immunofluorescence staining. A.Perilesional skin from a patient with mucous membrane pemphigoid. Direct immunofluorescence demonstrates linear deposition of IgG along the basement membrane zone. Reproduced by permission from Wolters Kluver Health, Inc. open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND). Published in J Bronchol Intervent Pulmonol, 2017. B. Direct Immunofluorescence of perilesional tracheal epithelium. Linear basement membrane zone fluorescence with anti-human IgG is indicated by arrows. Reproduced by Permission from Springer Nature 2019. Published in The dermatologist in case reports, 2019.

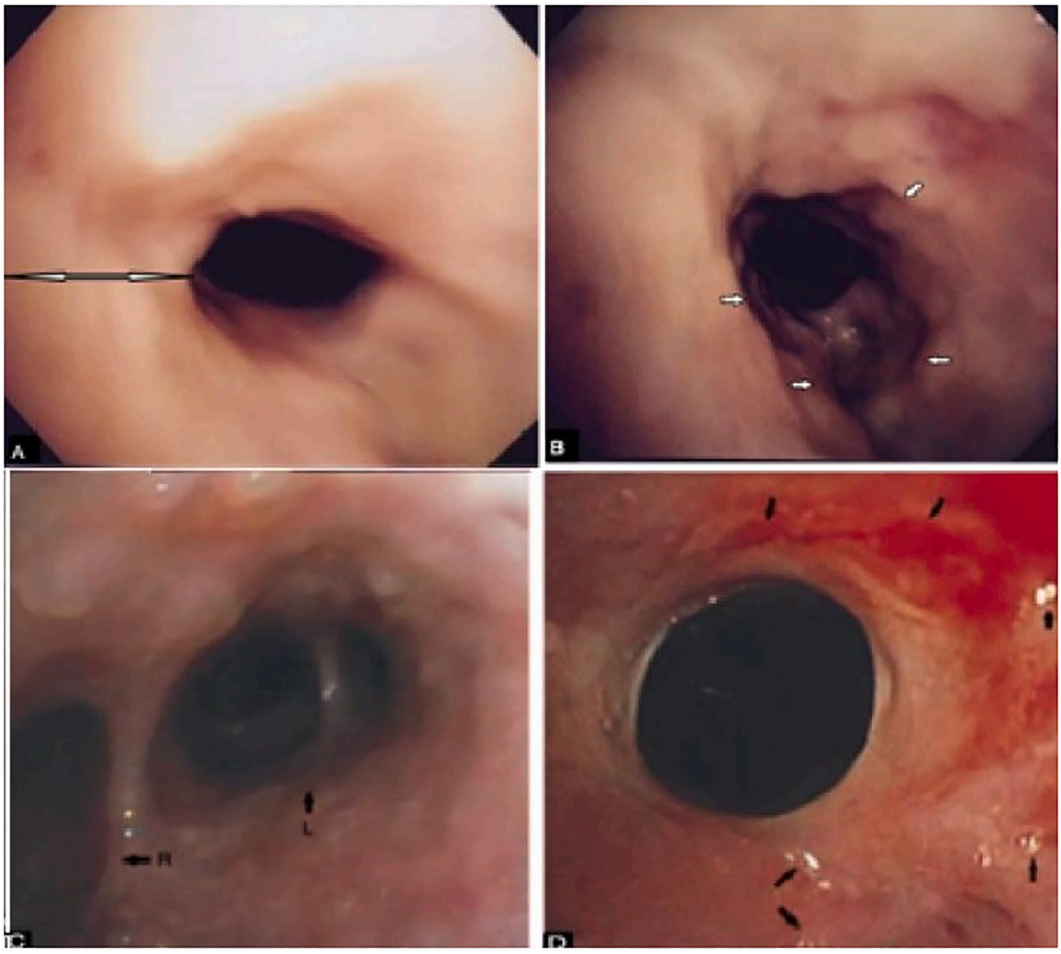

Fig. 2. Photographs from bronchoscopy. A. Highlights tracheal stenosis with abnormal edematous greyish white tracheal mucosa. B. Area below vocal cord demonstrates sloughing of tracheal mucosa, intense inflammation, and tissue debris. Reproduced by permission from an open-access article distributed under the Creative Commons Attribution License. Published by Hindawi Publishing Corporation in Case Reports in Pulmonology, 2016. C. Stenosis of the left bronchial main stem. L (Left main bronchus demonstrates significant narrowing, due to scarring of lumen), R (Right bronchus is normal and unaffected by MMP) D. Several small bullous lesions of mucous membrane pemphigoid. Black arrows demonstrate the bullae on the mucosa on the right side and inferior to the bronchus. Erosions are seen superior to the bronchial lumen. This photograph demonstrates active disease with acute inflammation, erosions and bullae. Reproduced by permission from Wolters Kluver Health, Inc. open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND). Published in J Bronchol Intervent Pulmonol, 2017.

between the patients who were in clinical remission and those who died. No protocol was uniformly used. Ten of the 11 patients were treated with a variety of medications, depending on disease severity [16,22,25,26]. One patient did not receive any drug therapy, since the relapse of MMP was not recognized until autopsy [24]. Nine of 10 patients were treated with at least two or more conventional immunosuppressive agents (ISA) [16,17,19–23,25,26].

Four of 11 (36%) patients, who were unresponsive to ISA, were treated with a B-cell depleting agent, Rituximab (RTX) [16,17,19,20]. Rituximab is a CD20+ B cell depleting agent, which has been used off-label to treat MMP [32,33]. The protocols for RTX therapy were variable. In one patient, two doses of RTX (1000 mg, two weeks apart) were given [19]. Another was treated with three months of RTX but no specific information on dosage was provided [20]. In two patients, a total of 10 doses of RTX were given in 6 months. The dose was 750 mg/wk. [10] and 900 mg/wk. [17] for eight weeks and then monthly. In only one patient, RTX was used in combination with IVIg and plasmapheresis, but the patient was non-responsive to this regime [17]. Subsequently, this patient was treated with Bortezomib (a proteasome inhibitor and anti-neoplastic agent). Four cycles were given over ten months. The patient had significant improvement and achieved clinical remission [17].

Surgical management was required for persistent dyspnea when airway scarring blocked airflow. In five patients, a tracheostomy was required to prevent asphyxiation from necrotic tissue, which could have resulted in sudden death. In two patients, it was done on an emergency basis. In one patient, a Montgomery cannula system was used instead of a classical tracheostomy [25]. Similarly, in one patient with recurrent supraglottic, glottic, and subglottic stenosis, a T-tube was placed via a tracheostomy [21]. One patient was treated twice with carbon dioxide laser vaporization for supraglottic obstruction from scarring [25] and one patient was treated with a stent [21]. Three patients required balloon or mechanical dilatation of areas of bronchial stenosis [18,19,21]. Concomitantly, topical triamcinolone, dexamethasone, and mitomycin C injections were used during bronchoscopy to treat airway stenosis [19]. In six of the 11 patients, surgical interventions were necessary [16,18,19,21,23,25]. Some needed more than one procedure [19]. In one patient, an endotracheal mass occluding the trachea was successfully removed by Laser (Holmium) resection [18]. Müller et al. treated tracheal stenosis by sleeve resection and end-to-end anastomosis [23].

Symptoms of pulmonary pemphigoid mimicked asthma or chronic obstructive pulmonary disease (COPD) and required symptomatic management. Inhaler or nebulizer with corticosteroids, cholinergics, and long or short-acting beta antagonists were used. Humidifying the

living space seemed to partially relieve hoarseness, wheezing, dyspnea, and sputum production. Nasal emollients, nasal irrigation, nasal steam inhalers, and gentle corticosteroid sprays were used to facilitate the removal of nasal crusts and debris.

5. Prognosis

Prognosis was one of the most important aspects in the analysis of this review on POPS. To facilitate the readership in understanding the prognosis, under the section of prognosis, the authors have created minor subheadings of (i) Implications of Observations and (ii) Differentiation of Pulmonary Pemphigoid from common or usual pemphigoid, to clarify why POPS may be considered a specific subset of MMP.

Six patients had "clinical clearance/remission" with markedly symptomatic improvements [16–20,23]. Four of these six received RTX [16,17,19,20]. Three patients were in clinical remission after RTX therapy [16–18]. One patient non-responsive to RTX, responded to Bortezomib [17].

There is limited data regarding the period or duration of follow-up. The data was available on only three patients, who were in clinical remission [17,18,23]. The longest follow-up period was 14 months [17]. Lack of longterm follow-up precluded determining relapse rates.

Five of the eleven patients who died (45%) had significant and extensive scarring of the trachea and bronchi [21,22,24–26]. The median age at onset among the patients who died was 20 years (range 4–76). The median interval between onset of MMP and death was 18 months (range 3–192).

Pulmonary impairment was contributary to the cause of death in all five patients [21,22,24–26]. Before the definitive diagnosis was made through bronchoscopy, three of the five patients had a chest computed tomography (CT) scan and gallium scintigraphy [21,22,26]. In one patient, [21] a CT scan revealed a widened mediastinum with fibrosis, lung consolidation, and carinal, subcarinal and pretracheal lymphadenopathy. In that patient, the gallium scan was undiagnostic. Fine-needle aspiration of the widened mediastinum demonstrated no malignant, vasculitic or granulomatous processes, but there were chronic, nonspecific inflammatory changes. In the second patient, both CT scan and gallium scintigraphy were nonspecific [26]. In the third patient's CT scan, it showed hyperinflated lungs with distended bronchi and the patient had wheezed on examination [22].

The cause of death for four of the five patients was reported as cardiopulmonary arrest (CPA), secondary to respiratory failure [21,22,24,26]. The fifth patient died because of anoxic brain injury complicated with septicemia. This latter patient had severe pulmonary pemphigoid and the anoxic brain injury occurred during intubation [25]. Based on bronchoscopy findings [21,22,26] and autopsy data [22,24], patients had a combination of active disease, including inflammation, erosion and bullae, and chronic disease, as demonstrated by scarring of the trachea and bronchi. In two patients, infections were considered a contributory factor to the cause of death [25,26].

During the clinical course of MMP, five of 11 patients had systemic infections [18,20,22,25,28]. Four of these five patients had pulmonary infections [18,20,25,26], one of which was due to MRSA [20]. Two of these five patients had multiple respiratory infections [25,26]. One patient had a urinary tract infection [26], and another had herpes gingivostomatitis, herpes labialis, upper respiratory tract infection, and recurrent pneumonia followed by septicemia [25]. The rate of infection in those who died and those who survived was not significantly different.

5.1. Implications of observations

In this review on POPS, we present data on eleven patients with MMP who had tracheal and bronchial involvement. In neither of the 11 patients was pulmonary involvement identified as pulmonary pemphigoid, but simply considered as a pulmonary disease without the consideration of a late and rare subset of MMP. Hence, we refer to this clinical entity as pulmonary pemphigoid (PPg) or preferably Pemphigoid of the Pulmonary System (POPS).

5.2. POPS patients have different features from usual MMP patients

Based on the analysis of the data provided on these 11 patients, certain features may be considered characteristic of POPS. The patients were young with 55% under 20 and 82% under 40 years of age at disease onset. In contrast, in most reports on MMP, the age of onset was the sixth to seventh decade of life (Table 1) [34]. All the patients had severe widespread disease prior to the detection of POPS. Isolated POPS, without the involvement of other mucosae or skin, was not reported. A high infection rate, particularly pneumonia, was reported. Multiple factors are likely to contribute to the high incidence of pulmonary infections, including drug-induced immunosuppression and scarring of the lower airways leading to delayed clearing of mucous.

In this cohort of 11 patients, the mortality rate was 45%. The age at the time of death was 18 to 76 years (median of 20). The interval between onset of MMP and death was 3 to 192 months (median of 18 months). Interestingly, the time between bronchoscopic diagnosis and death was 1 to 6 months (median of 1.5 mo). This data would suggest that POPS was recognized late in the course of the disease. Furthermore, both bronchoscopic findings and autopsy data clearly showed that the trachea and bronchi had active disease, demonstrated by erosions and mucosal fragility, simultaneously with severe and extensive tracheal stenosis secondary to fibrosis. These observations highlighted the importance of the early involvement of a pulmonologist and the need for immediate bronchoscopy. Bronchoscopy should be performed using a small-size bronchoscope in order to avoid trauma to the mucosa that could result in new blister or erosion formation. It is suggested that early assessment of the airway is warranted whenever a patient with MMP has respiratory symptoms, since scarring of the lower airway was a frequent observation in patients in this review.

5.3. Pulmonary pemphigoid: A less recognized feature of MMP

This initial review on 11 patients should be considered important and enhance awareness and early recognition of this orphan disease. If POPS were identified, it would warrant urgency for therapeutic intervention. Physicians who treat MMP should caution their patients that if they experience coughing or other respiratory symptoms, they should contact them immediately. In pemphigus, the most common cause of death is opportunistic infections, secondary to immunosuppressive therapy [35]. In contrast, the data in this review would suggest that the cause of death in POPS was the disease which caused respiratory failure.

A somewhat parallel situation occurred in paraneoplastic pemphigus (PNP). First described in 1990 as a new clinical entity, with only five patients that were collected from multiple sources [36]. Once clinicians became aware, a large number of patients were reported from all over the world. In 1999, pulmonary involvement was described in PNP [37]. Since then, death in many patients has been attributed to the sloughing of bronchial tissue and to bronchiolitis obliterans [38]. Eventually, the nomenclature changed to paraneoplastic autoimmune multi-organ syndrome (PAMS) [39].

6. Discussion

MMP is a mucosal disease with increased predilection for oral mucosa followed by ocular, skin, genital, anal and respiratory tract mucosa [2,8]. The most distinctive feature of MMP is that of lesions of which irreversible scarring occurs. Scarring can lead to devastating complications, such as loss of vision due to conjunctival involvement [11,39] and scarring of laryngeal mucosae, which can cause stenosis and may lead to asphyxiation and death [12,40,41]. In some patients, the consequences of scarring may result in the need for surgical interventions, like

tracheostomy tubes or stent placement [21,25]. Pulmonary involvement was a late sequela of this orphan disease (MMP) [42]. Pulmonary involvement was usually associated with involvement of other mucosae. Oral involvement was present in all the patients [43]. DIF demonstrated deposition of IgG and C3 in a linear pattern on BMZ of perilesional tissue and histological findings were consistent with submucosal bulla with mixed inflammatory cell infiltrate in the submucosal and subepidermal regions.

This review describes a cohort of 11 MMP patients, who presented with extensive involvement of the pulmonary system (POPS). 54% achieved clinical remission [16–20,23]. 36% patients were treated with RTX. There was no uniformity in the protocols used for Rituximab therapy. Three out of four patients who received RTX achieved clinical remission [16,18,19], while one was treated with Bortezomib [17]. However, the longest follow-up was only 14 months [19]. When used alone, RTX is associated with a high relapse rate [44,45]. Studies in pemphigus vulgaris have documented that relapse rates increase with increase in the duration of follow-up [46]. When RTX is used in combination with IVIg, longterm remissions are frequently documented [47]. Mechanism of unresponsiveness to RTX can be attributed to IgA producing plasma cells as observed in previous studies [48,49].

Data in this analysis has demonstrated that age of onset of POPS patients was significantly younger than most MMP patients. Another noteworthy observation made in this analysis was the delay of identification of pulmonary involvement, with a median of 24 months. Perhaps the most significant, was the high mortality rate of 45% in POPS. Association of systemic infections was the leading cause of death in bullous pemphigoid [50].

Use of RTX in MMP with concomitant immunosuppressive therapies warrants careful monitoring for systemic infections. Only careful long-term follow-up can help in creating a protocol most effective for use of RTX in POPS. In the future, physicians who treat such patients should carefully document length of follow-up, the protocol used, data on CD20+ B-cell depletion and repopulation and any associations with relapses. Early identification, diagnosis, and subsequent appropriate intervention, based on individual case, may be essential for preventing mortality [51].

MMP is exceedingly rare. The reported incidence is one or two patients per one million population per year [2]. It is entirely possible that pulmonary involvement may occur in a small fraction of MMP patients. Suspicion of POPS should come when patients with MMP have persistent cough and shortness of breath. POPS should be considered if the cough is productive and blood or bronchial tissue is expectorated. Whenever coughed up tissue is available, it should be examined by histology and immunopathology. Since 100% of patients in this review had oral disease, this awareness is important for practioners of dental medicine. POPS should be considered by specialists in oral medicine, dermatology, and ophthalmology since these providers are more likely to encounter MMP patients in the initial stages of their clinical disease. This review highlights the fact that MMP patients are best treated by a team of physicians from multiple specialties, who work together in the best interest of the patient.

The limitation of this review is that the data is retrospective. Since multiple authors were involved, there was a lack of uniformity in data reported. Limited follow-ups did not allow reporting of relapse or length of remission. While diagnosis of MMP was confirmed by DIF from multiple sites, not all patients had DIF of the trachea or bronchi. In some reports, serological studies were not provided, possibly because they may not have been available.

MMP currently has subsets identified by the predominant clinical involvement and the putative antigen involved in the pathogenesis. These subsets include oral pemphigoid [51], ocular cicatricial pemphigoid (OCP) now referred to as ocular MMP [11], laminin-332 pemphigoid [52], p200 pemphigoid [53] and anti-laminin-ϒ1 pemphigoid [54]. In none of these subsets has pulmonary involvement been described. Hence, the need to describe POPS as a subset of late stage of MMP, a less recognized feature.

7. Conclusions

Patients with POPS have significant, severe, widespread MMP initially. POPS occurs later in the course of the disease. This interval can be extremely variable and was one of the important factors contributing to the delay in diagnosis. Consequently, it was often not recognized as an integral component of MMP. Certain clinical characteristics were observed in most patients, but the most noteworthy and distinguishing feature was the young age of the patients at the onset of MMP. POPS was frequently associated with extensive irreversible scarring of the trachea and bronchi. Resultantly, there was a delay in consulting a pulmonologist for the diagnosis of POPS, which was eventually established by bronchoscopy and biopsy of bronchial tissues. Treatment was difficult and often unsatisfactory. Many patients had serious infections, especially pneumonia. The mortality rate in this cohort was 45% and the evidence would suggest that the cause of death was respiratory failure and therefore, disease related. Early recognition of POPS may improve prognosis by aggressive, appropriate systemic and local therapy, reduce scarring, and hopefully reduce the mortality rate.

Take home message

Pulmonary involvement occurs late in the clinical course of MMP. The late onset makes it difficult for the treating physicians to associate the tracheobronchial involvement to MMP.

Patients may respond to immunosuppressive therapy. Some patients responded to Rituximab.

A 45% mortality rate was observed in this cohort. Many patients had pulmonary infections and pulmonary failure. In all likelihood, the cause of death could be attributed to the disease process.

Early diagnosis with appropriate management could produce better clinical outcomes and prevent mortality in this orphan disease.

Declaration

This manuscript has not been previously published and is not under consideration for submission elsewhere. The manuscript is approved by all the authors.

If accepted, this manuscript will not be published elsewhere in the same form.

Authorship

All the authors have made substantial contributions to the concept and design of the review, data collection, analysis and interpretation and in the drafting, revisions and final approval of this manuscript.

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All the authors report no conflicts of interest. The authors alone are responsible for the content and preparation of this manuscript.

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Appendix A. Supplementary data

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