Research Article

Mucous membrane pemphigoid: our 14 years' experience

María del Pilar Beruschi[1], Mónica Bolatti[2], Sandra Marinescu[3], Claudia Ardissone[4], Laura López[4], Jorge O. Zárate[5], Eduardo Zeitlin[6], Ana Kaminsky[7], Elina Dancziger[8]

Abstract

Introduction. Mucous membrane pemphigoid includes a group of subepithelial immunobullous diseases mainly affecting mucous membranes and occasionally the skin. Evolution is chronic and progressive, leading to cicatricial sequelae, which produce morbidity, disability, and sometimes death.
Objective: To describe epidemiological and clinical aspects, and the evolution of mucous and cutaneous lesions in our patients.
Materials and methods. The retrospective, observational, and descriptive study included 41 patients with confirmed mucous membrane pemphigoid diagnosis consulting the Dermatology Department between 1994 and 2008. Ocular involvement was graded using the Foster staging system. Each patient received systemic and local treatment.
Results. Thirty nine patients had only ocular involvement and 2 patients had ocular, oral and cutaneous disease, with female predominance of the disease. Mean age was 60 years, 46.34 percent had history of severe ocular injury, 17.07 percent had used topical glaucoma medications, and 80.48 percent consulted for chronic conjunctivitis. In 60.96 percent of the cases, diagnosis was confirmed in advanced stages of ocular disease. 62.41 percent of patients had over 5 years evolution before diagnosis. Cutaneous and oral lesions responded to therapy in less than 2 months. Ocular lesions remission according to stage was as follows: stage I, 83.33 percent; stage II, 40 percent; and stage III, 30.43 percent. No immunosuppressive treatment was given in stage IV. No improvement was achieved in terminal ocular disease patients.
Conclusion. Ocular involvement is prognostic. Diagnosis was made in advanced stages of ocular disease. Remission was achieved only with early treatment. (Dermatol Argent 2009; 15(4):260-266).

Key words: *Mucous membrane pemphigoid, cicatricial pemphigoid..*

Introduction

Mucous membrane pemphigoid comprises a group of subepithelial immunobullous diseases mainly affecting mucous membranes and secondly the skin. Evolution occurs by recurrent outbreaks characterized by the appearance of blisters, erosions, and marked scarring.[1]
Most frequent location is oral mucosa, followed by conjunctiva, skin, pharynx, external genitals, nasal mucosa, larynx, anus, and esophagus. Cicatricial sequelae are an important cause of morbidity and disability; if involving larynx or esophagus, they may lead to death.[2]
This work comprises 14 years' observation experience of this infrequent pathology.

Objectives

To describe epidemiological aspects (age, gender distribution, history of ocular injury or use of eye drops for glaucoma treatment), clinical aspects (consultation cause, evolution time from symptoms onset to diagnosis, stage of ocular disease), and the evolution of mucocutaneous lesions in our patients.

Design

Retrospective, observational, descriptive.

Reception date: 20/5/09 | **Approval date:** 15/7/09

1. Staff Physician of Dermatology Department. Hospital General de Agudos "C. Durand".
2. Staff Physician of Oculoplasty Department. Hospital de Oftalmología "P. Lagleyze".
3. Emergency Physician. Hospital "P. Lagleyze".
4. Dermatologist.
5. Director of Ophtalmology and Visual Research Laboratory. Pathology Department, UBA.
6. Head of Pathology Department. Hospital "C. Durand".
7. Named Professor of Dermatology.
8. Head of Dermatology Department. Hospital "C. Durand". Hospital General de Agudos "C. Durand". Autonomous City of Buenos Aires, Argentine Republic.

Correspondence
María del Pilar Beruschi. Corrientes 486. (CP 1640) Martínez, Buenos Aires, Argentine Republic | piliberuschi@yahoo.com.ar

Materials and methods

The study included 41 patients with confirmed diagnosis of mucous membrane pemphigoid, who appeared at the Dermatology Department of our Hospital between June 1994 and June 2008. A clinical examination of skin and mucous membranes was performed in all patients. Ocular involvement was assessed by the ophtalmologist and classified according to the Foster staging system, which describes four stages:

- *Stage I*: subconjunctival fibrosis (**Figure 1**).
- *Stage II*: shortening of inferior fornix (**Figure 2**).
- *Stage III*: symblepharon (**Figure 3**).
- *Stage IV*: ankyloblepharon (**Figure 4**).[3]

Diagnosis was confirmed by conjunctival (in patients with only ocular involvement) or skin biopsy. Samples were analyzed with hematoxilin-eosin stain and direct immunofluorescence in all cases (**Figures 7** and **8**).[1]

All patients received systemic and local treatment. Systemic treatment included: dapsone, methylprednisone, cyclophosphamide, azathioprine, metothrexate, cyclosporine, colchicine and antibiotics. Local treatment consisted of tear substitutes, antibiotics, corticosteroids, and cyclosporine.

Stage IV patients received no immunosuppressive treatment, only ocular lubricants and antibiotics for the treatment of infectious complications.

Average patient follow-up was 38 months, with a 1 to 97-month range. Ocular disease remission was construed as the absence of inflammatory activity (white eye). Skin lesion remission consisted in complete blister epithelization and the absence of new lesions.

Results

Of the 41 patients included in the study, 26 were female and 15 were male.

Female:male ratio was 1.7:1.

Average age at diagnosis was 60 years, with a 32 to 82-year range.

Nineteen patients (46.34 percent) had history of severe ocular injury. Most frequently recorded trauma background was surgery (10 patients), followed by trauma (6 patients), Stevens-Johnson's syndrome (3 patients), severe conjunctivitis (2 patients), ophtalmic zoster (1 patient), contact with metal dust (1 patient).

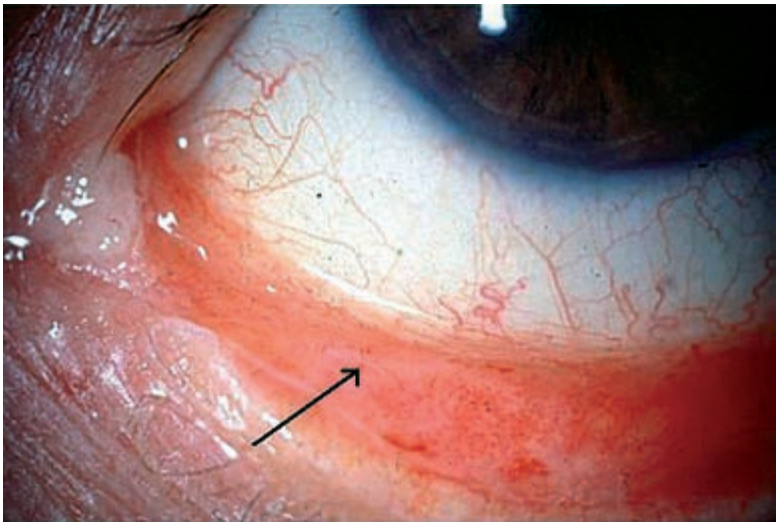

Figure 1. *Stage I. Subconjuncival fibrosis* ***(arrow)****.*

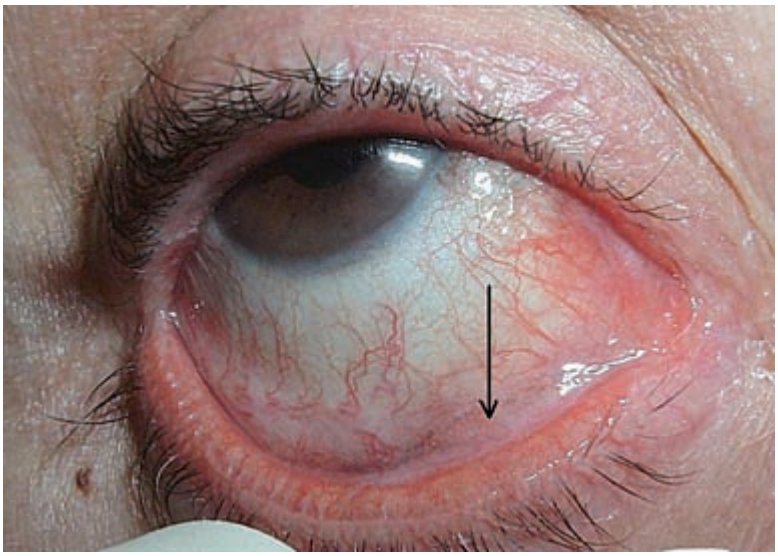

Figure 2. *Stage II.* ***Arrow*** *indicates inferior fornix shortening.*

Three patients had association of different traumatic events.

Seven of the 41 patients (17.07 percent) referred use of eyedrops for treatment of glaucoma. All 41 patients had conjunctival mucosa involvement; 39 patients had only ocular involvement, and 2 patients had conjunctival, oral and cutaneous involvement (**Figures 5** and **6**) (**Table 1**).

Chronic conjunctivitis was the most frequent consultation cause in 33 patients (80.48 percent); 5 (12.19 percent) consulted for dry eye. The 2 patients with skin lesions (4.87 percent) consulted first at the Dermatology Department, where diagnosis was confirmed. One patient (2.43 percent) consulted for epiphora.

In 41.46 percent of patients, diagnosis was set 10 years after symptom onset (**Table 2**).

In 25 patients (60.96 percent), diagnosis was confirmed in advanced stages of ocular disease (**Chart 1**).

When female and male populations were analyzed separately, we found that half of females had diagnosis in stages I and II, while 79.99 percent of men had diagnosis in stages III and IV (**Chart 2** y **3**).

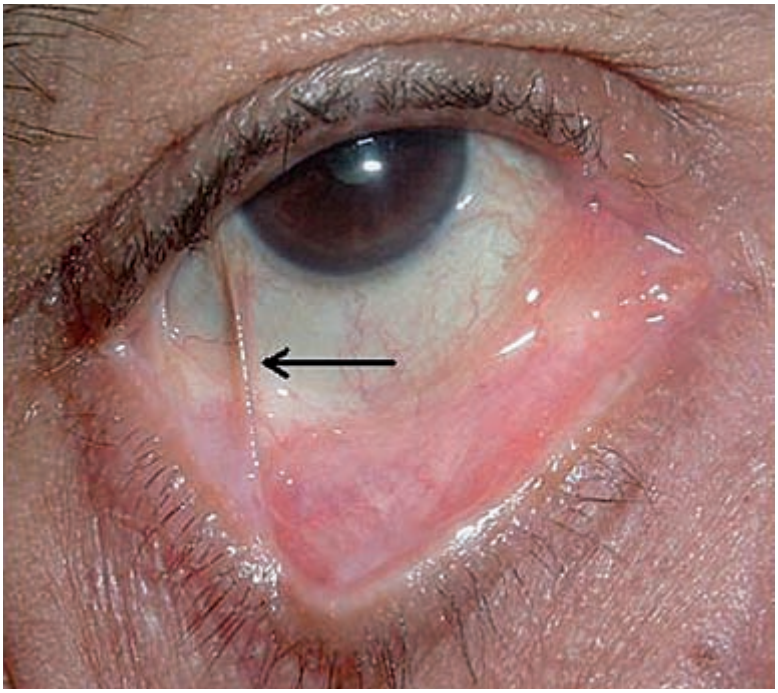

Figure 3. *Stage III. Symblepharon* ***(arrow).***

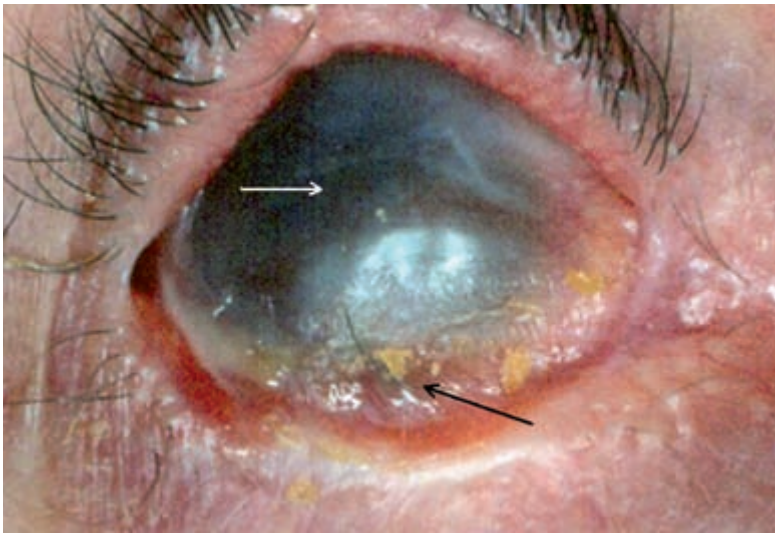

Figure 4: *Stage IV. Ankyloblepharon.* ***Arrows*** *mark fusion of tarsal conjunctiva and bulbar conjunctiva, and corneal clouding.*

In the 2 patients with cutaneous and oral lesions, remission was achieved in skin and oral mucosa 2 month after onset of treatment. Remission of ocular disease occurred only in 16 patients (39.02 percent).

Remission occurred in 83.33 percent of the cases in stage I; this percentage decreased when therapy was started in more advanced stages (**Table 3**).

Of the 9 patients remitting in stages I and II, 7 remained in this condition between 3 months and 2 years after treatment discontinuation.

All remitting patients in stage III required continuing support medication.

Two patients progressed from stage II to III due to early medication discontinuation.

Two patients progressed from stage III to IV, one due to irregular treatment compliance and the other due to lack of response.

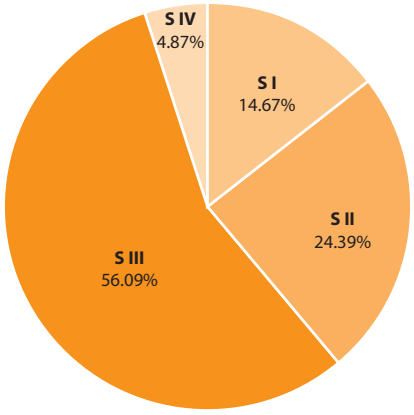

Chart 1. *Ocular disease stage (S) at diagnosis (n = 41).*

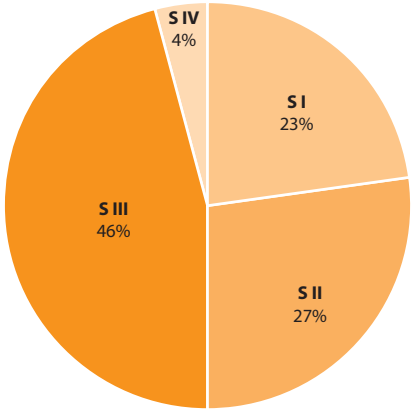

Chart 2. *Ocular disease stage (S) in female (n = 26).*

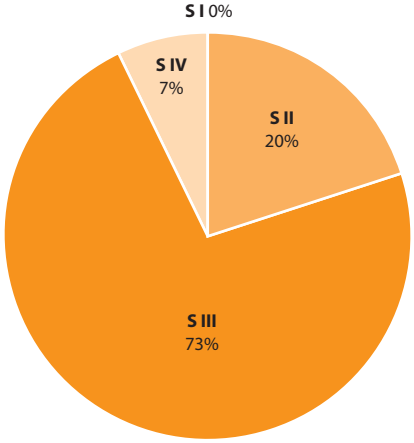

Chart 3. *Ocular disease stage (S) in males (n = 15). S I 0%*

TABLE 1. CASE-CONTROL STUDY.

Case	Gender	Age	Location	OI	ET	OS	F-up	Evolution
1	F	69	Ocular	-	29y	III	38m	R
2	F	57	Ocular	-	40y	III	60m	I
3	F	58	Ocular	-	10y	III	64m	R
4	F	59	Ocular	-	6m	II	97m	R
5	F	56	Ocular	-	8y	I	92m	R
6	F	56	Ocular	C	30y	III	60m	R
7	F	58	Ocular	T+ Sx	35y	II	67m	R
8	F	45	Ocular	-	2y	I	48m	R
9	F	73	Ocular	S	2y	I	48m	R
10	F	72	Ocular	T	18y	III	72m	R
11	F	63	Ocular	S	10y	II	2m	R
12	F	67	Ocular	T+ Sx	15y	III	55m	NA
13	F	34	Ocular	SSJ	30y	III	90m	R
14	F	72	Ocular	Sx	6y	III	22m	I
15	F	68	Ocular	-	2y	I	19m	R
16	F	55	Ocular	-	15y	IV	16m	-
17	F	89	Ocular	-	5y	III	60m	NA
18	F	51	Ocular	-	2y	I	77m	R
19	F	82	Ocular	Sx	2y	II	3m	I
20	F	83	Ocular	-	2y	II	1m	NA
21	F	77	Ocular	-	12y	III	2m	R
22	F	64	Ocular	-	10y	II	43m	P
23	F	60	Ocular	T+Sx+C	7y	II	16m	NA
24	F	32	Ocular	-	9y	III	1m	NA
25	F	32	Ocular	Sx	3m	I	3m	NA
26	F	56	Ocular	HZ	5y	III	12m	NA
27	M	45	Ocular	-	4y	III	6m	NA
28	M	55	Ocular	MD	1y	II	39m	I
29	M	55	Ocular	T	4y	III	89m	P
30	M	70	Ocular	-	20y	II	36m	P
31	M	67	Ocular	-	5y	III	39m	I
32	M	54	Ocular	-	10y	III	42m	I
33	M	74	Ocular	-	4y	III	33m	I
34	M	64	Ocular-skin-oral	-	2y	III	16m	R
35	M	79	Ocular	Sx	3y	II	81m	R
36	M	34	Ocular	SSJ	22y	IV	18m	-
37	M	64	Ocular	T	30y	III	6m	I
38	M	45	Ocular-skin-oral	-	6y	III	72m	-
39	M	41	Ocular	SSJ	30y	III	5m	NA
40	M	80	Ocular	Sx	4y	III	7m	I
41	M	76	Ocular	-	6y	III	27m	I

ET: evolution time before diagnosis. **OS:** ocular disease stage. **y:** years. **m:** months. **F-up:** follow-up. **OI:** ocular injury. **C:** conjunctivitis. **T:** trauma. **Sx:** surgery. **SSJ:** Stevens-Johnson syndrome. **HZ:** herpes zoster. **MD:** metal dust. **R:** remission. **I:** improvement. **P:** progression. **NA:** non-assessable.

Nine of the total patients were not assessed due to control failure or treatment discontinuation (**Table 3**).

Discussion

Mucous membrane pemphigoid is a rare disease of unknown incidence and prevalence. An incidence between 1:12,000 and 1:40,000 is estimated, although subdiagnosis is suspected, especially in early stages of the disease.[4,5] Some cases have been described in children, but the usual age

TABLE 2. EVOLUTION TIME BEFORE DIAGNOSIS.

< 6 months	1 (2.43 %)
6 months – 2 years	2 (4.87 %)
2 years to 5 years	12 (29.96 %)
5 years – 10 years	9 (21.5 %)
> 10 years	17 (41.6 %)

TABLE 3. OCULAR INVOLVEMENT EVOLUTION.

	S I (n=6)	S II (n=10)	S III (n=23)	S IV (n=2)
Remission	5	4	7	0
Inflammatory activity	0	2	8	0
Progression	0	2	2	2
Non-assessable	1	2	6	0
Remission percentage	83.33%	40%	30.43%	0%

at diagnosis is from 60 to 80 years.[6,9] A female dominance is observed, with a 1.5-2.2:1 ratio matching our case material.[9,10]

Etiopathogenesis is unclear, but as in all autoimmune diseases, both genetic and environmental factors are probably included.[11]

The presence of HLA-DR4 allele may increase risk of ocular disease.[12,13] Prevalence of HLA-DQB1 0301 allele was described in patients with only ocular disease, but was later found associated with all locations of the disease.[14,15] This allele may be related to production of IgG against basement membrane antigens. A relation between this allele and severity of the disease is also suggested.[15]

The condition is characterized by production of immunoglobulin G (IgG) autoantibodies targeting different molecules present in the basement membrane area, such as 180-kDa bullous pemphigoid antigen (BPAg 180), b4 integrin, and laminin V.[16–23]

Although the role of environmental factors is still unclear, it is believed that antibodies produced against infectious agents or drugs may cross-react with basement membrane antigens (molecular mimetism). Exposure of conjunctival epithelium antigens caused by severe ocular injury (surgeries, trauma, burns, Stevens-Johnson syndrome, and others) may favor their processing by immune system cells.[24-26]

Many drugs are also described, especially eyedrops indicated for treatment of glaucoma, as mucous membrane pemphigoid triggering factors.[27-32] We found both types of background in our case material.

The disease involves mainly mucosae. Locations are, in order of frequency: oral mucosa (85 percent), conjunctiva (64 percent), skin (24 percent), pharynx

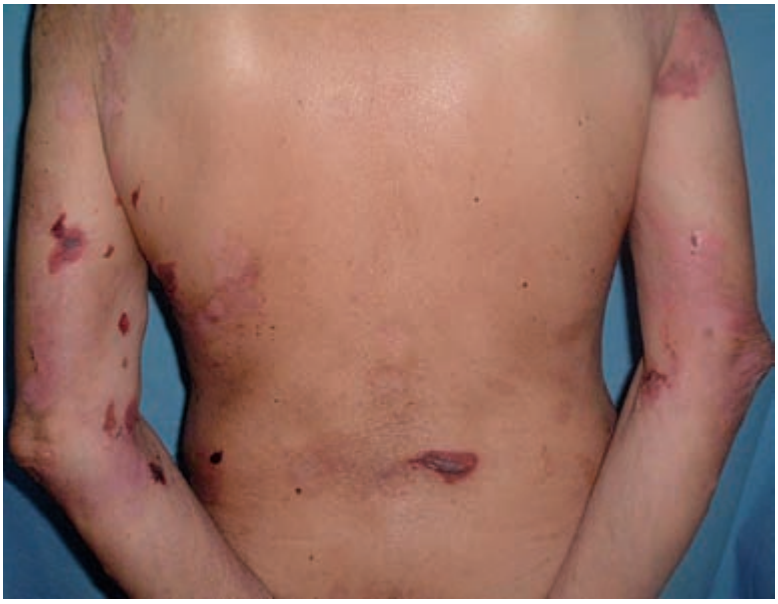

Figure 5. *Skin involvement: general bullous eruption.*

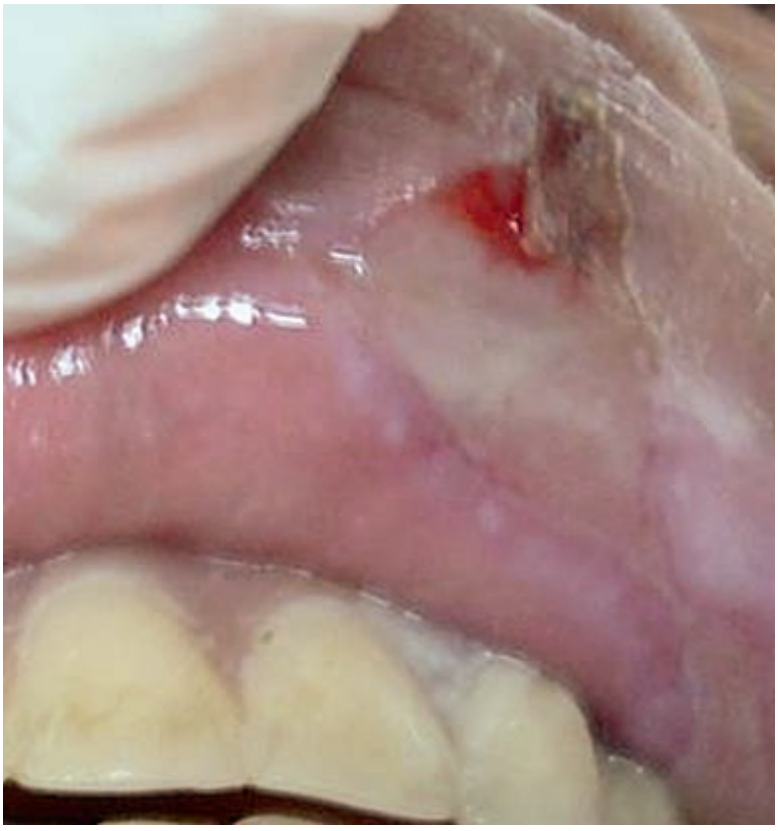

Figure 6. *Oral mucosa erosions.*

(19 percent), external genitals (17 percent), nasal mucosa (15 percent), larynx (8 percent), anus (4 percent), an esophagus (4 percent).[2,9]

Oral involvement usually appears as desquamative gingivitis and mucosal erosions.[10]

Response to treatment is usually favorable, and may occur with local therapy.[1]

Conjunctiva may be the only location of disease, as occurred with most of our patients.[3,33,34] It starts with a chronic conjunctivitis developing in outbreaks.[35,36] In time, conjunctival fibrosis with fornix shortening and production of symblepharon occurs. Eyelids fuse and conjunctival sacs obliterate in late stages (ankyloblepharon).[3,33,36] Fibrosis also obliterates channels, tear glands and Meibomian glands, with alterations of the tear layer. Tarsal conjunctiva scarring causes trichiasis and entropion, which as the dry eye cause corneal damage with pannus formation, ulceration, posterior clouding of the cornea, and blindness.[33,35,36]

All these alterations were evidenced in our case material.

Skin lesions are rarely predominant. Two types of skin lesions are described. The first is a general bullous eruption similar to bullous pemphigoid.[2,3,37,38]

The second form is located in head and neck (Brunsting-Perry), and consists of occasionally itching erythematous base blisters that heal with atrophy and may leave cicatricial alopecia if the scalp is involved.[39-41]

A vegetating form is also described.[42]

Marked clinical and immunologic variability exists among patients. Four main groups are described, probably related to different target antigens. One group refers to only ocular disease, with IgG antibodies targeted against b4 integrin, or IgA antibodies against a 45-kDa antigen.[18,43] The second group consists of patients with mucocutaneous lesions and IgG and IgA against BPAg 180.[20]

The cicatricial phenotype differs from bullous pemphigoid, probably because the antibodies recognize different antigen molecule epitopes more deeply located in the basement membrane.

Only oral variety refers to a group of IgG against BPAg 180.[44]

The fourth group includes patients with multiple mucosal and no skin involvement.[11]

A last group of patients with anti-laminin V antibodies is described, which may be associated with neoplasias.[21,22,45,46]

Currently, mucous membrane pemphigoid is understood as a set of syndromes characterized by having autoantibodies with different specificities, and not as one single entity.[1,2,11]

Clinical differential diagnosis include: bullous pemphigoid, epidermolysis bullosa acquisita, linear IgA dermatosis, bullous lupus, and paraneoplastic pemphigus.[2,11]

Drug-induced ocular pseudo-pemphigoid must

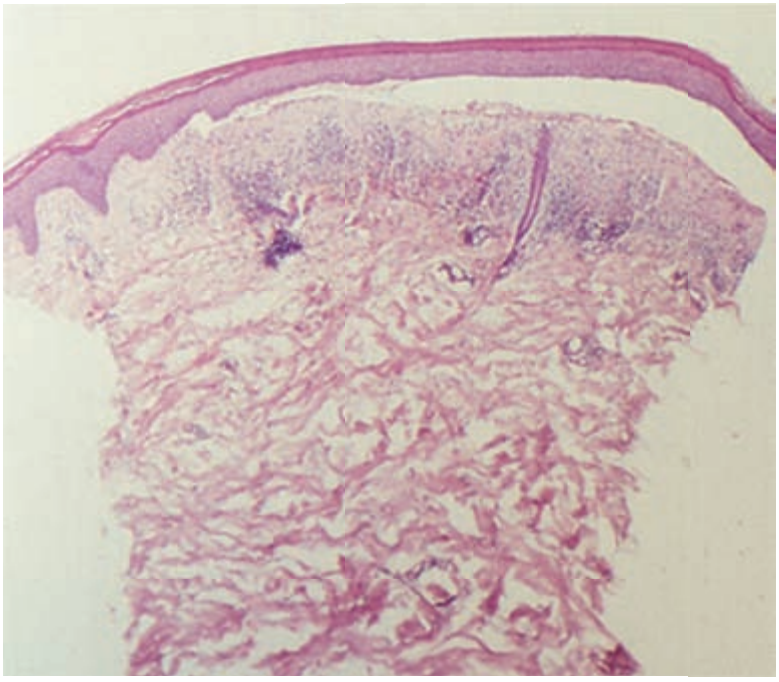

Figure 7. *Subepidermal blister (H-E).*

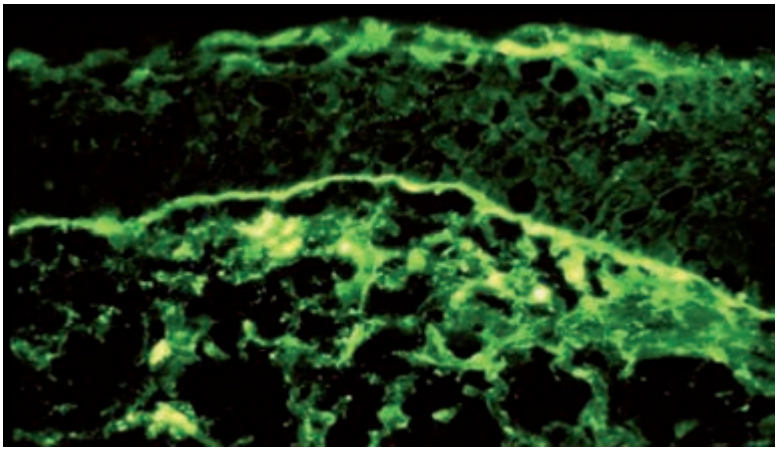

Figure 8. *DIF of conjunctiva. Lineal IgG deposit on basement membrane.*

also be ruled out, as well as other causes of non-immunological cicatricial conjunctivitis.[47,48]

Ocular disease was dominant in our case material, because most of our patients came from an ophtalmology hospital.

Epidemiological, clinical and evolution aspects coincided with data published in the available literature.

In all cases, ocular involvement marked prognosis of disease. Early stage therapy allowed a higher remission percentage.

In advanced stages, disease complications complications (dry eye, infections, corneal abrasion caused by eyelashes) generate a permanent inflammatory stimulus that contributes to disease activity perpetuation, thus hindering remission.[49,50]

Since it is a disabling and occasionally fatal disease, we wish to highlight the need for an early diagnosis in order to implement timely therapy and multidisciplinary approaches, thus preventing or delaying irreversible sequelae occurrence.

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