Characteristics Upon Presentation of Ocular Mucous Membrane Pemphigoid Patients in Puerto Rico

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Objective: To describe the characteristics upon presentation of a cohort of Hispanic patients living in Puerto Rico with ocular mucous membrane pemphigoid (MMP).

Methods: Retrospective chart review of subjects with ocular MMP at one academic institution and one private practice. Patients with clinical evidence of ocular MMP, along with a positive mucous membrane biopsy revealing linear antibody or C3 deposition in the basement membrane zone, or with a positive indirect immunofluorescence assay were included. Descriptive statistical analysis was performed.

Results: Eight patients with ocular mucous membrane pemphigoid were identified. The median age upon presentation was 60.5 years; however, 2 patients were in their 4th decade and one in the 5th decade of life. Females constituted 62.5% of the cohort. All patients presented with stage III ocular MMP in at least one eye and 50% had history of trichiasis. Seven out of eight patients (87.5%) had extraocular symptoms for a median duration of 36 months (range 2-144 months). The most common site of extraocular involvement was the oropharynx, present in 87.5% of patients.

Conclusion: Our results suggest that in Puerto Rico ocular MMP most commonly presents in the seventh decade of life. The presence of symblepharon, trichiasis or oropharyngeal mucosal disease should prompt further evaluation and consideration for immunopathological tissue analysis and an IIF assay. [*P R Health Sci J 2020;39:34-38*]

Key words: Ocular Cicatricial Pemphigoid, Mucous Membrane Pemphigoid, Puerto Rico

Mucous membrane pemphigoid (MMP) is a multi-systemic autoimmune disease in which autoantibodies bind the basement membrane zone (BMZ), potentially affecting mucous membranes throughout the body (1,2). It is a rare disease, with its incidence estimated between 1:20,000 to 1:40,000 ophthalmic cases (2,3). It most commonly affects elderly patients in their seventh decade of life, has a slight female predominance, and carries no racial or geographic predilection (2). MMP may involve the oropharyngeal, nasal, anogenital, and ocular mucosa; moreover, its potential to involve the esophageal and tracheal mucosa renders it a potentially life-threatening condition (1).

Approximately seventy to eighty percent of patients with MMP have ocular involvement (3,4). It remains the leading cause of cicatrizing conjunctivitis in developed countries (4). Ophthalmologically, the natural course of this condition is to progress from a chronic conjunctivitis to fornix foreshortening, symblepharon formation, ankyloblepharon, and eventually to complete keratinization of the ocular surface (2). If untreated, patients will eventually become blind in both eyes (1,2).

Clinically, ocular MMP is difficult to differentiate from other etiologies of cicatricial conjunctivitis (pseudopemphigoid) (1). A conjunctival biopsy using either direct immunofluorescence (DIF) or immunoperoxidase technique has a sensitivity of approximately 80% and is a favorable method of establishing the diagnosis (1). The goal of the biopsy is to establish a definite evidence of MMP while revealing a linear deposition of immunoreactants such as IgG, IgM, IgA, or complement 3 component (C3) at the BMZ. Alternately, indirect immunofluorescence (IIF) assays for the presence of circulating antibodies to the BMZ have a sensitivity that, in optimal scenarios, approaches 52% (2).

Recent advances have led to a better understanding on how this condition is best managed with immunosuppressive therapy (3,4). Typically, ocular MMP is managed with oral

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corticosteroids and cyclophosphamide, although recently, there have been several reports regarding the successful use of rituximab in this condition (3,5,6). Alternate means of therapy for cases who have failed conventional treatment include intravenous immunoglobulin and anti-tumor necrosis factor (TNF) alpha agents, which have been used with various degrees of success (2,4,7). Certain characteristics upon presentation such as trichiasis, prior eyelid surgery, and esophageal involvement have been associated with less likelihood of achieving ocular remission (3). Despite the therapeutic challenge that ocular MMP represents, in one series 91% of patients achieved remission within two years after having started therapy with oral prednisone and cyclophosphamide (3).

To the best of our knowledge, there are no reports in the medical literature characterizing a cohort of ocular-involving MMP patients of Hispanic origin in Latin America, including Puerto Rico. The aim of our study is to describe the demographic and clinical characteristics upon presentation of a cohort of Hispanic patients living in Puerto Rico with a diagnosis of ocular MMP.

Methods

The medical records of all subjects, regardless of age, with a diagnosis of ocular MMP presenting for evaluation and management at the University of Puerto Rico Department of Ophthalmology outpatient clinics and at one private practice from July 2006 to May 2019 were reviewed. The MMP diagnosis ascertainment was made by a combination of the characteristic clinical findings and either a mucous membrane biopsy specimen showing linear deposition of autoantibodies (IgG, IgM, or IgA) or C3 along the BMZ or by the presence of circulating anti- BMZ antibodies in the patient's serum detected by means of an IIF assay. Patients in which ocular MMP was suspected and whose diagnosis had not been confirmed by means of biopsy or IIF were excluded from the study.

The staging of the conjunctival scarring was accomplished by using the Foster Classification System (8). Stage I disease is described as chronic conjunctivitis with subepithelial fibrosis. Stage II is characterized by inferior fornix foreshortening. Stage III is characterized by symblepharon formation. End-stage disease with ankyloblepharon and extreme conjunctival keratinization is defined as stage IV MMP.

The data obtained from the review of medical records of ocular MMP patients meeting the study criteria was prospectively entered into a new database for analysis. The database included demographic and clinical data, as well as biopsy and serum results. Descriptive statistical analysis was performed using Microsoft Excel® software program. Frequencies of clinical and demographic variables were tabulated to facilitate analysis. The University of Puerto Rico, Medical Sciences Campus Internal Review Board reviewed and approved this protocol.

Results

Eight patients with ocular mucous membrane pemphigoid were identified over a 13-year period. The median age upon presentation was 60.5 years with a range from 36 to 66 years (See Figure 1). Five out of eight patients were female (62.5%). All the patients included in the study identified themselves as Hispanic and lived in the Commonwealth of Puerto Rico. The demographic and clinical characteristics have been summarized (See Table 1).

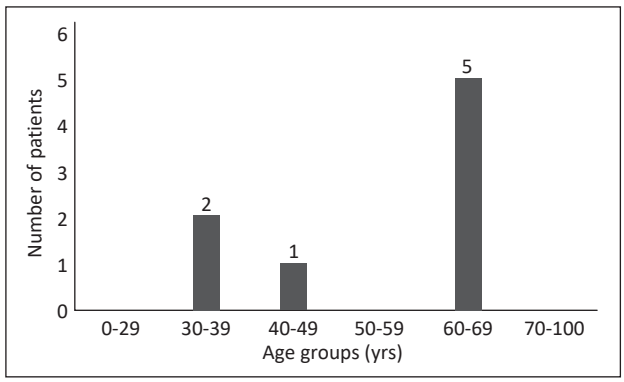

Figure 1. Ocular MMP patient's distribution per age group (n=8).

Sixteen eyes of 8 patients were included in the analysis. The median visual acuity (VA) on the better eye was 20/30 with a range from 20/20 to 20/50. The median VA on the worse eye was 20/40 with a range from 20/20 to 20/200. None of the patients had history of glaucoma and 50% had history of trichiasis. All of the patients had at least one eye with stage III ocular MMP upon presentation. The median duration of ocular symptoms was 8.5 months with a range from 3 to 24 months. All 8 patients in our study had a conjunctival biopsy compatible with the diagnosis of MMP. All 8 (100%) had IgG, 7 (87.5%) had C3, and 1 (12.5%) had IgA detected at the conjunctival BMZ. None of our patients had anti-BMZ IgM detected at the conjunctival biopsy. IIF assay for circulating anti-BMZ antibodies was performed in six out of eight (75%) patients; blood samples for IIF were obtained concomitantly on the same day as the conjunctival biopsy. Out of the six patients assessed for circulating antibodies against BMZ, 2 (33%) of them had a positive result.

Seven out of eight patients (87.5%) had extraocular manifestations of MMP. A prior extraocular site biopsy had been performed in 62.5% of patients, none of which were diagnostic. The median duration of the extraocular symptoms was 36 months with a range from 2 to 144 months. The most common site of extraocular MMP was the oropharynx, with 87.5% of patients affected. Nasal mucosal involvement was documented in 37.5% of patients. Laryngeal and genital involvement was present in 25% and 12.5% of included patients, respectively. None of our patients had either anal or esophageal involvement.

Table 1. Demographic and clinical characteristics of patients with ocular mucous membrane pemphigoid upon presentation

	MMP patients (N=8)
Demographics	
Median age, yrs. (range)	60.5 (36-66)
Sex, % female	62.5
Race, % Hispanic	100
Clinical characteristics	
Stage I on presentation, worse eye, %	0
Stage II on presentation, worse eye, %	0
Stage III on presentation, worse eye, %	100
Stage IV on presentation, worse eye, %	0
History of glaucoma, %	0
History of trichiasis, %	50
Median duration of ocular symptoms, mo. (range)	8.5 (3-24)
Median VA, better eye (range)	20/30 (20/20-20/50)
Median VA, worse eye (range)	20/40 (20/20-20/200)
Extraocular MMP, %	87.5
Positive conjunctival biopsy, %	100
Prior extraocular site biopsy %	62.5%
Positive extraocular site biopsy, %	0
Positive circulating antibodies to the BMZ, %	30*
IgG present in positive biopsy, %	100
IgA present in positive biopsy, %	12.5
IgM present in positive biopsy, %	0
C3 present in positive biopsy, %	87.5
Linear IgA, %	12.5
Median duration of extraocular symptoms, months (range)	36 (2-144)
Oropharyngeal involvement	87.5
Nose involvement	37.5
Skin involvement	50
Esophageal involvement	0
Laryngeal involvement	25
Genitalia involvement	12.5
Anal involvement	0

MMP = mucous membrane pemphigoid, VA = visual acuity, BMZ = basement membrane zone, IgG = immunoglobulin G, IgA = immunoglobulin A, IgM = immunoglobulin M, C3 = complement component 3. *Two patients were not tested for circulating anti-BMZ antibodies (n=6)

Discussion

MMP is a systemic autoimmune disease that when affecting the eyes causes a cicatricial conjunctivitis that, if untreated, gradually progresses towards complete keratinization of the ocular surface and bilateral blindness (2). MMP is rare and at times difficult to diagnose; however, recognition of its clinical findings is crucial for timely diagnosis (9). This is due to its destructive nature as well as its requirement for aggressive immunomodulatory management that differs it from other clinically similar etiologies of cicatricial conjunctivitis (2,10). Therefore, its description is very important, hence the germination of various studies on this topic. To the best of our knowledge, our study is the first to characterize a cohort of Hispanic patients with ocular-involving MMP.

Patients in our cohort presented with a median age of 60.5 years. This follows an already established pattern observed by other authors such as J.E. Thorne et al. in 2004 as well as Dr. C. Stephen Foster in his 1986 Cicatricial Pemphigoid manuscript (1,8). In the former, patients with ocular MMP had a median age of 67.4, slightly older than in our cohort, while the latter describes the disease as that of people aged 60 to 70 (1,8). It is noteworthy that 3 out of our 8 patients (37.5%) were in the younger age range with two of them presenting in the fourth and one in the fifth decade of life (See Figure). Although MMP has been established in many publications as a disease of the elderly, its presence has been recognized as early as the third decade of life (8). In our study, 62.5% of patients were female, this is similar to the slight female predominance noted for this condition by other authors (1,2,8).

All patients in our cohort presented with stage III ocular MMP in at least one eye. In many instances, the majority of patients present upon progression to stage III disease, as in stages I and II, and many cases may remain unrecognized and therefore untreated (1,8). In Foster's cohort, 86% of patients had stage III disease and 40% had a VA of 20/200 or less in at least one eye (8). In a cohort by Thorne et al., ocular MMP patients had a median VA of 20/50 in the worst eye, with 92% of their population presenting at stage III or IV and with the worst VA reaching NLP (1). Our sample population showed a median VA of 20/40 in the worse eye, with one out of sixteen eyes (6.25%) having 20/200 VA. The difference in VA amongst the cohorts may be explained by the difference in the median duration of ocular symptoms. In our study, the median duration was of 8.5 months, whereas Thorne et al. had a median duration of 9.5 months and Foster reported a mean of 2.8 years (1,8). Longer time with ocular exposure without treatment could further worsen VA by continued corneal scarring with longer time of untreated disease. This further emphasizes the importance of early diagnosis and treatment of MMP.

Extraocular involvement was also assessed in our study. The buccal and pharyngeal mucosa are the most frequently involved sites in patients with MMP (1,11). As expected, our results show that 87.5% of patients had extraocular involvement with oral mucosa most commonly affected (87.5%) followed by the skin (50%), and then the nasal mucosa (37.5%). Such a high frequency of comorbidity can be attributed to the disease's systemic nature. This is important to consider as the disease has the potential to become life-threatening if tracheal or esophageal involvement occurs (1,11). Noteworthy, 25% of cases in our cohort had a history of laryngeal involvement. Esophageal involvement was not noted in our cohort; however, esophageal strictures can at times be silent until near death or completely fatal asphyxiation occurs due to food bolus passage hindrance (8). Tracheal involvement has also been reported as asymptomatic by other authors and can eventually present with severe complications (10). These facts further highlight the need for rapid and aggressive immunosuppressive drug therapy when diagnosing ocular MMP.

Early diagnosis and treatment are imperative in mild presentations of MMP to avoid life-threatening complications; however, according to the First International Consensus on

Mucous Membrane Pemphigoid, patients with negative direct immunopathology cannot be diagnosed as MMP (11). This diagnostic criterion poses as a challenge for faster detection as various studies have shown false-negative results to be relatively common (1,2). In a study to explore the validity of the First International Consensus on Mucous Membrane Pemphigoid diagnosis guidelines, Hon Shing Ong et al. presented a subset of patients with negative DIF results (10). They proposed their results to be due to low antibody levels in said patients, low sensitivity in the conjunctiva, operator dependence, or cell-mediated response subset without circulating antibodies (10). In our cohort, 5 (62.5%) patients had previous extraocular biopsies, which were all negative. However, in those 5 patients, 100% of the conjunctival biopsies were diagnostic and 40% of them had positive circulating antibodies detected the same day as the conjunctival biopsy. This challenges (Ong et al., 2018)'s theory for low conjunctival biopsy sensitivity; however, it supports the consideration of diagnosing and treating MMP, in DIF negative patients whose clinical picture is highly suspicious and alternative diagnoses have been ruled out. Multiple studies have revealed that a single negative DIF test result does not exclude MMP and that multiple and repeated biopsies increase the sensitivity of DIF (1,12). Alternatively, Radford et al. suggested considering ocular MMP in any case of trichiasis or recurrent conjunctivitis with early conjunctival biopsy as standard of care (9). This recommendation is reinforced by our study population in which 50% presented with trichiasis. Patients with early stages of the disease often remain unrecognized, increasing their risk of progressing and acquiring potentially blinding ocular complications from their disease (8). Furthermore, fatality can ensue in cases of extraocular involvement (1,2,11). Delayed diagnosis and treatment are detrimental to a patient's quality of life; therefore, we advise pursuing aggressive diagnostic interventions before ruling out MMP after negative DIF or circulating antibodies tests.

As with all retrospective studies, caution should be exercised when interpreting the data. Our results are limited by a small size and ascertainment bias. The senior author is the only ocular immunology specialist in Puerto Rico who performs conjunctival biopsies for DIF and who is also trained in the use of immunomodulators to treat these patients. For such reasons, referral bias may have been introduced as it is possible that only the most recalcitrant cases of cicatricial conjunctivitis were sent to him for evaluation. In addition, patients with negative biopsies often return to the referring ophthalmologist for further care and those with negative biopsies who remain for follow-up, yet are suspicious for ocular MMP, do not appear as MMP in our database, disabling us from further analyzing false negatives. Therefore, we may have introduced selection bias as we only analyzed patients with positive biopsies. However small, we believe our cohort is likely representative of the disease in Puerto Rico as the senior author's practices likely receive most of the cicatricial conjunctivitis referrals within the commonwealth. Furthermore, in some instances, evidence of extraocular involvement was obtained by direct patient report and disease in more private anatomical sites such as the anogenital regions may have been underreported. In addition, examination of often asymptomatic sites such as the esophagus was not pursued unless the patient reported symptoms suggestive of upper gastrointestinal tract involvement.

Resumen

Objetivo: Describir las características al momento de presentación de una cohorte de pacientes Hispanos que viven en Puerto Rico con penfigoide de membrana mucosa ocular (MMP). Métodos: Se realizó una revisión retrospectiva de los sujetos con MMP ocular en una institución académica y una práctica privada. Pacientes con evidencia clínica de MMP ocular, junto con una biopsia de membrana mucosa positiva que revelase un anticuerpo lineal o la deposición de C3 en la zona de la membrana basal, o con un ensayo positivo de inmunofluorescencia indirecta fueron incluidos. Se realizó un análisis estadístico descriptivo. Resultados: Se identificaron ocho pacientes con penfigoide de membrana mucosa ocular. La edad media de presentación fue de 60.5 años; sin embargo, 2 pacientes estaban en su cuarta década y uno en la quinta década de la vida. Féminas constituyeron el 62.5% de la cohorte. Todos los pacientes se presentaron con MMP ocular en estadio III en al menos un ojo y el 50% tenía antecedentes de triquiasis. Siete de los ocho pacientes (87.5%) tuvieron síntomas extraoculares con una duración media de 36 meses (rango 2-144 meses). El sitio más común de afectación extraocular fue la orofaringe, presente en el 87.5% de los pacientes. Conclusiones: Nuestros resultados sugieren que en Puerto Rico la MMP ocular se presenta con mayor frecuencia en la séptima década de la vida. La presencia de simbléfaron, triquiasis o enfermedad de la mucosa orofaríngea debe inducir una evaluación adicional y consideración para análisis inmunopatológico del tejido y un ensayo de IFI.

References

1. Thorne JE, Anhalt GJ, Jabs DA. Mucous Membrane Pemphigoid and Pseudopemphigoid. Ophthalmology 2004;111:45–52.
2. Ahmed M, Zein G, Khawaja F, Foster CS. Ocular cicatricial pemphigoid: pathogenesis, diagnosis and treatment. Prog Retin Eye Res 2004;23: 579–92.
3. Thorne JE, Woreta FA, Jabs DA, Anhalt GJ. Treatment of Ocular Mucous Membrane Pemphigoid with Immunosuppressive Drug Therapy. Ophthalmology 2008;115:2146-2152.
4. Georgoudis P, Sabatino F, Szentmary N, et al. Ocular Mucous Membrane Pemphigoid: Current State of Pathophysiology, Diagnostics and Treatment. Ophthalmology and Therapy 2019;8:5–17.
5. Rübsam A, Stefaniak R, Worm M, Pleyer U. Rituximab preserves vision in ocular mucous membrane pemphigoid. Expert Opin Biol Ther 2015;15:927–33.
6. Maley A, Warren M, Haberman I, Swerlick R, Kharod-Dholakia B, Feldman R. Rituximab combined with conventional therapy versus conventional therapy alone for the treatment of mucous membrane pemphigoid (MMP). J Am Acad Dermatol 2016;74:835-840.

7. John H, Whallett A, Quinlan M. Successful biologic treatment of ocular mucous membrane pemphigoid with anti-TNF-α. Eye 2007;21:1434–1435.
8. Foster CS. Cicatricial pemphigoid. Trans Am Ophthalmol Soc 1986;84:527–663.
9. Radford CF, Rauz S, Williams GP, Saw VPJ, Dart JKG. Incidence, presenting features, and diagnosis of cicatrising conjunctivitis in the United Kingdom. Eye 2012;26:1199–208.
10. Ong HS, Setterfield JF, Minassian DC, Dart JK, Mucous Membrane Pemphigoid Study Group 2009–2014. Mucous Membrane Pemphigoid with Ocular Involvement: The Clinical Phenotype and Its Relationship to Direct Immunofluorescence Findings. Ophthalmology 2018;125: 496–504.
11. 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
12. Shimanovich I, Nitz JM, Zillikens D. Multiple and repeated sampling increases the sensitivity of direct immunofluorescence testing for the diagnosis of mucous membrane pemphigoid. J Am Acad Dermatol 2017;77:700-705.