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Original Research Article

An analytical study on the ocular manifestations of autoimmune blistering skin disorders, in patients attending a tertiary care hospital

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ABSTRACT

Context: Autoimmune blistering skin diseases are a heterogeneous group of diseases that have as their common feature autoantibodies directed against desmosomal structural proteins. They can sometimes affect the eye, with manifestations ranging from mild to potentially vision threatening.
Aim: To evaluate the spectrum and incidence of ocular manifestations and to analyze whether early ophthalmological examination will be beneficial in reducing ocular morbidity.\r\n
Settings and Design: Hospital based analytical study conducted at Coimbatore Medical College and Hospital, Coimbatore, Tamil Nadu.
Materials and Methods: This study involved 100 patients diagnosed with autoimmune blistering skin disorder attending Dermatology and Ophthalmology outpatient department and included a comprehensive ocular examination of the patients.
Statistical Analyses: The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To find the association of significance in categorical data the Chi-Square test was used. In the above statistical tool, the probability value .05 was considered as significant level.
Results: Autoimmune blistering skin diseases were associated with a significant proportion of ocular manifestations, of which in this study, dry eye and conjunctivitis were the most common.
Conclusion: Dry eye and conjunctivitis were the most common ocular manifestations in this study. Though none of the patients had vision threatening manifestations, a comprehensive ocular examination and follow up of these patients is necessary.

1. Introduction

Autoimmune blistering skin diseases are a group of diseases that have as their common feature autoantibodies directed against structural proteins. Desmosomes are primarily responsible for epidermal adhesion. Immune mediated bullous disorders are classified as intraepithelial and subepidermal blistering disorders. Intraepithelial diseases are pemphigus and its variants, subepidermal include bullous pemphigoid, mucous membrane pemphigoid and others.[1,2]

These autoimmune disorders can sometimes involve the eye, with manifestations ranging from mild to potentially vision threatening. The study aims to find out the spectrum of ocular manifestations seen in these patients, and the importance of early ophthalmological evaluation.

2. Materials and Methods

This study was done in a total of 100 patients diagnosed as having an autoimmune blistering skin disorder. Age was not a criteria for exclusion. HIV positive individuals, patients with pre-existing ocular diseases and those with comorbidities like diabetes and hypertension were excluded

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from the study.

2.1. Procedure methodology

Patients diagnosed as having autoimmune bullous skin disorder by histopathology were selected for the study. The diagnoses and management of the dermatological condition were primarily being done by the Dermatology department with involvement of other specialists as when needed. A detailed history was recorded from all patients including ocular symptoms and their duration; duration of skin disease and the treatment undertaken for the same; co-morbid diseases like diabetes and hypertension were ruled out. A detailed past medical history and treatment history were recorded.

A comprehensive ophthalmological examination was done and recorded. Uncorrected and best corrected visual acuity, intraocular pressure, anterior segment examination were done. Ocular surface staining was done using fluorescein. Dry eye tests – Schirmer's test, tear film break up time (T-BUT) and dilated fundus examination was done. Logistical regression analyses were used to estimate the association between the various skin disorders and their ocular manifestations. The association of significance in categorical data was found out by the chi-square test.

3. Results

Majority of the patients in this study were in the age group of 31-40 years and there was a slight male predominance. Pemphigus vulgaris accounted for the highest number among the skin diagnoses; 47 out of 100 patients had a diagnosis of pemphigus vulgaris. 22 patients had bullous pemphigoid and 21 patients had pemphigus foliaceous. Taken together, pemphigus group of disorders accounted for 68 patients. The other bullous disorders encountered were linear IgA disease (9 patients) and only one case of mucous membrane pemphigoid.

Table 1: Diagnosis of skin disease

	Frequency	Percent
Bullous pemphigoid	22	22.0
Linear IgA disease	9	9.0
Mucous membrane pemphigoid	1	1.0
Pemphigus foliaceous	21	21.0
Pemphigus vulgaris	47	47.0
Total	100	100.0

Among the 100 patients, 54 patients had ocular manifestations, distributed among the various bullous disorders. 5 patients had developed presenile posterior subcapsular cataract as a complication of long-term steroid usage, among which, 2 did not have any other ocular manifestation of the specific skin disease.

Table 2: Frequency of ocular manifestations

	Frequency	Percent
No. of patients with ocular manifestations	54	54.0
No. of patients without ocular manifestations	46	46.0
Total	100	100.0

Among the 54 patients who had ocular manifestations, 26 of them were pemphigus vulgaris patients, 9 of pemphigus foliaceous, 14 of bullous pemphigoid, 1 patient of mucous membrane pemphigoid, 4 of linear IgA disease.

Table 3: Frequency of ocular manifestations by skin diagnosis

Diagnosis of skin disease	Frequency of ocular manifestations	
	Frequency	Percent
Pemphigus vulgaris	26	48
Pemphigus foliaceous	9	16
Bullous pemphigoid	14	26
Linear IgA disease	4	8
Mucous membrane pemphigoid	1	2
	54	100.0

Among the 100 patients analysed, 17 of them had conjunctivitis as the ocular manifestation, of which 5 had cicatrizing conjunctivitis and 12 had non cicatrizing conjunctivitis. The conjunctivitis was bilateral in all the patients.

Table 4: Frequency of conjunctivitis

	Frequency	Percent
Cicatrizing	5	5.0
Non-cicatrizing	12	12.0
Nil	83	83.0
Total	100	100.0

Among 100 patients, 37 patients had dry eye, which was seen bilaterally. Of these 37, 11 had mild dry eye, 13 patients had moderate and 13 patients had severe dry eye.

Moderate to severe dry eye patients also had associated features such as superficial punctate keratitis, symblepharon, conjunctival scarring and conjunctival erosions. These complications of dry eye were also seen bilaterally in all the patients, with minor variations in the extent of involvement between both eyes. Dry eye associated with these features needed to be aggressively managed to prevent complications.

Dry eye and its severity was diagnosed based on the presenting symptoms, the results of Schirmer's test and the T-BUT values.

Patients with mild dry eye had a Schirmer's value between 10-15mm at 5 minutes, those with moderate dry eye had values between 5-10mm and those with severe dry

Table 5: Frequency of dry eye

	Frequency	Percent
Mild	11	11.0
Moderate	13	13.0
Severe	13	13.0
Nil	63	63.0
Total	100	100.0

eye had values less than 5mm at the end of five minutes. T-BUT values were less than 10 seconds in those with moderate dry eye while those with severe dry eye developed dry spots immediately on ocular surface staining.

Table 6: Diagnosis of dry eye and severity

Severity of dry eye	Schirmer's values	T-BUT values	Superficial punctate keratitis
Mild	10-15mm	>10 seconds	-
Moderate	5-10mm	<10 seconds	+
Severe	<5mm	Immediate staining	++

In addition, 8 out of the 100 patients analysed had superficial punctate keratitis. All these 8 patients had dry eye and hence the SPK was probably a manifestation of the severity of the dry eye and not of the skin disease proper. 6 of the 8 patients with SPK had severe dry eye and 2 had moderate dry eye.

Table 7: Frequency of superficial punctate keratitis

		Frequency	Percent
Absent		92	92.0
Present			
Moderate dry eye	2	8	8.0
Severe dry eye	6		
Total		100	100.0

In the analysis of conjunctivitis as an ocular manifestation of bullous skin diseases, a total of 17 patients had bilateral conjunctivitis. 8 patients of bullous pemphigoid had conjunctivitis of which 3 had cicatrizing and 5 had non-cicatrizing. 3 patients of pemphigus foliaceous had conjunctivitis; all 3 had the non-cicatrizing form. 6 patients of pemphigus vulgaris had conjunctivitis, of which 2 had cicatrizing and 4 had non-cicatrizing conjunctivitis.

In the analysis of dry eye and bullous skin diseases, 37 patients had bilateral dry eye which turned out to be the most common ocular manifestation among patients of bullous skin disorders in our study.

Of the 37 patients –

1. Twenty had pemphigus vulgaris
2. Six had bullous pemphigoid
3. Six had pemphigus foliaceous

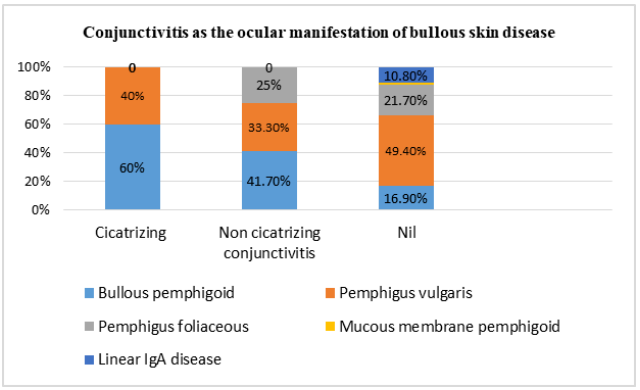

Fig. 1: Conjunctivitis as the ocular manifestation of bullous skin disease

4. Four had linear IgA disease
5. One had mucous membrane pemphigoid

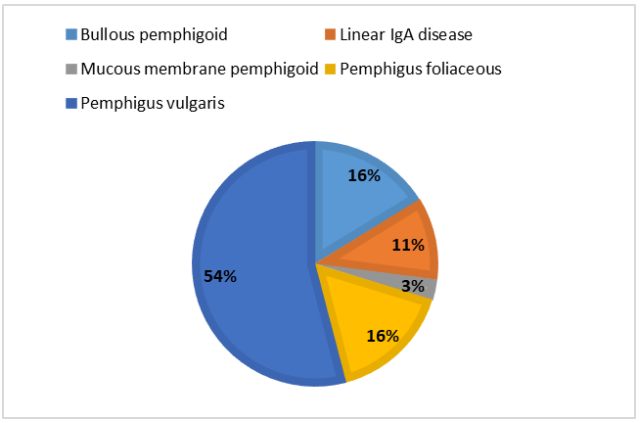

Fig. 2: Distribution of dry eye among various bullous skin diseases

25 patients of pemphigus vulgaris had ocular manifestations of which 19 had dry eye, 5 had conjunctivitis and 1 had both.

Of the 10 patients of pemphigus foliaceous who had ocular manifestations, 3 had conjunctivitis, 6 had dry eye and one had blepharitis with lid margin erosions.

Of the 14 patients of bullous pemphigoid with ocular involvement, 8 had conjunctivitis, 6 had dry eye.

All 4 patients of liner IgA with eye involvement had dry eye and the one patient of mucous membrane pemphigoid also had dry eye.

1. Pemphigus vulgaris – Out of 47 patients with pemphigus vulgaris, 26 had ocular features, of which
   (a) 7.6% had cicatrizing conjunctivitis
   (b) 15.3% had non-cicatrizing conjunctivitis
   (c) 26.9% had mild dry eye
   (d) 30.7% had moderate dry eye

Table 8: Diagnosis of skin disease with conjunctivitis

			Conjunctivitis			Total	2 - value	P-value
			Cicatrizing	Non cicatrizing	Nil			
Diagnosis	Bullous pemphigoid	Count	3	5	14	22	10.224	0.250
		%	60.0%	41.7%	16.9%	22.0%		
	Linear IgA disease	Count	0	0	9	9		
		%	0.0%	0.0%	10.8%	9.0%		
	Mucous membrane pemphigoid	Count	0	0	1	1		
		%	0.0%	0.0%	1.2%	1.0%		
	Pemphigus foliaceous	Count	0	3	18	21		
		%	0.0%	25.0%	21.7%	21.0%		
	Pemphigus vulgaris	Count	2	4	41	47		
		%	40.0%	33.3%	49.4%	47.0%		
Total		Count	5	12	83	100		
		%	100.0%	100.0%	100.0%	100.0%		

Table 9: Diagnosis of skin disease with dry eye

			Dry Eye				Total	2 - value	P-value
			Mild	Moderate	Severe	Nil			
Diagnosis	Bullous pemphigoid	Count	2	0	4	16	22	17.387	0.0136
		%	18.2%	0.0%	30.8%	25.4%	22.0%		
	Linear IgA disease	Count	1	3	0	5	9		
		%	9.1%	23.1%	0.0%	7.9%	9.0%		
	Mucous membrane pemphigoid	Count	0	0	1	0	1		
		%	0.0%	0.0%	7.7%	0.0%	1.0%		
	Pemphigus foliaceous	Count	1	2	3	15	21		
		%	9.1%	15.4%	23.1%	23.8%	21.0%		
	Pemphigus vulgaris	Count	7	8	5	27	47		
		%	63.6%	61.5%	38.5%	42.9%	47.0%		
Total		Count	11	13	13	63	100		
		%	100.0%	100.0%	100.0%	100.0%	100.0%		

Table 10: Summary of ocular manifestations by skin disease

	Conjunctivitis		Dry eye				Others
	Cicatrizing	Non-cicatrizing	Mild	Moderate	Severe	Total	
Pemphigus vulgaris Total = 47	2	4	7	8	5	26	Conjunctival erosions, SPK, conjunctival scarring
	7.6%	15.3%	26.9%	30.7%	19.2%	100%	
Pemphigus foliaceous Total = 21	-	3	1	2	3	9	Blepharitis with lid margin erosions, SPK
	0%	33.3%	11.1%	22.2%	33.3%	100%	
Bullous pemphigoid Total = 22	3	5	2	-	4	14	Conjunctival erosions, symblepharon, SPK
	21.4%	35.7%	14.2%	0%	28.5%	100%	
Mucous membrane pemphigoid Total = 1	-	-	-	-	1	1	SPK, symblepharon
	0%	0%	0%	0%	100%	100%	
Linear IgA disease Total = 9	-	-	1	3	-	4	Conjunctival scarring, SPK
	0%	0%	25%	75%	0%	100%	

(e) 19.2% had severe dry eye

2. Pemphigus foliaceous – Out of 21 patients, 9 had ocular manifestations of which
   (a) 33.3% had non cicatrizing conjunctivitis
   (b) 11.1% had mild dry eye
   (c) 22.2% had moderate dry eye
   (d) 33.3% had severe dry eye
3. Bullous pemphigoid – Out of 22 patients, 14 had ocular manifestations of which
   (a) 21.4% had cicatrizing conjunctivitis
   (b) 35.7% had non-cicatrizing conjunctivitis
   (c) 14.2% had mild dry eye
   (d) 28.5% had severe dry eye
4. Mucous membrane pemphigoid – only one case of MMP was encountered in this study and this patient had severe dry eye.
5. Linear IgA disease – Out of 9 patients with this disease, 4 had ocular manifestations of which
   (a) 25% had mild dry eye
   (b) 75% had moderate dry eye

The less frequent ocular manifestations encountered in this study were lid margin erosions, conjunctival erosions, conjunctival scarring and symblepharon. These findings were commonly seen in association with dry eye and were present bilaterally. 5 patients were also diagnosed to have bilateral presenile posterior subcapsular cataract, which occurred as a complication of systemic steroids used to treat the skin disease. Of these, 2 patients did not have any other ocular features of the disease.

4. Discussion

Autoimmune blistering skin diseases or bullous dermatoses are a group of skin diseases characterised by autoantibodies against structural desmosomal proteins. Since the desmosomal proteins are primarily responsible for epidermal adhesions, autoimmune diseases targeting these proteins result in separation of the epithelium from the basal layer, manifesting as bullous lesions.[1,2]

In this study, pemphigus vulgaris accounted for 47% of the patients, bullous pemphigoid accounted for 22% of the patients, pemphigus foliaceous accounted for 21%, linear IgA disease accounted for 9%, mucous membrane pemphigoid for 1%.[3,4]

53% patients were male and 47% were female. The incidence was found to be almost equal.[5]

The incidence of ocular manifestations in pemphigus vulgaris was found to be 46%, 26% in bullous pemphigoid, and 8% in linear IgA disease. The lower incidence of ocular manifestations in bullous pemphigoid and linear IgA disease in this study is probably due to the lower number of patients of the same, encountered.

The most common ocular manifestations encountered among patients of autoimmune bullous skin diseases in this study were dry eye followed by conjunctivitis. Of the 100 patients, 37 patients had dry eye of which 11 had mild dry eye, 13 had moderate dry eye and 13 had severe dry eye ($p < 0.05$).

Among the 100 patients, 17 had conjunctivitis of which 5 had cicatrizing and 12 had non-cicatrizing conjunctivitis.

Ocular manifestations in pemphigus were confined to the lids, conjunctiva and cornea i.e. the ocular surface. The most common ocular manifestation was dry eye followed by conjunctivitis.[6–9] 26 of the 68 patients with pemphigus had dry eye which approximated to 40% and the most common symptom reported was chronic irritation. 9 of the 68 patients had conjunctivitis as the ocular manifestation accounting for approximately 15%.

No correlation was found between the duration, activity, and severity of skin disease and ocular manifestations.[10,11] Vision threatening manifestations were also not encountered in patients with pemphigus.[12]

Among the 100 patients in this study, 22 had a diagnosis of bullous pemphigoid of which 14 had ocular manifestations. Of the 14 patients, 8 had conjunctivitis and 6 had dry eye.

All our patients were being treated with systemic steroids for their dermatological condition, either by the intravenous or oral route; alone or in combination with other immunosuppressive drugs such as cyclophosphamide (as part of the DCP pulse therapy), methotrexate or azathioprine.

Since most of these skin disorders are chronic and require long term treatment, the complications of long-term steroid and immunosuppressive treatment should be borne in mind.

With regards to the ocular complications of steroids, patients have to be monitored for the development of steroid induced glaucoma and cataract. None of the 100 patients in our study had raised IOP. 5 of the100 patients had presenile posterior subcapsular cataract as a complication of long-term steroid usage. 4 of the 5 patients were in the age group of 40-50 years. One patient was less than 40 years of age. All the 5 patients who developed steroid induced cataract were being treated with intravenous dexamethasone.[13,14]

5. Conclusion

More than 50% of patients in this study had ocular manifestations secondary to their skin disease and as a consequence of steroid therapy. Dry eye followed by conjunctivitis were the most common ocular manifestations encountered. Though no vision threatening manifestations were seen, a comprehensive ophthalmological examination and follow up of these patients is necessary for the early diagnosis and management of any ocular manifestations that might develop during the course of the disease and thereby prevent vision debilitating sequelae. The

limitation of the study was that the patients were unequally distributed among the various skin disorders, so the ocular manifestations of disorders like linear IgA disease and mucous membrane pemphigoid could not be properly analysed and the sample size was small even with the other bullous skin diseases. But the study has shed light on the likely ocular manifestations to be expected in these patients so that appropriate referrals and interventions can be undertaken.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

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