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Research Article

The Clinical Characteristics of Patients with Ocular Cicatricial Pemphigoid in a Tertiary Eye Hospital in Riyadh, Saudi Arabia

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Abstract

Purpose: To determine the clinical characteristics of patients diagnosed with Ocular Mucous membranes pemphigoid (OMMP).

Setting: Retrospective study conducted at a tertiary eye hospital in Riyadh, Saudi Arabia.

Methods: Database search of medical charts from 2014 to 2020 with a referral request or diagnosis of OMMP was conducted. All patients with a diagnosis of Ocular Mucous membranes pemphigoid (OMMP). with a regular follow up were included. The following patient characteristics were reviewed and recorded: patient demographics, methods of diagnosis, visual acuity, ocular features, disease stage by means of Foster's staging system, presence of systemic involvement and type of immunosuppressive treatment.

Results: A total of 60 patients (120 eyes) were identified, with female gender predominance (61.6%). Half of the patients (50%) had a true Ocular MMP. The mean age was 69.6 years and 73.5 years in true OMMP and pseudo- OMMP groups, respectively. Mean follow up time was 49.9 months (ranges from 4 months to 73 months). Majority of patient diagnoses were based on clinical signs. Conjunctival biopsy for direct immunofluorescence was performed in 16 cases (26.6%) cases but were found to be positive in only 3 patients of true OMMP and 4 patients of pseudo-OMMP group. The bulk of patients 31% and 45% had stage-3 and stage-4 of Foster's Classification System at diagnosis, respectively. Whereas 78% of cases were found to be in stage-4 at last visit. Thirty-six patients (53.7%) were reported to have systemic manifestation involving skin, mouth and genital at the time of presentation, yet only two of those patients went to a dermatologist. Total patients who received systematic immunotherapy were 13 (21.7%) and among those cases, 12 patients were found to have true OMMP. The most used systematic immunotherapy agent is Mycophenolate mofetil followed by Prednisolone.

Conclusion: Over a 6-year period, 60 patients were referred to a tertiary eye center in Riyadh, indicating the rarity and diagnostic complexity of the disease.

Keywords: *Ocular Cicatricial Pemphigoid (OCP); Cornea; Conjunctiva; Inflammation*

Introduction

Mucous membranes pemphigoid (MMP) is a heterogeneous group of multi-systemic, chronic, inflammatory, and immunologically mediated mucocutaneous diseases [1-5]. They can affect a multitude of mucous membranes in the body including the eyes, nose, mouth, upper respiratory, and gastrointestinal (GI) tracts. The oral mucosa is most frequently involved [5]. Despite the benign status of the condition, systemic and severe multi-organ association may arise, resulting in a life-threatening ailment such as asphyxiation if the trachea or esophagus are involved [2].

MMP involving and affecting the conjunctiva produces chronic cicatricial conjunctival inflammation currently known as an Ocular Mucous membranes pemphigoid (OMMP). OMMP presents as progressive cicatrizing conjunctivitis that, if left untreated, results in scarring and obliteration of the conjunctival fornices (symblepharon), corneal ulceration and scarring, and severe dry eye leading to blindness and loss of the eye. It is a relatively rare disease with females predominate. Currently, the diagnosis of Ocular MMP is mainly based on patient clinical signs as well as their positive direct immunofluorescence testing of the conjunctival [3-5].

Current treatment guidelines recommend topical supportive therapy and systemic corticosteroids, with possible supplementations with immunosuppressive agents such as azathioprine, mycophenolate mofetil, or methotrexate as first-line therapy. However, the inability to achieve long-lasting remission coalesced with the occurrence of serious adverse events (e.g. hypogammaglobulinemia), has led to the exploration of substitute treatments. Also, off-label use of the anti-CD20 antibody rituximab has also been shown to be effective in inducing complete remission in most patients with refractory disease [2,6-8].

Early diagnosis and treatment of Ocular MMP are of paramount importance. Yet, many experienced clinicians report extreme difficulty in diagnosing and treating this disease [9]. Furthermore, the clinical characteristics and prevalence of patients with OCP has been inadequately studied in Saudi Arabia.

Aim of the Study

Therefore, the study aimed to determine the clinical characteristics of patients diagnosed with ocular cicatricial pemphigoid (OCP) in a tertiary eye hospital in Riyadh.

Methods

Research ethics

This study was approved by the Institutional Review Board (IRB) of King Khaled Eye Specialist Hospital (KKESH) in Riyadh, Saudi Arabia.

Study setting and study design

This was a retrospective, observational study that aimed to determine the clinical characteristics of patients diagnosed with Ocular Mucous membranes pemphigoid (OMMP) in a tertiary eye hospital in Riyadh. With a population of seven million, Riyadh serves as Saudi Arabia's biggest city.

A comprehensive review of medical charts from 2014 - 2020 with a referral request or diagnosis of true OMMP was conducted. All patients with a diagnosis of OMMP and having regular follow-ups were included. Patient demographics (age, gender, and eye laterality), as well as a diagnostic method, visual acuity (VA), ocular features, Foster's Classification System, presence and location of systemic involvement, and the type of immunosuppressive treatment prescribed, were all documented and recorded.

True OMMP was defined as conjunctival cicatrization and classified using the four-step Foster scale [10]. Stage I was the presence of chronic conjunctivitis with subepithelial fibrosis. Stage II was comprised of inferior fornix foreshortening along with stage -1 changes. Stage III was described by the presence of a symblepharon. Stage IV was an end-stage disease with ankyloblepharon and extreme ocular surface keratinization [10]. Cicatrizing conjunctivitis due to chronic use of glaucoma drops was labeled as drug induced OCP. Presumed OMMP was defined as a biopsy negative condition with very strong clinical suspicion of OMMP.

The diagnosis of ocular MMP was made by the clinical findings of cicatrizing conjunctivitis with or without extraocular manifestations of MMP and was confirmed by conjunctival biopsy. Conjunctival biopsy of 3 mm x^2 mm of inferior or superior fornice conjunctiva was excised and divided into 2 halves. The first half was placed in Michel's medium and sent for immunofluorescences study. The other half was set in formalin and sent for histopathology. Linear deposition of immunoreactants (most commonly IgG, IgE, and complement C3 or C4) at the basement membrane zones of the biopsy specimen of inflamed conjunctiva. A biopsy negative for basement membrane staining does not exclude OMMP [11]. Yet we have considered a positive biopsy to be the gold standard for the diagnosis of OMMP.

VA was classified into good, mild, moderate, severe, and profound, visual loss as per WHO criteria. 20/30 to 20/60 was considered mild vision loss, or near-normal vision. 20/70 to 20/160, 20/200 to 20/400, 20/500 to 20/1,000, and more than 20/1,000 were considered moderate, severe, profound, and near-total visual impairment, respectively. No light perception (NLP) was considered a total visual impairment, or total blindness.

Statistical analysis

A descriptive analysis was conducted to understand the clinical differences between patients. Continuous variables were summarized as means and standard deviations, and categorical variables were summarized as frequencies and percentages. All statistical analyses were conducted using Microsoft Office Excel 2016.

Results

A total of 60 patients (120 eyes) were identified, with female gender predominance (61.6%). Half of the patients (50%) had a true Ocular MMP. The mean age was found to be 69.6 years and 73.5 years in true OMMP and pseudo-OMMP groups, respectively. Mean follow up time was 49.9 months (ranges from 4 months to 73 months). Majority of patient diagnoses were based on clinical signs. Out of all patients, only 8 patients (13.3%) had unilateral signs at the first presentation (Table 1).

Patient Characteristic	True OMMP (n = 30)	Pseudo OMMP (n = 30)
	Mean (range)	
Age	69.6 (42-99)	73.5 (24-94)
Gender	N (%)	
Females	20 (66.7%)	17 (56.3%)
Males	10 (33.3%)	13 (43.3%
Biopsy Results	N (%)	
Positive	3 (18.2%)	4 (13.3%)
Negative	7 (27.3%)	2 (6.6%)
No Known Information	20 (54.5%)	24 (80%)

***Table 1**: Patient characteristics, biopsy results, and Foster Classification.*
N: Number of cases.

The bulk of patients 31% and 45% had stage-3 and stage-4 of Foster's Classification System at the first presentation, respectively. Whereas 78% of cases were found to be in stage-4 at last visit (Table 2).

	True OMMP (N = 30)		Pseudo OMMP (N = 30)	
	First presentation	Last presentation	First presentation	Last presentation
	Number of eyes (%)	Number of eyes (%)	Number of eyes (%)	Number of eyes (%)
Stage				
1	6 (10%)	1 (1.6%)	0 (0%)	0 (0%)
2	9 (15%)	4 (6.6%)	3 (5%)	0 (0%)
3	21 (35%)	12 (20%)	26 (43.3%)	11 (18.3%)
4	24 (40%)	43 (71.6%)	31 (51.7%)	49 (81.7%)
Visual Acuity				
Total visual impairment	4 (6.7%)	7 (11.7%)	8 (13.3%)	12 (20%)
Near-total visual impairment (>20/1,000)	12 (20%)	21 (35%)	24 (40%)	24 (40%)
Severe visual impairment (20/200 - 20/400)	15 (25%)	12 (20%)	19 (31.7%)	16 (26.6%)
Moderate visual impairment (20/70 - 20/160)	15 (25%)	9 (15%)	4 (6.7%)	4 (6.7%)
Mild vision impairment (20/30 - 20/60)	8 (13.4%)	7 (11.7%)	5 (8.4%)	4 (6.7%)
Good vision (20/20 – 20/25)	6 (10%)	4 (6. 7%)	0 (0%)	0 (0%)

***Table 2**: Foster stages and visual acuity at the first and last follow up.*

Conjunctival biopsy for direct immunofluorescence was performed in 16 cases (26.6%) cases but were found to be positive in only 3 patients of true OMMP and 4 patients of pseudo-OMMP group (Table 1). Furthermore, 36 patients (53.7%) were reported to have had some sort of systemic manifestation involving skin, mouth, and genital at the time of presentation, yet only two of those patients went to a dermatologist.

Total patients who have received treatment of systemic immunosuppressive therapy is found to be 13 patients (21.7%) and majority of those patients have true OCP (12/13) (Table 3).

Patients	Previous	Current	VA				stage			
			1st OD	Last OD	1st OS	Last OS	1st OD	Last OD	1st OS	Last OS
1	MMF	Rituximab	400	300	50	300	4	4	4	4
2		MMF and PRDL	2	2	125	1	4	4	4	4
3		MMF	20	20	40	25	2	2	2	3
4		MMF	200	1	160	1	3	3	2	3
5	AZA and PRDL	AZA	25	125	1	1	3	4	3	4
6		MTX and PRDL	25	100	50	100	3	4	3	4
7		MMF	3	3	70	160	4	4	2	2
8		MMF and PRDL	300	25	200	1	3	3	3	3
9		MMF	400	400	200	400	4	4	4	4
10		MMF and PRDL	70	1	80	3	3	4	3	4
11		PRDL	80	1	80	100	4	4	4	4
12	MTX	PRDL	80	50	100	50	1	3	1	3

Table 3*: Foster stages and visual acuity of patients with true OCP on immunosuppressive therapy.*
MMF: Mycophenolate Mofetil; PRDL: Prednisolone; AZA: Azathioprine; MTX: Methotrexate.

Following the diagnosis of OMMP, the bulk of the cases required either initiation of immunosuppression or alteration of the current therapy to a more potent regimen (step-up). The most used systemic immunosuppressant in those with true OCP was Mycophenolate mofetil (8/12), followed by Prednisolone, Azathioprine, and Methotrexate in 7, 1, and 2 cases, respectively. Only one patient was on Rituximab.

In 11 eyes treated with either Prednisolone or CellCept® (mycophenolate mofetil) have lost more than 2 lines in Snellen visual acuity and 6 eyes had advanced in stage according to Foster staging system. Two cases that were using MTX also had decreased VA and progression in their Foster stages. The patient on a regimen of azathioprine and prednisolone have lost more than 2 lines in Snellen visual acuity and progress to stage 4. Eyes managed with and/or Rituximab exhibited a decreased in VA but stabilization in their stage and control of inflammation.

Boston Keratoprosthesis (KPro) had been placed in 18% of the cases. Corneal transplantation was performed in 19.5% of the cases however 13% of which had a graft rejection. At the last follow up, 2 patients develop secondary glaucoma and one patient undergone evisceration.

Discussion

This study aimed to illustrate the clinical characteristics of patients with OMMP presenting to a tertiary eye hospital in Riyadh, Saudi Arabia. Our study demonstrated that patients with OMMP present relatively late in life mean age 69.6 years and 73.5 years in true OMMP and pseudo- OMMP groups, respectively. While these data are comparable to the United States, [12] they are in stark contrast to studies from Iran [13], Kuwait [14], and Turkey [15], and India [16] which report a mean age 41.4, 36, and 48 years, respectively.

The gender predisposition has exhibited contrasting outcomes. Although, an equal sex predilection has been described in local and international repots before [17-19]. A female preponderance has been observed among our cases (61.6%). This is in agreement with reports from Italy [20], Tel Aviv [21], Turkey [15], and Tunisia [22]. The causes of this difference are indistinct and have not been studied in detail by any of the researchers.

In the current study, out of 60 cases who were diagnosed with OMMP, only 7 (11.6%) cases were confirmed to have a biopsy proven OMMP. Radford., *et al*. [25] reported biopsy-proven cicatrizing conjunctivitis in United Kingdom to be 22 (44%). However, while our study had a sizeable number of unavailable biopsies 44 (73.3%), Radford., *et al* [25]. only reported 4 patients with missing/unavailable biopsies. Diagnosis of MMP is often delayed because of the nonspecific presentations in the early stage or inconclusive biopsies [12]. Patients initially complain of redness, tearing, reduced vision, and foreign body sensation. The reluctance to implement a conjunctival biopsy is likely due to concern about producing more harm before starting the immunosuppression. Moreover, the challenge lies not only in recognizing the primary disease and defining which cases will progress but also in identifying when it will occur [23]. It is alleged that if OMMP is suspected, a biopsy of the conjunctiva, and tissue from other sites of potential involvement, should be part of an acceptable standard of care and with appropriate precautions, the bulbar conjunctival biopsy is safe [23-25]. Most of our patients 31% and 45% had stage-3 and stage-4 of Foster's Classification System at the first presentation, respectively. Whereas 78% of cases were found to be in stage-4 at the last visit. This because most of our patients traveled long distances to our center and this may signify an obstacle to early tertiary care of this rare disease, resulting in starting of suboptimal immunomodulation and/or surgery [23].

Furthermore, our study demonstrates the systemic nature of MMP, as 36 (53.7%) of OMMP patients had extra-ocular involvement at presentation. Similarly, Hong., *et al.* retrospectively chart reviewed of 162 biopsies proven MMP patients in Wilmer Eye Institute (John Hopkins) and reported a higher number (71.6%) of extraocular associations with an ocular MMP [4]. Radford., *et al.* also found that 57% of patients who had missing/unavailable biopsy results had extraocular manifestations [25]. Perhaps, these data support the use of systemic immunosuppressive drug therapy in OMMP patients [9,25]. However, in the case of a non-progressive/end-stage disease, systemic treatment would not be recommended [9].

The systemic immunosuppressant Mycophenolate mofetil was frequently used (8/12), followed by Prednisolone, Azathioprine, Rituximab, and Methotrexate in 7, 1,1 and 2 cases, respectively. Systemic corticosteroids and cyclophosphamide, given alone or in combination, are both well-established approaches of management for pemphigus [26-29]. Side-effects of corticosteroids and cyclophosphamide are minor and clinically insignificant except for enlarged susceptibility to infections [26]. Mycophenolate is typically used either for intensification of the treatment or in cases of remission failure. Moreover, a recent cohort study reported the use of rituximab as a second-line treatment for severe forms of OMMP. Which showed effectiveness of 86% after a cycle of 4 courses of 375 $mg/m^2/w$ with a suitable safety profile [27]. The initial treatment with Methotrexate have shown to successfully control the activity of conjunctival inflammation and inhibited the advancement of cicatrization [28]. Consequently, even for patients with progressive OMMP, Methotrexate can still efficiently reverse the ocular surface keratinization stopping the fast progression of the disease. Additionally, Rituximab exhibited a promising therapeutic choice for patients with otherwise treatment resistant OMMP. Treatment was well tolerated, however high costs and inadequate knowledge of long-term effects limit its use in certain cases [29].

Given that we only included patients seen at one Eye Hospital, the relatively small sample size, and the retrospective nature of this study all are accounted as limitation difficulties and have also been previously reported by other studies. Nevertheless, this is the largest series of patients with OCP reported from Saudi Arabia and the results from this study can prove to be helpful to clinicians in diagnosing and managing OCP cases.

Conclusion

In conclusion, this study indicated the rarity and diagnostic complexity of OCP in one tertiary center in Riyadh, Saudi Arabia. Our data has many health policy implications.

Author's Contributions

S-Al, TA-Al, M-A and AA designed the study. R-Al and AA acquired the data. AA and L-A analyzed the data which S-Al and M-A revised it. AA wrote the manuscript and all authors reviewed and approved it.

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Rawan Hawasi contribution in data collection.

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