A Dissertation on

AN ANALYTICAL STUDY ON THE OCULAR MANIFESTATIONS IN PATIENTS WITH AUTOIMMUNE BLISTERING SKIN DISORDERS IN A TERTIARY CARE HOSPITAL

Dissertation submitted for

M.S degree in Ophthalmology

May 2020

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

REGISTER NO: 221713201

DECLARATION

I hereby declare that this dissertation titled **" AN ANALYTICAL STUDY ON THE OCULAR MANIFESTATIONS IN PATIENTS WITH AUTOIMMUNE BLISTERING SKIN DISORDERS'** is a bonafide and genuine research work carried out by me under the guidance of **Dr.S.PADMANABAN M.S., D.O,** Associate Professor, Department of Ophthalmology, Coimbatore Medical College & Hospital, Coimbatore.

This is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of regulations required for the M.S Ophthalmology, Branch III Degree Examination to be held in May 2020

Date:

Place: **DR ANUPAMA VINUPAL**

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"AN ANALYTICAL STUDY ON THE OCULAR MANIFESTATIONS IN PATIENTS WITH AUTOIMMUNE BLISTERING SKIN DISORDERS"** is a bonafide and research work done by Dr ANUPAMA VINUPAL Post Graduate in M.S. Ophthalmology under my direct guidance and supervision to my satisfaction in partial fulfillment of the requirement for the degree of Master of Surgery in Ophthalmology, Branch III .

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CERTIFICATE OF APPROVAL

To
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Dear Dr.Anupama Vinupal

The Institutional Ethics Committee of Coimbatore Medical College, reviewed and discussed your application for approval of the proposal entitled "**An Analytical Study on the Ocular Manifestations in Patients with autoimmune Blistering Skin disorders.**"No.045/2017.

The following members of Ethics Committee were present in the meeting held on 23.11.2017.conducted at MM - II Seminar Hall, Coimbatore Medical College Hospital Coimbatore-18.

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We approve the Proposal to be conducted in its presented form.

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The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

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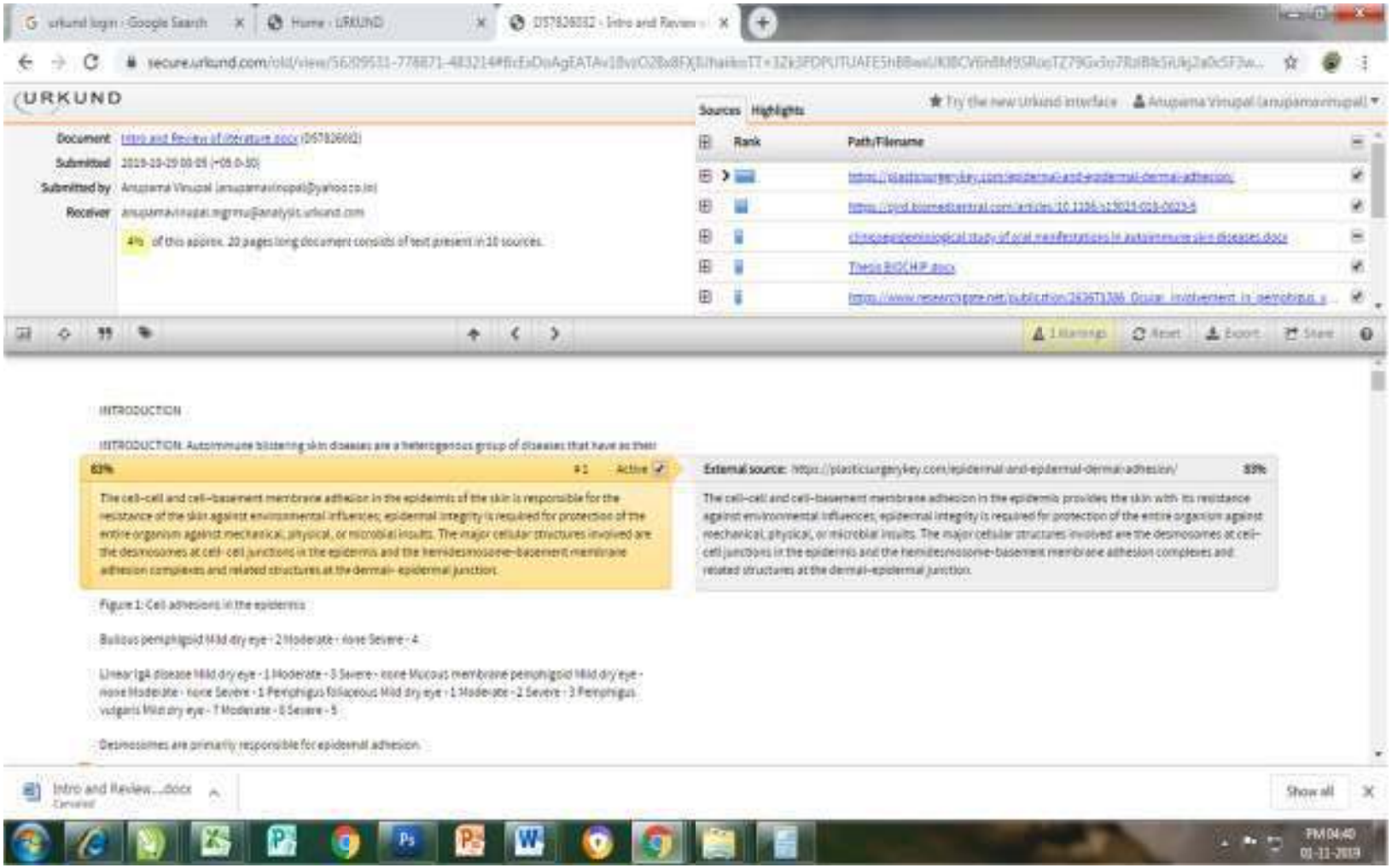
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INTRODUCTION
INTRODUCTION Autoimmune blistering skin diseases are a heterogenous group of diseases that have as their
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The cell–cell and cell–basement membrane adhesion in the epidermis of the skin is responsible for the resistance of the skin against environmental influences; epidermal integrity is required for protection of the entire organism against mechanical, physical, or microbial insults. The major cellular structures involved are the desmosomes at cell- cell junctions in the epidermis and the hemidesmosome-basement membrane adhesion complexes and related structures at the dermal- epidermal junction.
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The cell–cell and cell–basement membrane adhesion in the epidermis provides the skin with its resistance against environmental influences; epidermal integrity is required for protection of the entire organism against mechanical, physical, or microbial insults. The major cellular structures involved are the desmosomes at cell–cell junctions in the epidermis and the hemidesmosome-basement membrane adhesion complexes and related structures at the dermal–epidermal junction.
Figure 1: Cell adhesions in the epidermis
Bullous pemphigoid Mild dry eye - 2 Moderate - none Severe - 4
Linear IgA disease Mild dry eye - 1 Moderate - 3 Severe - none Mucous membrane pemphigoid Mild dry eye - none Moderate - none Severe - 1 Pemphigus foliaceous Mild dry eye - 1 Moderate - 2 Severe - 3 Pemphigus vulgaris Mild dry eye - 7 Moderate - 0 Severe - 5
Desmosomes are primarily responsible for epidermal adhesion.
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Date:

Place: Dr ANUPAMA VINUPAL

ABBREVIATIONS

PV	–	Pemphigus vulgaris
PF	–	Pemphigus foliaceous
MMP	–	Mucous membrane pemphigoid
BP	–	Bullous pemphigoid
IgA	–	Immunoglobulin A
DCP	–	Dexamethasone – cyclophosphamide pulse therapy
SPK	–	Superficial punctate keratitis
PSCC	–	Posterior subcapsular cataract
IOP	–	Intraocular pressure
DIF	–	Direct immunofluorescence
ELISA	–	Enzyme linked immunosorbent assay
T-BUT	-	Tear Film Breakup Time

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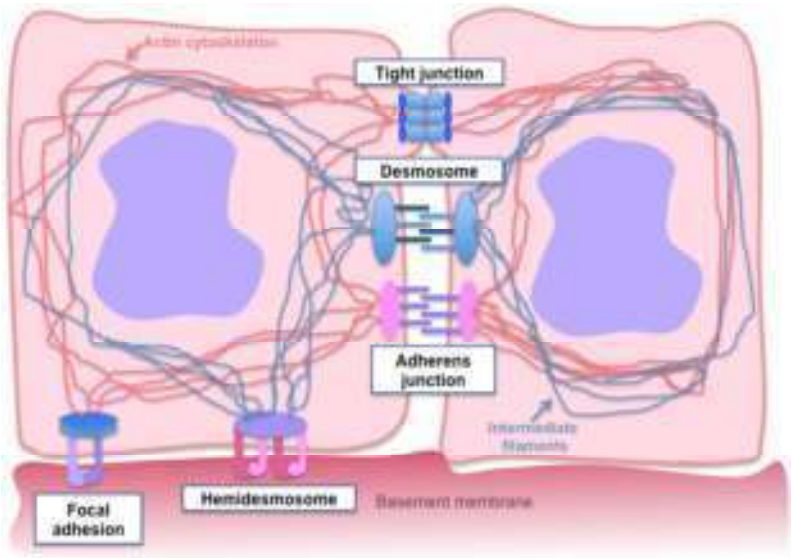
INTRODUCTION

Autoimmune blistering skin diseases are a heterogenous group of diseases that have as their common feature autoantibodies directed against desmosomal structural proteins.

The cell–cell and cell–basement membrane adhesion in the epidermis of the skin is responsible for the resistance of the skin against environmental influences; epidermal integrity is required for protection of the entire organism against mechanical, physical, or microbial insults. The major cellular structures involved are the desmosomes at cell- cell junctions in the epidermis and the hemidesmosome–basement membrane adhesion complexes and related structures at the dermal– epidermal junction.

Figure 1: Cell adhesions in the epidermis



Desmosomes are primarily responsible for epidermal adhesion. Protein components of desmosomes, hemidesmosomes, and epidermal basement membrane are the primary targets in autoimmune blistering diseases of the pemphigus or pemphigoid group and in epidermolysis bullosa acquisita.

A blister is defined as a fluid filled cavity that is formed within or beneath the epidermis. Blisters may be classified as vesicles or bullae. A vesicle is a fluid filled blister that is less than 0.5cm and a bulla is a fluid filled blister larger than 0.5cm. The fluid within a blister may be clear, serous, purulent or haemorrhagic.(1,2)

The term pemphigus was introduced and the identification and characterisation of the disease began as early as the 1700's. It was Wichmann in 1791 who gave the word pemphigus its present meaning, that of a chronic bullous disease.

Bullous disorders can be classified by various criteria such as histology and pathogenesis, etiology- whether autoimmune or not, and morphological characteristics of the lesion.

Immune mediated bullous disorders are further classified into intraepithelial and subepidermal blistering disorders.

The intraepithelial blistering disorders include:

- Pemphigus and its variants

Subepidermal diseases include:

- Bullous pemphigoid
- Mucous membrane pemphigoid
- Linear IgA bullous dermatosis
- Epidermolysis bullosa acquisita
- Pemphigoid gestationalis and
- Dermatitis herpetiformis.

Pemphigus group of disorders are classified into two major groups depending on the location of the blister in the epidermis - pemphigus foliaceus (PF), pemphigus erythematosus and endemic pemphigus foliaceus are diseases in which the blister is located superficially. Pemphigus vulgaris and its variant, pemphigus vegetans consists of deeper location of blisters.(1,2)

Keratinocytes in the epidermis are bound to each other by structures called desmosomes. In pemphigus, the desmosomes become disrupted and the cells become rounded and separate. Desmosomes contain desmosomal cadherins, desmoglein and desmocollins as transmembrane components and desmoplakin and plakoglobin as cytoplasmic components. Desmoglein exists in 4 isoforms namely desmoglein 1-4. Desmoglein 3 and 1 are respectively the antigens in pemphigus vulgaris and pemphigus foliaceus.(3)

Desmoglien-3 is expressed on the entire ocular surface including the cornea, bulbar and palpebral conjunctiva. It is also expressed in deeper structures in the eye, such as the retina. Ocular surface manifestations have been found to be more common.

Figure 2: Pathology of pemphigus

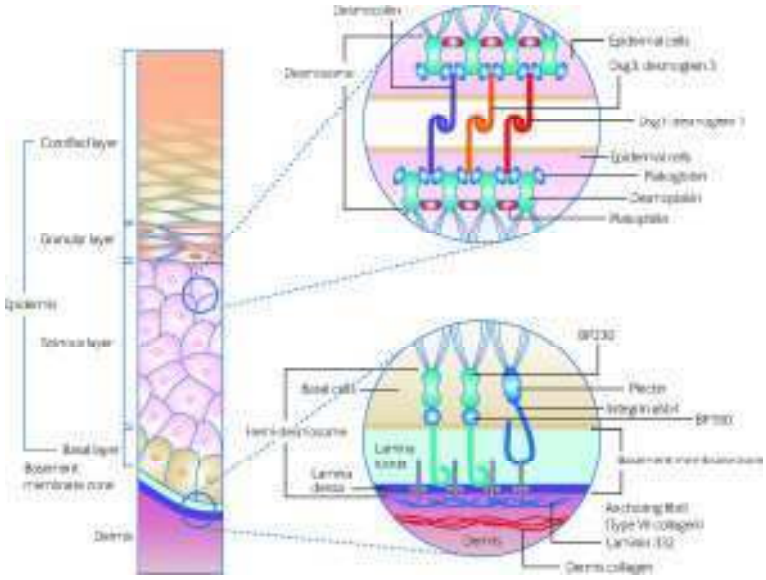
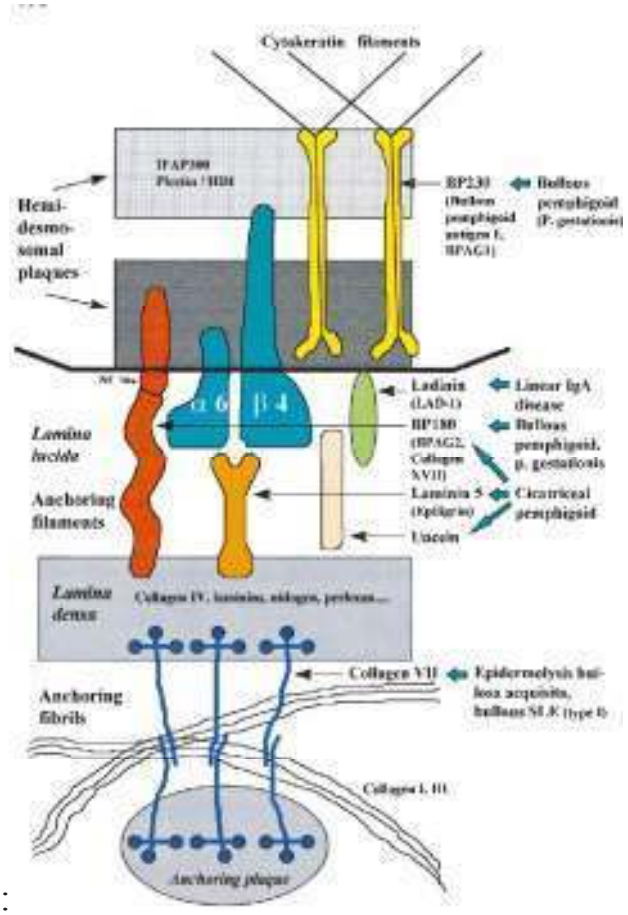


Table 1: Major Autoantigens in Bullous Diseases (4)

Disease	**Autoantigen**
Pemphigus Diseases	
Pemphigus vulgaris	Desmoglein 3, desmoglein 1
Pemphigus foliaceus	Desmoglein 1
Pemphigus erythematosus	Desmoglein 1, 3, ANAs
Paraneoplastic pemphigus	Desmoglein 1, desmoglein 3, desmoplakin, envoplakin, periplakin, BP230, alpha-2-macroglobuline-like-1, plectin, desmocollins 1-3
IgA pemphigus	Desmocollin 1-3, desmoglein 3
Pemphigoid Diseases	
Bullous pemphigoid	BP180, BP230
Pemphigoid gestationis	BP180, BP230
Mucous membrane pemphigoid	BP180, Laminin 332, A6B4 integrin

Disease	Autoantigen
Linear IgA disease	LAD-1 (BP180), BP230
Anti-p200 pemphigoid	p200 antigen (Laminin Γ1)
Epidermolysis bullosa acquisita	Collagen VII
Dermatitis herpetiformis	Tissue/epidermal transglutaminase

Figure 3: Pathology of bullous dermatoses



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Pemphigus vulgaris is the most common subtype and includes two clinical variants – one that produces mucosal lesions and another that produces mucosal and skin lesions. In India, pemphigus vulgaris is commonly seen in younger individuals with a slight male preponderance. The commonest age of onset is the 4^{th} and 5^{th} decade and it may occur in children also. (5)

Pemphigus vulgaris presents with oral blisters and erosions in 50-70% of individuals. The skin lesions may appear weeks or even a year later. The skin lesions are vesicles and bullae on apparently normal or erythematous skin. (6–9) The sites most commonly involved are the scalp, face, axillae and oral cavity where the antigen is maximally expressed. Any stratified squamous mucosal surface such as pharyngeal, laryngeal, esophageal, conjunctival, urethral, cervical, or anal regions may be affected, particularly in patients with severe disease.

Figure 4: Skin lesions in pemphigus vulgaris

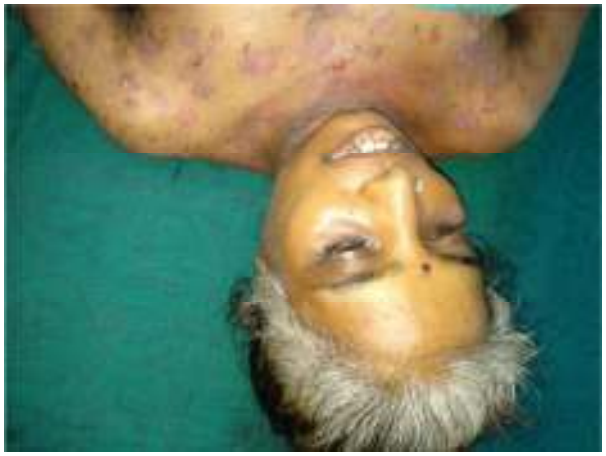


Figure 5: Skin lesions in pemphigus vulgaris

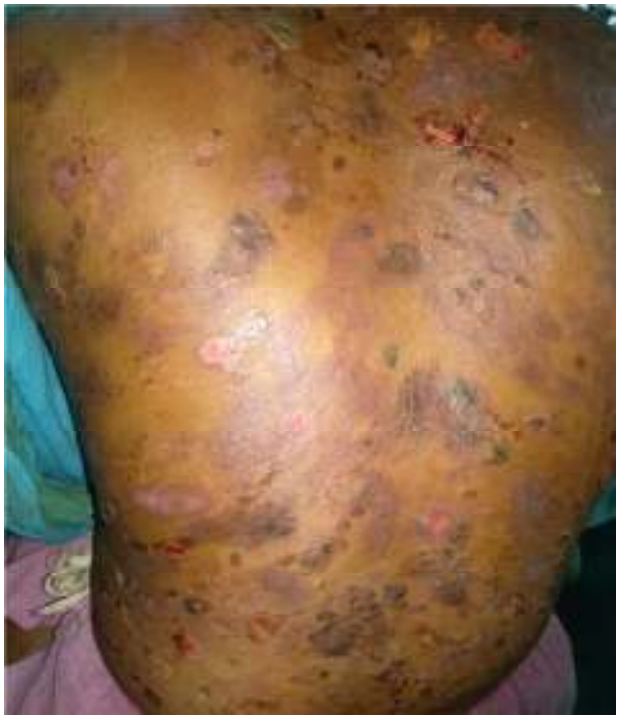


Figure 6: Oral lesions in pemphigus vulgaris

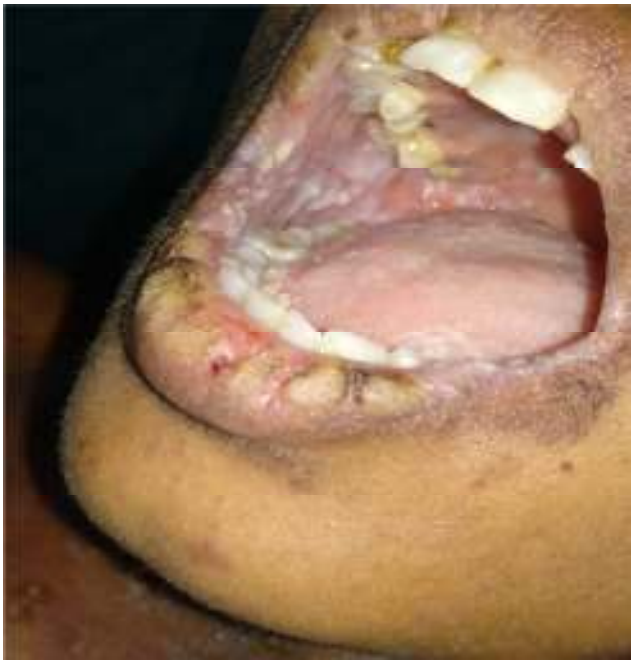


Figure 7: Skin lesions in pemphigus foliaceous

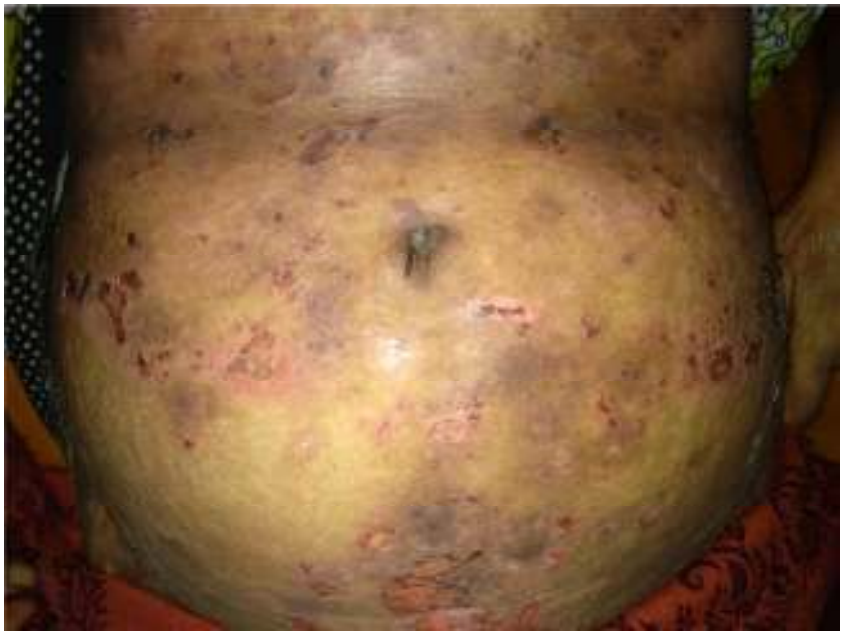


Figure 8: Skin lesions in pemphigus foliaceous

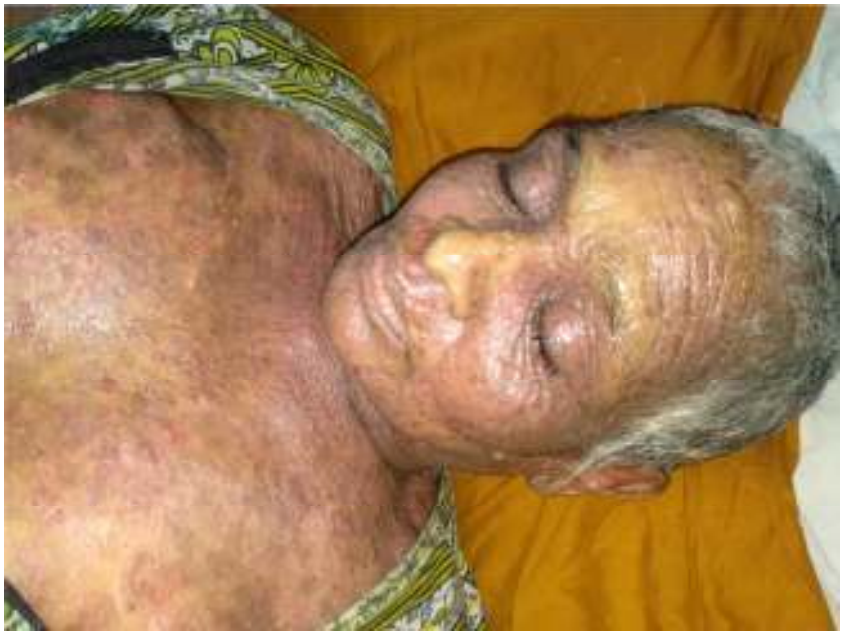
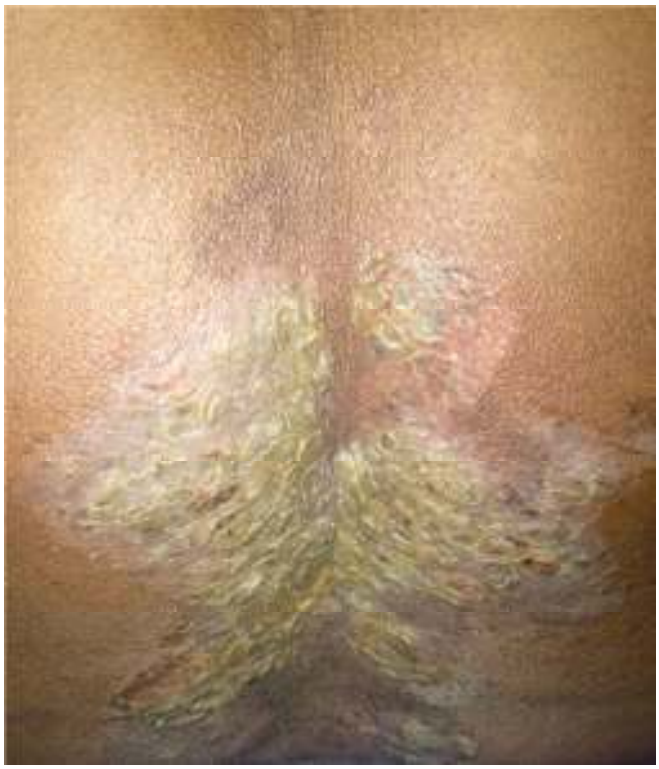


Figure 9: Skin lesions in pemphigus erythematosus

Figure 10: Skin lesions in pemphigus erythematosus



Eye involvement sometimes may precede other manifestations of pemphigus vulgaris. The manifestations can include mucopurulent conjunctivitis or non-specific conjunctival hyperemia. (10–13) Mild to moderate bilateral non cicatrizing conjunctivitis is the most common.(14–17) More severe manifestations include palpebral conjunctival and lid margin erosions. (7,9,18) Conjunctival lesions in both the acute and chronic stages are similar. (14,19) Ocular manifestations of pemphigus vulgaris commonly occurred during flare up of the mucocutaneous disease and never as the only mucosal involvement. Ocular lesions of pemphigus were associated with greater disease activity and usually followed a benign course. (1,9) In chronic cases, repeated bullae formation leads to conjunctival cicatrisation (symblepharon) with progressive contraction of the conjunctival sac, always more marked in the lower fornix. (16,20)

Pemphigus vegetans is a benign and rare variant of pemphigus vulgaris. The lesions commonly involve the intertriginous areas such as the axillae, groins and inframammary folds and the flexural areas.

The other variants of pemphigus are herpetiform pemphigus, drug induced pemphigus, paraneoplastic pemphigus and IgA pemphigus.

Patients of pemphigus foliaceus have scaly, crusted cutaneous erosions on an erythematous base but do not have clinically apparent mucosal involvement even in widespread disease.

Paraneoplastic pemphigus refers to disease associated with both benign and malignant neoplasms. The most common neoplasms associated with paraneoplastic pemphigus are non-Hodgkin's lymphoma and chronic lymphocytic leukaemia and the both taken together account for about two-thirds of the cases. Patients with paraneoplastic pemphigus may have severe pseudomembranous conjunctivitis that may progress to scarring and obliteration of the conjunctival fornices. (1,2,8)

IgA pemphigus is a group of autoimmune blistering skin disorder characterised by vesiculopustular eruption, neutrophilic infiltration of the skin and circulating IgA autoantibodies against the cell surface of keratinocytes, and absence of IgG autoantibodies. Mucous membrane involvement is rare.

The differential diagnosis of mucous membrane involvement of pemphigus vulgaris includes Steven Johnson syndrome, systemic lupus erythematosus and ocular cicatricial (mucous membrane) pemphigoid.

Bullous pemphigoid is the most common autoimmune subepidermal blistering skin disorder most commonly seen in the elderly. It has a chronic course marked by exacerbations and spontaneous remissions. It is characterised by two phases – non bullous and bullous phase.(21–23) Bullous phase is marked by the presence of blisters and vesicles and mucosal involvement occurs in this phase. Oral cavity is the most common mucosal site involved and the eyes are rarely involved. In those patients who develop ocular disease, many patients have non-specific symptoms such as irritation, redness and foreign body sensation. Signs may also be non-specific and includes conjunctival congestion and chemosis. About 40% patients develop advanced features of the disease such as conjunctival scarring and symblepharon formation.(1,20,24,25)

Figure 11: Bullae in bullous pemphigoid

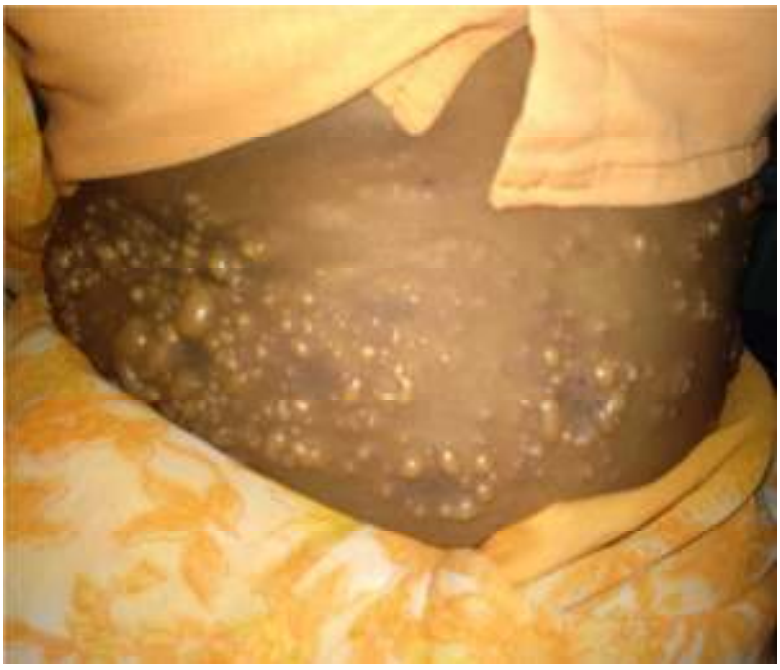
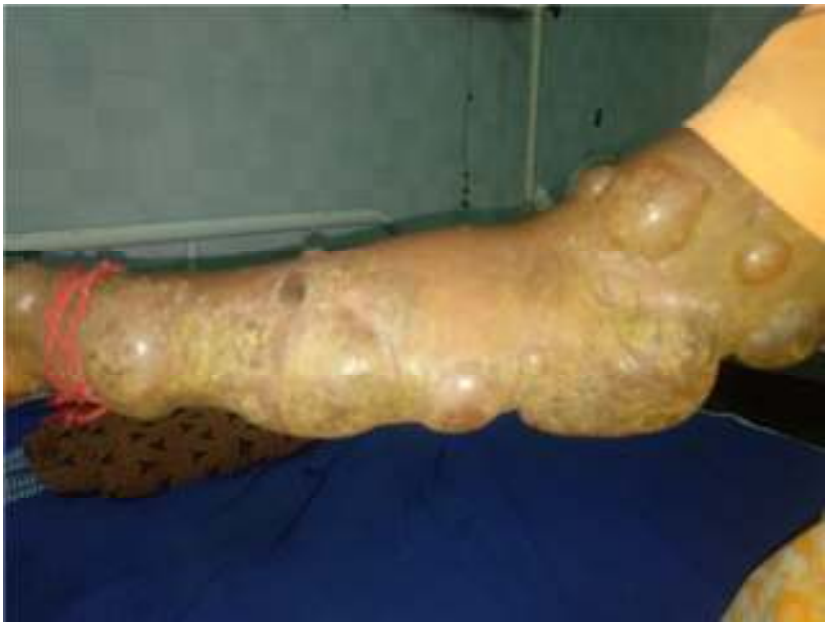


Figure 12: Bullae in bullous pemphigoid



Mucous membrane (cicatricial) pemphigoid is a chronic autoimmune subepidermal blistering disease that predominantly involves the external mucous membranes and has a tendency for scarring. It is a progressive disease with a chronic course that can result in serious local complications. It is most commonly seen in the elderly with a mean age of diagnosis between 60 and 80 years and a female preponderance.

The pathogenesis of the disease is the binding of autoantibodies to the basement membrane zone of the stratified epithelia of the skin and mucous membrane. For patients with ocular disease, increased expression of collagen binding heat shock protein 47 and transforming growth factor ß1 (TGF ß1) by conjunctival fibroblasts led to conjunctival scarring.

Mucous membrane pemphigoid can be subdivided into four subgroups based on the reactivity profile of the patients' autoantibodies. It is the second subset of patients that have pure or predominantly ocular disease and is called the ocular mucous membrane pemphigoid.

The two most common sites involved in the mucous membrane pemphigoid phenotype are the oral mucosa and the conjunctival mucosa.(26) Conjunctival involvement is common and if left unnoticed and untreated can lead to blindness.(27–29) Sometimes it might be the only site affected. Lesions commonly start bilaterally but unilateral presentation is not uncommon.

Ocular involvement starts as a chronic non-specific conjunctivitis and the patients may present with non-specific symptoms such as soreness, burning and foreign body sensation and mucous production. Exacerbations and remissions are typical of the disease that eventually progress to subepithelial conjunctival fibrosis.

Isolated involvement of the oral mucosae in OMP is usually associated with a benign course, whereas those who have ocular involvement commonly have resistance to treatment and are likely to develop blindness due to scarring.(30)

Conjunctival blisters and vesicles are rare on the tarsal conjunctiva. Chronic inflammation may result in progressive scar tissue formation that may lead onto shortening of the inferior fornices and symblepharon formation. The sequelae of conjunctival fibrosis include trichiasis and entropion. Recurrent inflammation results in loss of goblet cells and scarring of the lacrimal gland ductules causing aqueous and mucous tear deficiency. Progressive subepithelial fibrosis causes destruction of limbal stem cells leading onto limbal stem cell deficiency and ocular keratinization.(31) The end result of uncontrolled and untreated disease is superficial corneal trauma, corneal neovascularisation and corneal ulceration as a result of trichiasis, entropion and xerosis ultimately leading to blindness.(27,32)

Ocular involvement of MMP is considered high risk and carries a poorer prognosis despite treatment than when oral mucosa and/or skin alone are affected. Up to one third of patients with oral disease progress to ocular involvement.(24,25,31,33)

Several clinical scoring systems are available for ocular cicatricial pemphigoid. Two of them are listed below:

1. **Mondino's Classification System** (34) is based on inferior forniceal depth. A normal inferior forniceal depth is approximately 11 mm

    - Stage I: up to 25% inferior forniceal depth loss
    - Stage II: 25-50% inferior forniceal depth loss
    - Stage III: 50-75% inferior forniceal depth loss
    - Stage IV: greater than 75% inferior forniceal depth loss

2. **Foster's Classification System** has four stages as well and is based on specific clinical signs

    - Stage 1 – subconjunctival fibrosis
    - Stage 2 – forniceal shortening
    - Stage 3 – symblepharon formation
    - Stage 4 – keratinisation of the ocular surface and ankyloblepharon formation.

Cicatricial pemphigoid should be differentiated from other cicatrising conditions such as Steven Johnson syndrome, trachoma, chemical burns, linear IgA disease, radiation and neoplasm.

A condition that is commonly confused with cicatricial pemphigoid is pseudo-pemphigoid which results from the use of topical medications such as pilocarpine, timolol, epinephrine etc. Since pemphigoid is a deeper insult, it can induce scarring while pemphigus vulgaris is less likely to cause scarring.

Linear IgA disease is a subepidermal vesicular dermatosis characterised by the binding of IgA antibodies to the dermal-epidermal junction. It is the most frequent autoimmune blistering disease in infants and children. The incidence was reported to be higher in India and other developing countries compared to the developed nations. There is a bimodal age distribution; one peak below 5 years of age and the other between 60-65 years of age.(32)

The average incidence has been reported to be around 0.58/200,000 individuals. The disease was reported to be severe and aggressive with rapid progression in men even though it also affects the female gender and paediatric population.(35)

The disease presents as tense blisters and vesicles, urticated plaques, erosions and erythema. Mucous membrane involvement is common, seen in approximately 70% of patients with the oral mucosa being the commonest site.

The ocular manifestations of linear IgA dermatoses can resemble and overlap those of mucous membrane pemphigoid. It may present as fine subconjunctival scarring and subconjunctival fibrosis that can lead to distortion of the lid architecture. This can cause entropion, trichiasis, shortening of inferior fornices and symblepharon formation and secondary corneal scarring. (2,36) Corneal perforations also have been reported. (37,38)

The definitive diagnosis of all the autoimmune blistering skin disorders is by biopsy of the lesion followed by light and electron microscopic examination and immunofluorescence study. (39–44) Immunofluorescence study can be direct or indirect immunofluorescence. Other advanced modalities used for diagnosis include ELISA, immunoblotting and immunoelectron microscopy.

Pemphigus vulgaris on DIF shows intraepidermal deposits of IgG (+/- C3) with an intercellular pattern. Pemphigus foliaceous too shows the same pattern on DIF. (45,46)

On DIF, bullous pemphigoid shows deposition of IgG along the dermal-epidermal junction, commonly IgG1 and IgG4. (47)

Diagnosis of OMP is based on the demonstration of linear deposition of IgG, IgA or complement component 3 in the epithelial basement membrane. (48)

Linear IgA dermatoses on DIF show a smooth, linear pattern of IgA deposition in the basement membrane in contrast to dermatitis herpetiformis where there are granular deposits of IgA within the papillary dermis. (49)

Figure 13: DIF findings in bullous dermatoses (50)

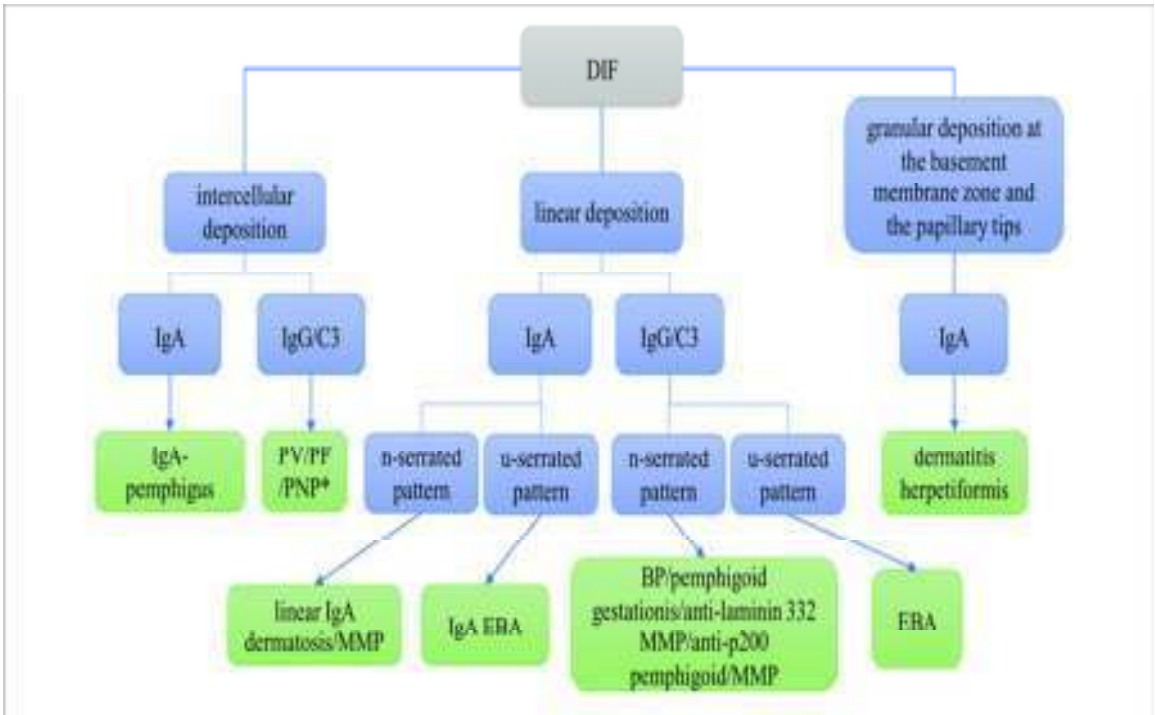
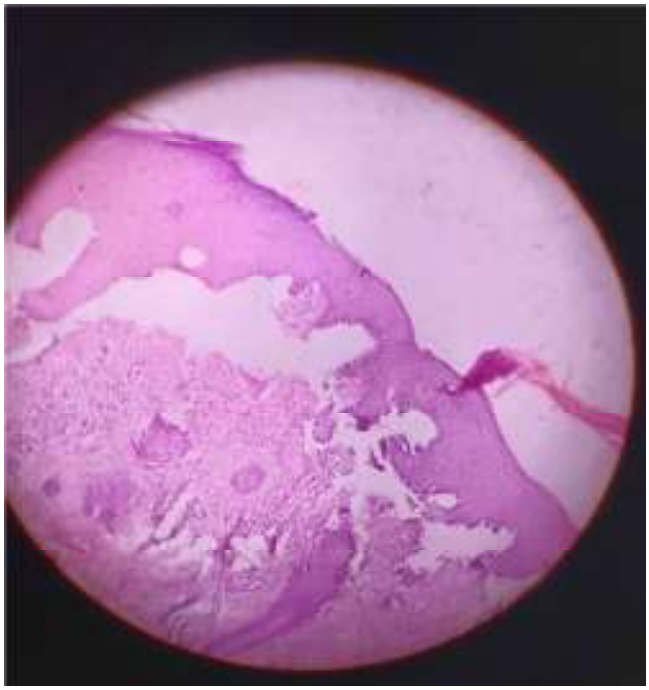


Figure 14: Subepidermal bulla on HPE



Although the spectrum of autoimmune blistering skin disorders is broad, according to one study, diseases which are commonly associated with ocular involvement are pemphigus vulgaris, cicatricial pemphigoid and paraneoplastic pemphigus.(25)

The treatment of pemphigus group of diseases has been revolutionised by the introduction of the dexamethasone cyclophosphamide pulse therapy.(51–53) This therapy consists of four phases:

- Phase 1: given in the presence of active signs and symptoms. Dexamethasone (100 mg in 500ml of 5% dextrose) is given intravenously over 2 hours on 3 consecutive days +

cyclophosphamide 500mg on day 1. This is repeated every 4 weeks. In between these pulses, oral cyclophosphamide 50mg is given daily.

- Phase 2: when patients are in remission. Monthly pulse therapy of DCP and daily oral cyclophosphamide is continued for 9 months.

- Phase 3: Only oral cyclophosphamide 50mg is given daily for 9 months.

- Phase 4: All treatments are withdrawn and patients are followed up for the occurrence of relapses, if any. (51,54,55)

Corticosteroids have recently been complemented by the anti-CD 20 antibody Rituximab in patients with moderate and severe disease. (56) Rituximab has also been reported to be effective in controlling the disease activity in patients with cicatrizing lesions of the ocular surface such as recalcitrant cicatrizing conjunctivitis associated with OMP or Steven Johnson's syndrome. (57)

The treatment of mucous membrane pemphigoid varies for oral pemphigoid and generalised pemphigoid. For oral pemphigoid, the first line therapy includes oral hygiene and topical steroids. The second line

therapy includes first line therapy plus dapsone and/or sulfapyridine/ sulphamethoxypyridazine or anti-inflammatory antibiotics.(58, 59)

For generalised mucous membrane pemphigoid without rapid progression in conjunctiva, larynx, or oesophagus, the first line therapy is dapsone plus prednisolone. The second line of management includes mycophenolates plus prednisolone.

For generalised mucous membrane pemphigoid with rapid progression in conjunctiva, larynx or oesophagus, the first line therapy includes cyclophosphamide (oral and/or intravenous) plus prednisolone. The second line therapy includes mycophenolates plus prednisolone. (42)

The treatment of bullous pemphigoid depends on the extent of the disease. Localised lesions can be treated with topical corticosteroids alone and are usually sufficient. More extensive lesions are treated with oral prednisolone. Other immunosuppressive drugs like azathioprine, mycophenolate mofetil, cyclophosphamide are used as steroid sparing agents.(60–63)

Since most of these blistering disorders are treated with topical and/or systemic steroids, the steroid induced ocular complications like cataract and glaucoma should also be borne in mind while evaluating these patients in addition to the ocular manifestations of the specific

diseases.(64–67) Hence eliciting a proper and complete treatment history is important.

The aim of this study is to analyse the varied ocular manifestations, if any, their spectrum and incidence, occurring in patients with autoimmune blistering skin diseases in a tertiary care hospital, during a period of one year.

Since some of the ocular manifestations can be severe and sight threatening if not detected and managed early, knowledge about the various ocular manifestations will help in screening such patients and prevent sight threatening ocular complications.

REVIEW OF LITERATURE

Autoimmune blistering skin disorders are a group of diseases characterised by autoantibodies directed against desmosomal structural proteins. Bullous disorders can be classified by various criteria such as histology and pathogenesis, etiology- whether autoimmune or not, and morphological characteristics of the lesion.

Immune mediated blistering diseases are further sub-classified as intraepithelial and subepidermal blistering diseases.

The intraepithelial diseases include pemphigus and its variants and the subepidermal diseases include bullous pemphigoid, mucous membrane pemphigoid, linear IgA dermatosis and others.

Amrinder et al. (5) have found that the incidence of pemphigus in India varies from that of Western countries in different aspects. The incidence of pemphigus among patients attending outpatient department has been found to vary from 0.09 to 1.8%. Among the pemphigus variants, pemphigus vulgaris is the most common accounting for about 75-92% of all pemphigus patients. The second common variant was pemphigus foliaceous. In the UK, the incidence of pemphigus vulgaris and foliaceous was found to be almost equal.

A significant proportion of Indian patients were found to be younger than 40 years of age, in contrast to other parts of the world, where pemphigus occurs commonly between 40 and 60 years of age.

The estimation of gender predilection has yielded varying results, with some studies showing equal incidence while others revealing either female/male preponderance. Overall it appears that the incidence is almost equal. The equal incidence rate among men and women has been supported in a study by **Bose T et al. (52)**

In another study by **Ramassamy et al.(3),** the incidence of pemphigus vulgaris was found to be 89% and that of pemphigus foliaceous was 10%. A study by **Omeed Memar et al.** (68) reported the prevalence of ocular manifestations in pemphigus vulgaris to be between 7% and 16%.

According to a review article by **Sepehr Feizi et al.(32),** the incidence of ocular manifestations in mucous membrane pemphigoid was estimated to be about 61-80%. The disease was estimated to be confined to the eye (ocular pemphigoid) in approximately 20%.

Brendon W.H. Lee (69) reported that the incidence of ocular manifestations in mucous membrane pemphigoid ranged from 64-89% usually between the ages of 30-90 with a female preponderance. In cases

where the diagnosis or treatment is delayed, severe ocular surface disease causing vision loss was reported in 33% of patients.

Bose.T et al.(54) reported that ocular mucous membrane pemphigoid occurs more commonly in women with a female to male ratio of 2:1. Ocular involvement was reported in 60-77% of cases in this study. Red eyes and itching were reported as the two most common symptoms.

Williams GP et al.(58) reported that the progression of disease in ocular pemphigoid occurred despite the absence of clinically detectable inflammation and hence there is a need for regular follow up of patients with ocular mucous membrane pemphigoid.

The incidence of ocular manifestations in pemphigus vulgaris was reported to be approximately 16.5%. Ocular involvement in pemphigus vulgaris was confined to the eyelids and conjunctiva and visual acuity was usually unaffected. Mild to moderate non-cicatrizing conjunctivitis was the most common ocular manifestation reported in the study.

Omeed Memar et al.(68) reported that the most common ocular manifestations were chronic and refractory blepharitis and conjunctivitis. The cutaneous manifestations may also extend to the lids causing lid malposition. But overall the prevalence of vision loss in PV was rare.(68)

Hiroyuki Namba et al. (13) reported that ocular manifestations in pemphigus are rare and the majority of patients who had ocular manifestations had cicatricial conjunctivitis. He reported a rare case of a patient with pemphigus vulgaris who had giant conjunctival papillae which responded poorly to topical medications and was treated with systemic immunosuppression. It was suggested that if a patient with pemphigus developed ocular lesions, systemic immunosuppression was better than topical ophthalmic medications because of the generalised immunological involvement.

Pemphigus that is localised to the eye and presenting as erosive conjunctivitis is a rare manifestation. There has been a report by **Sehgal et al.** where a patient had isolated ocular pemphigus for more than a year.(71) A study by **Brendon W H Lee et al.** also reported that ocular pemphigus is very rare. It commonly involves only the eyelid skin and spares the conjunctiva.

Brackley et al. (11) proposed that ocular manifestations in pemphigus could imply severe disease. This has also been corroborated by other studies. In contrast, study by **Akhyani et al. (18)** reported that there was no significant correlation between ocular involvement and disease activity. This was supported by **Palleschi et al. (72)** who also proposed that there was no correlation but that the ocular manifestations

may persist chronically after healing of cutaneous lesions. This view has also been supported by **Brendon W H Lee et al.** in their study of ocular involvement in chronic immunobullous skin diseases.

Though ocular manifestations of pemphigus do not usually threaten vision, there have been case reports of severe eye involvement in patients of pemphigus. A case report by **Lifshitz et al. (12)** described a case of pemphigus vulgaris that presented with bilateral severe swelling, induration and thickening of eyelids; multiple conjunctival and lid margin erosions and high intraocular pressure as a complication of steroid treatment. **Baykal et al. (16)** reported a case of a 56-year-old man with pemphigus vulgaris who developed corneal ulceration and perforation despite immunosuppressive therapy.

Chirinos Saldana et al.(17) reported that all the patients in their study had ocular cicatricial changes with low visual acuity and four of them had corneal perforation.

Study by **Chirinos Saldana et al.** has revealed that the presence of ocular manifestations in pemphigus indicated severe disease and tends to occur several months after the onset of skin and other mucosal lesions. However, few studies have also reported that ocular manifestations can precede the development of other mucosal lesions. **Hodak et al.** reported

that that about 72.7% of patients in their study had ocular symptoms prior to the development of oral or cutaneous lesions.

A study of 13 cases by **Arthur J. Bedell (73)** revealed that all 13 cases presented initially with ocular symptoms followed by the development of mucocutaneous lesions. In a study by **Hodak E et al.(15)** of 11 patients with pemphigus vulgaris and eye complaints, in whom conjunctival biopsies were done for histopathological and direct immunofluorescence studies, in 8 of them, ocular manifestations preceded the other manifestations of pemphigus. The conjunctivitis in 3 of them were proved to be due to pemphigus vulgaris on DIF study.

Daoud YJ et al. (74) reported a case of pemphigus foliaceous that presented with involvement of both eyelids. This patient had only eyelid involvement and the conjunctiva were spared. The patient did not respond to conventional immunosuppressive therapy and was treated with intravenous immunoglobulins.

Ocular involvement occurred in approximately 50% of patients with linear IgA disease. The manifestations included fine conjunctival scarring, subconjunctival fibrosis, loss of lid architecture resulting in entropion, trichiasis, shortening of inferior fornices and symblepharon formation. Since ocular manifestations are common and can be

asymptomatic or non-specific, ocular examination is recommended in all patients of linear IgA disease.

Brendon W H Lee et al. also reported that ocular manifestations in Linear IgA disease occurred in 50-60% of patients. The patients may have dry eye disease or may present with symptoms such as foreign body sensation, mucous discharge and burning sensation. On clinical examination, the patient may have conjunctival scarring and subconjunctival fibrosis along with secondary corneal clouding that might cause visual impairment. The disease can also cause structural complications and their sequelae such as entropion, trichiasis, corneal opacification that can ultimately lead to blindness.(75) It is of paramount clinical importance that Linear IgA disease may sometimes be difficult to distinguish from ocular mucous membrane pemphigoid.

Study by **Peggy A Frith et al. (26)** which analysed cases of cicatricial pemphigoid and bullous pemphigoid demonstrated considerable overlap between the two. The mean age of onset of the two conditions was found to be between 65-75 years. The incidence of ocular manifestations was found to be 62% in cicatricial pemphigoid and 56% in bullous pemphigoid.

Miyamoto D et al.(21) in their article on bullous pemphigoid reported the annual incidence of the disease in Asia to be approximately 2.6-7.5 cases/million and the frequency of the disease increases in those over 80 years of age. Ocular manifestations were rarely reported.

In a study by **Alpsoy et al. (59)** on the geographic variations of pemphigus and bullous pemphigoid, the overall incidence of BP was found to be slightly higher in females, though after the age of 80, it was found to be more common among males.

Santi CG et al. (61) reported that among the mucous membranes involved in bullous pemphigoid, oral cavity was most frequently involved with an incidence of 10% to 30% amongst those affected. The incidence of ocular manifestations as well as other mucous membrane involvement was rare.

Clape et al. (21) analysed 97 patients with bullous pemphigoid of which 79 had typical clinical features of the disease with no mucosal involvement and 18 patients presented with mucosal lesions in addition to the skin lesions. Among the 18 patients with mucosal involvement, oral lesions were observed in 17 and anogenital lesions in 1 patient. None of the 18 patients had conjunctival or nasal mucosal involvement. The presence of mucosal lesions did not corelate with age or gender of the patients. The occurrence of skin and mucosal lesions was found to occur

concomitantly during the disease process. The mucosal involvement in BP was found to occur more commonly in severe disease although it has been reported in milder disease also. In the above study, specific immunological and biological mechanisms were also reported to be responsible for the higher incidence of mucosal involvement in some patients as compared to others.

In another study by **Eftekhari H et al.(23)** mucosal involvement was reported in 40% of patients. In contrast to the above study, a correlation was found between lower age and mucosal involvement. IgA and C3 deposition at the dermoepidermal junction were found to be a marker for mucosal involvement.

Venning V A et al. (26) in their clinical and immunopathological study on the mucosal involvement in bullous and cicatricial pemphigoid, studied 36 patients with bullous pemphigoid and 15 with cicatricial pemphigoid. 21 patients with BP and all the patients with MMP were found to have mucosal involvement. Majority of them had involvement of the oral mucosa and involvement of other mucous membranes was also reported in both the groups. Fine scarring of the conjunctiva was found in both the groups and one patient of BP and 3 of MMP were found to have symblepharon.

Before the 1980's the mainstay of pemphigus management was high dose of corticosteroids mainly oral prednisolone. But this treatment resulted in a high incidence of steroid induced complications such as gastric ulceration, steroid induced diabetes mellitus and Cushing's disease and a large number of patients succumbed to the steroid induced complications.

Treatment of pemphigus was revolutionised by the introduction of the dexamethasone – cyclophosphamide pulse therapy. Patients treated with DCP therapy undergo more rapid healing of their lesions, achieve long term clinical remission and have fewer side effects compared to the conventional corticosteroid therapy. However, the adverse effects of long-term cyclophosphamide therapy such as gonadal toxicity should be kept in mind and patients should be carefully selected for this treatment regimen.

The knowledge of the treatment being instituted for pemphigus patients is important from the ophthalmological point of view because of the potential of steroid induced ocular complications especially cataract and glaucoma. Since steroids administered in any route have been implicated to cause ocular complications, this should be kept in mind while evaluating patients with autoimmune diseases.

Though topical ophthalmic treatment has been reported to be less effective in the management of ocular manifestations of bullous disorders because of the generalised immunological process involved, **Virginia C. Hall et al.(62)** in their case report reported a case of ocular mucous membrane pemphigoid and ocular pemphigus vulgaris, that was successfully treated with 0.03% topical tacrolimus eye ointment.

The need for regular ophthalmic monitoring and follow-up of patients with bullous disorders becomes imperative in view of the severe vison threatening complications that can occur if diagnosis and management is delayed.

Although the incidence and severity of ocular manifestations can vary among the various groups of immunobullous diseases, they are predominantly ocular surface disease manifestations and their resulting complications. There exists a need for scoring tools that can score and grade the ocular manifestations occurring in these diseases and hence guide management and follow up.

The first two grading systems that were used to grade ocular mucous membrane pemphigoid were the Mondino and Brown, and the Foster system. Both of them graded the disease into four grades; Mondino and Brown estimated the inferior fornix foreshortening and Foster system considered other clinical features such as fibrosis and symblepharon.

A system proposed by **Rowsey et al.(76)** estimated bulbar and tarsal conjunctival shrinkage by quantifying the degree of contracture between the lid margin and limbus in three different positions of gaze.

Munyangango et al. (63) proposed a system for grading active disease in MMP by dividing each eye into four quadrants and measuring erythema from 1 to 4 in each quadrant. Thus, this is predominantly a conjunctival inflammation grading system.

Tepelus et al. (74) advocated the use of in vivo confocal microscopy to analyse the morphological changes occurring in various corneal layers as well as the presence or absence of inflammatory cells. In vivo confocal microscopy facilitates assessment of the ocular surface by providing high resolution images by a minimally invasive technique.

The ocular surface disease index, the dry eye disease measurement guidelines proposed by the International Dry Eye Workshop (DEWS), have also been used to analyse and score the ocular surface. (78)

Though various methods of scoring and grading has been proposed by various authors and are in use, there is no recognised or validated system, that can be universally followed, to date. Future scoring systems will need to distinguish between “disease activity” and “damage”. ‘Activity’ refers to the findings resulting from inflammatory process

while ‘damage’ is persistent and lasting for more than or equal to 6 months and results in permanent damage to the anatomy, physiology, pathology and function to the ocular structures.

The need for regular and periodic follow up of patients with immunobullous diseases is imperative, especially from the ophthalmologists’ point of view, given the chronic nature of the diseases and the various sight threatening sequelae that can develop, which might be prevented by periodic follow up and early institution of therapy when indicated.

Since most of these patients require long-term treatment of their cutaneous condition and corticosteroids being one of the major groups of drugs that is used, steroid induced ocular complications should also be looked for, in addition to the specific manifestations of the particular bullous disorder.

A protocol that has been suggested by **Camisa et al.** in their study of immunobullous diseases with ocular involvement described monthly follow-up during initiation of treatment, and follow-up every 3-6 months once the patient has been stabilized.

Though different follow up protocols have been proposed, the follow up should be individualised and tailored to each patient depending on his/her skin disease; ocular manifestations at presentation; severity of ocular manifestations; treatment instituted; patients' compliance with treatment and likelihood of the patient being on regular follow up should also be taken into account.

The management of patients with immunobullous disorders and ocular involvement is a combined approach by the dermatologist and the ophthalmologist and also by the patient's physician. The dermatologist must be encouraged to refer patients to the ophthalmologist for screening and also be aware of the ocular symptoms the patient might report. This goes a long way in ensuring the early diagnosis of the patient's ocular condition and institution of appropriate and timely therapy.

AIM OF THE STUDY

The aim of the study is to evaluate the spectrum and incidence of ocular manifestations occurring in association with various autoimmune blistering skin disorders and to analyse whether early ophthalmological examination will be beneficial in the reduction of ocular morbidity associated with these conditions.

OBJECTIVES OF THE STUDY:

1. To analyse the spectrum and severity of ocular manifestations in bullous skin disorders.
2. Early Ophthalmological evaluation.
3. Periodical review and follow up.
4. Early intervention when needed.

MATERIALS AND METHODS

STUDY DESIGN, METHODOLOGY AND TECHNIQUES:

STUDY DESIGN:

This is a hospital based analytical study involving 100 patients of autoimmune blistering skin diseases.

STUDY SETTING:

The study was conducted at the Department of Ophthalmology, Coimbatore Medical College Hospital, Coimbatore, which is a tertiary care centre and a regional referral centre.

STUDY DURATION:

One-year period – from May 2018 to April 2019

STUDY POPULATION:

Patients attending Ophthalmology OPD and Dermatology OPD in Coimbatore medical college hospital during the study period and diagnosed as autoimmune blistering skin disease will be included in the study based on selection criteria. A minimum of 100 patients will be included in this.

INCLUSION CRITERIA:

1. Patients diagnosed as autoimmune blistering skin disorders.

2. All age groups will be included in the study.

EXCLUSION CRITERIA:

1. HIV positive individuals

2. Patients with pre-existing unrelated ocular manifestations

3. Co morbid systemic diseases like diabetes and hypertension.

4. Patients unwilling for study

STUDY METHODS:

Informed consent was obtained from all patients selected for the study. Data was collected using a structured questionnaire. A detailed history including the 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 was recorded.

A comprehensive ophthalmological examination was done and recorded. Uncorrected and best corrected visual acuity was recorded using Snellen's distant vision chart. Intraocular pressure was measured

using Goldmann applanation tonometer. Anterior segment examination was done using slit lamp with importance given to the ocular surface.

Ocular surface staining was done using 2% fluorescein strip. Tests for dry eye that were done were Schirmer's test and tear film break up time (T-BUT). Dilated fundus examination was done to look for retinal or optic nerve pathology.

Logistic 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.

Clinical Examination includes

1. Uncorrected visual Acuity
2. Best corrected visual acuity
3. Intra ocular pressure
4. Schirmer's test
5. Tear film breakup time (T-BUT)
6. Anterior segment examination by Slit lamp
7. Fundus examination

RESULTS

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. 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.

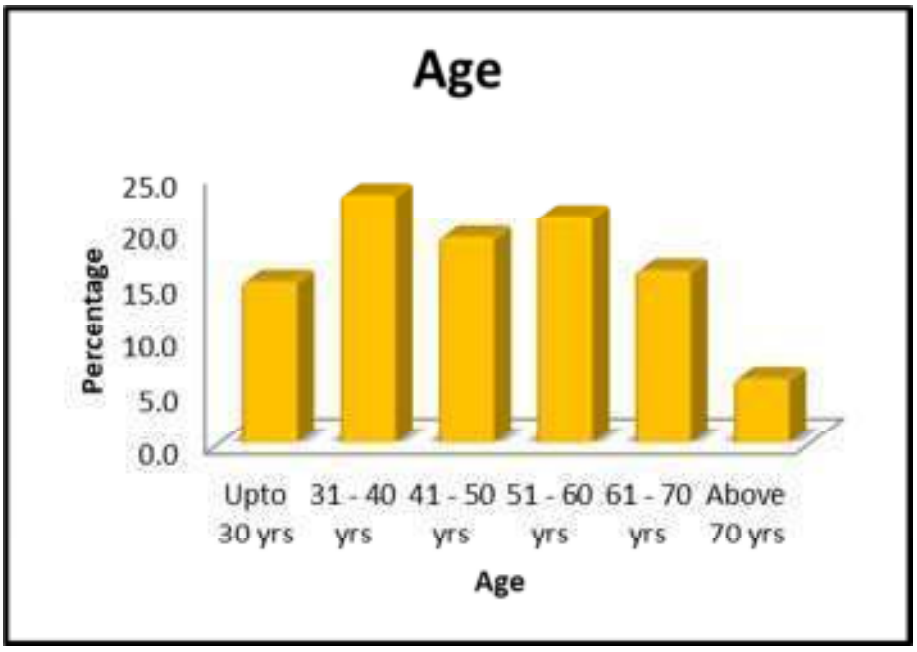
RESULTS AND OBSERVATION:

Among the 100 patients included in our study, the majority were in the age group of 31-40 years, followed by 51-60 years age group.

TABLE 2: AGE WISE DISTRIBUTION OF 100 PATIENTS

		Frequency	Percent
Valid	Upto 30 yrs	15	15.0
	31 - 40 yrs	23	23.0
	41 - 50 yrs	19	19.0
	51 - 60 yrs	21	21.0
	61 - 70 yrs	16	16.0
	Above 70 yrs	6	6.0
	Total	100	100.0

CHART 1: AGE WISE DISTRIBUTION OF 100 PATIENTS

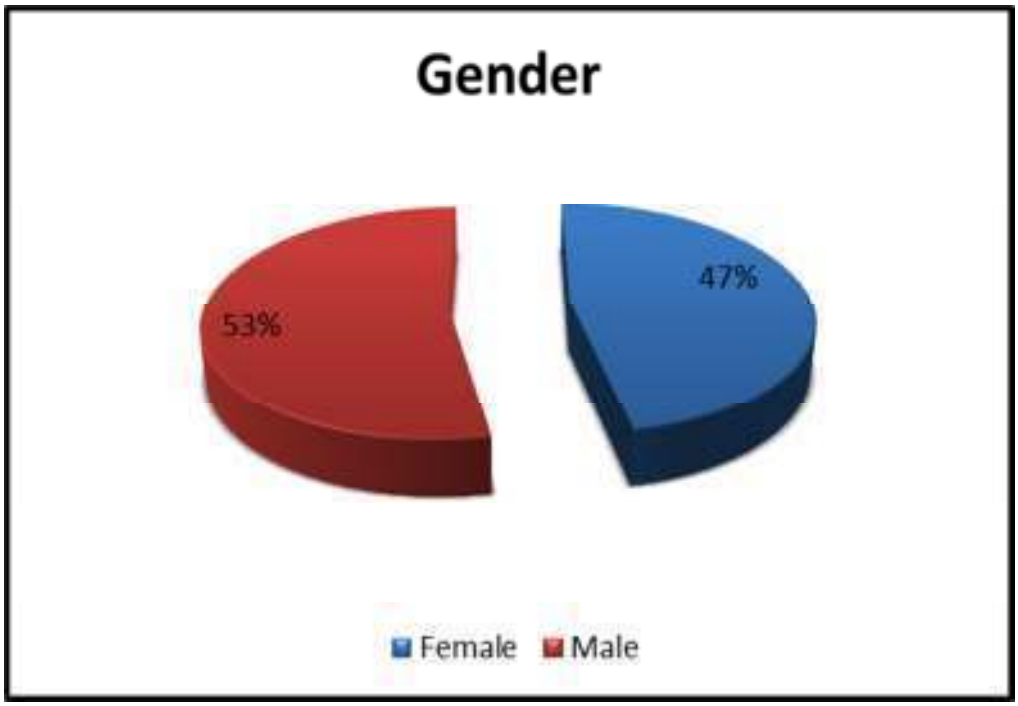


Among 100 patients, 53 were male and 47 were female.

TABLE 3: SEX WISE DISTRIBUTION OF 100 PATIENTS

		Frequency	Percent
	Female	47	47.0
	Male	53	53.0
	Total	100	100.0

CHART 2: SEX WISE DISTRIBUTION OF 100 PATIENTS

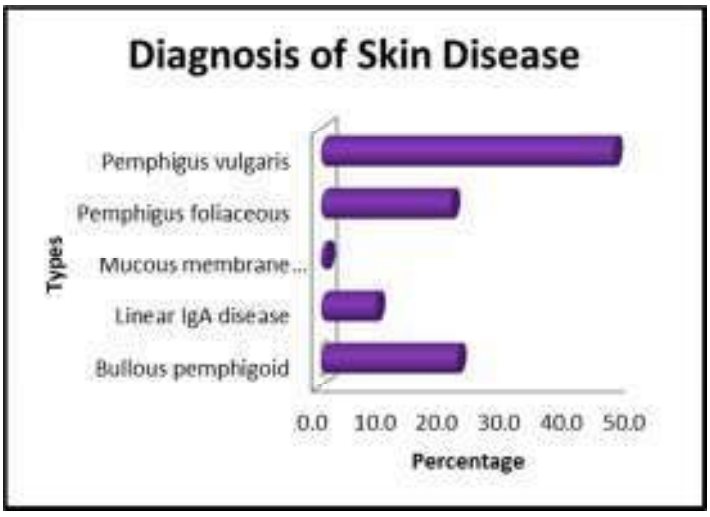


Among the 100 patients analysed in our study, pemphigus vulgaris accounted for the majority; 47 out of 100 patients had a diagnosis of pemphigus vulgaris. 22 patients had bullous pemphigoid and 21 patients had pemphigus foliaceous. Taken together, pemphigus group of disorders accounted for 68 patients. The other bullous disorders we encountered were linear IgA disease (9 patients) and only one case of mucous membrane pemphigoid.

TABLE 4: DIAGNOSIS OF SKIN DISEASE

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

CHART 3: DIAGNOSIS OF SKIN DISEASE

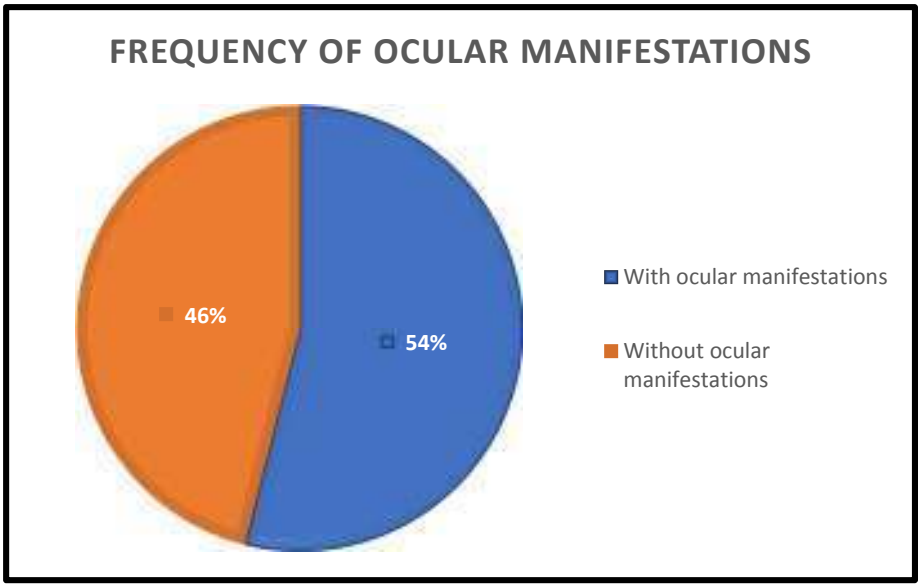


Among the 100 patients, 54 patients had ocular manifestations, distributed among the various bullous disorders. 5 patients had developed presenile posterior subcapsular cataract as a complication of long-term steroid usage, among which, 2 did not have any other ocular manifestation of the specific skin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

TABLE 5: FREQUENCY OF OCULAR MANIFESTATIONS

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

CHART 4: FREQUENCY OF OCULAR MANIFESTATIONS

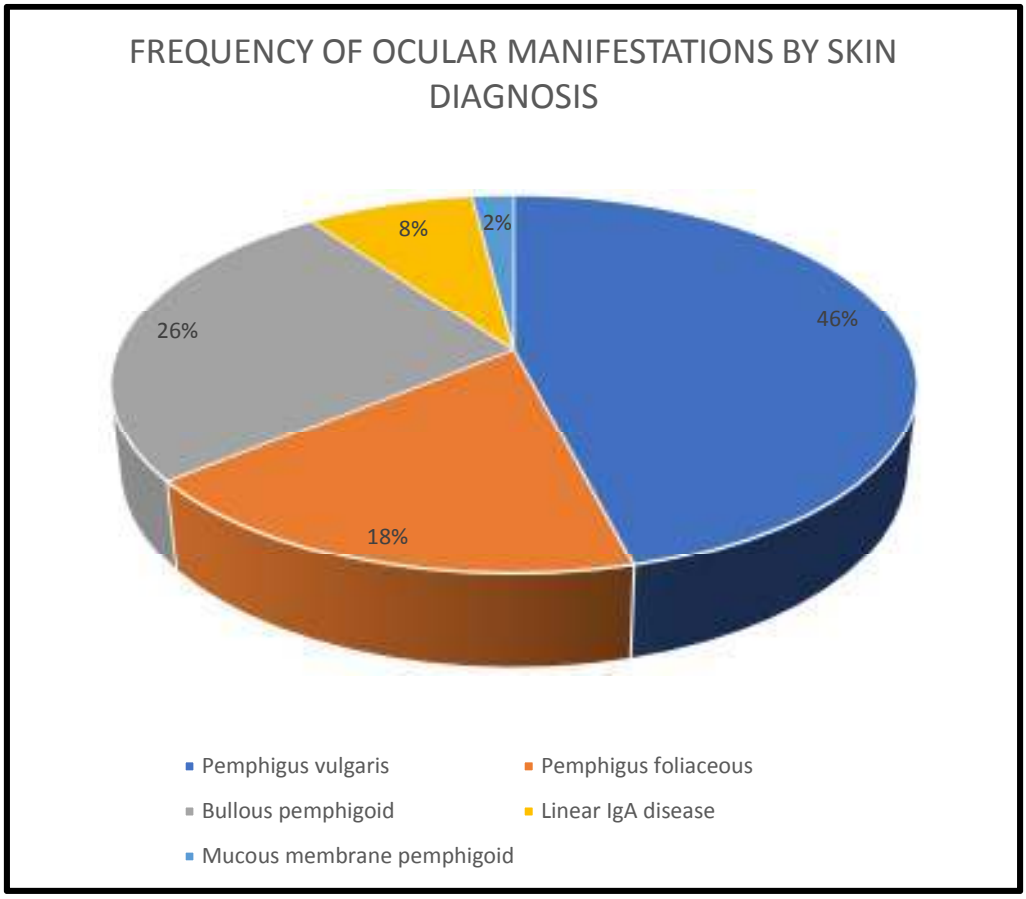


Among the 54 patients who had ocular manifestations, 25 of them were pemphigus vulgaris patients, 10 of pemphigus foliaceous, 14 of bullous pemphigoid, 1 patient of mucous membrane pemphigoid, 4 of linear IgA disease.

TABLE 6: FREQUENCY OF OCULAR MANIFESTATIONS BY SKIN DIAGNOSIS

Diagnosis of skin disease	Frequency of ocular manifestations	
	Frequency	Percentage
Pemphigus vulgaris	25	46
Pemphigus foliaceous	10	18
Bullous pemphigoid	14	26
Linear IgA disease	4	8
Mucous membrane pemphigoid	1	2
Total	54	100.0

CHART 5: FREQUENCY OF OCULAR MANIFESTATIONS BY SKIN DIAGNOSIS

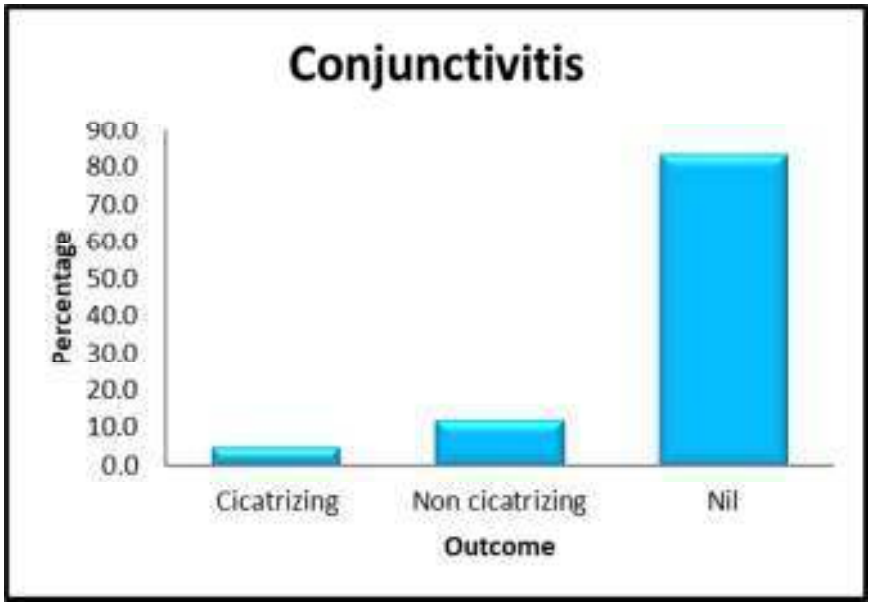


We found that among the 100 patients analysed, 17 of them had conjunctivitis as the ocular manifestation, of which 5 had cicatrizing conjunctivitis and 12 had non cicatrizing conjunctivitis.

TABLE 7: FREQUENCY OF CONJUNCTIVITIS

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

CHART 6: FREQUENCY OF CONJUNCTIVITIS

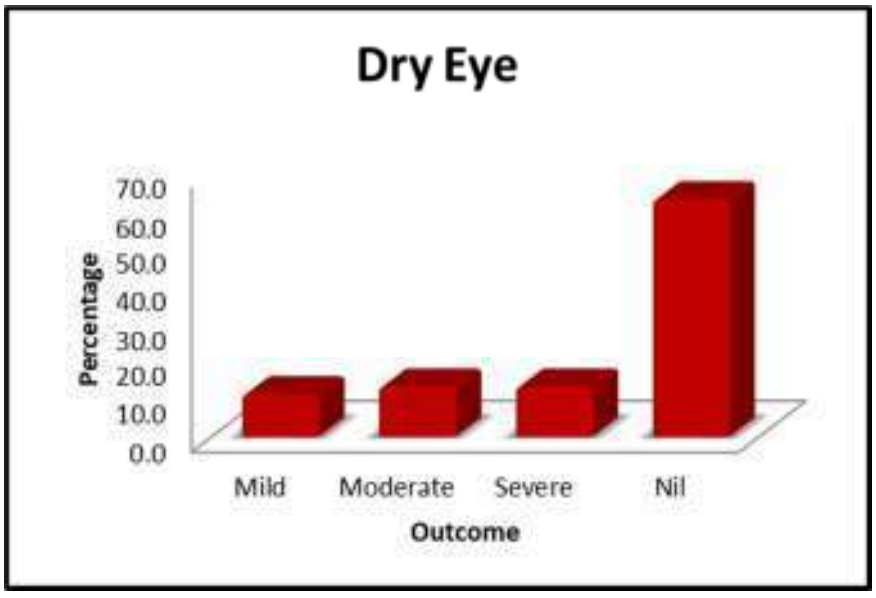


Among 100 patients, 37 patients had dry eye, of which 11 had mild dry eye, 13 patients had moderate and 13 patients had severe dry eye.

TABLE 8: 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

CHART 7: FREQUENCY OF DRY EYE

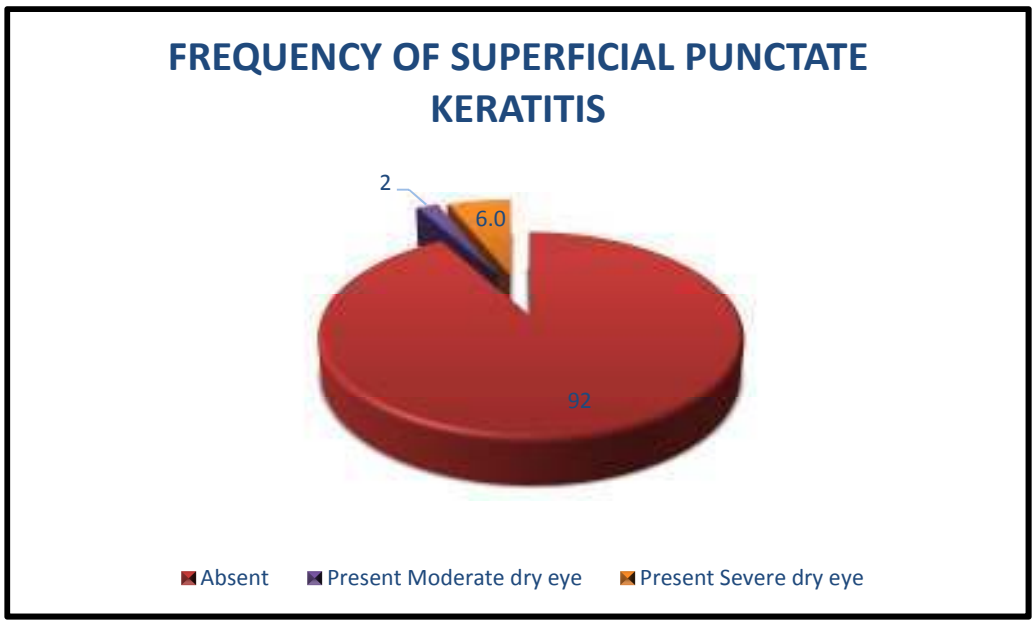


In addition, 8 out of the 100 patients analysed had superficial punctate keratitis. All these 8 patients had dry eye and hence the SPK was probably a manifestation of the severity of the dry eye and not of the skin disease proper. 6 of the 8 patients with SPK had severe dry eye and 2 had moderate dry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

TABLE 9: FREQUENCY OF SUPERFICIAL PUNCTATE KERATITIS

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

CHART 8: FREQUENCY OF SUPERFICIAL PUNCTATE KERATITIS

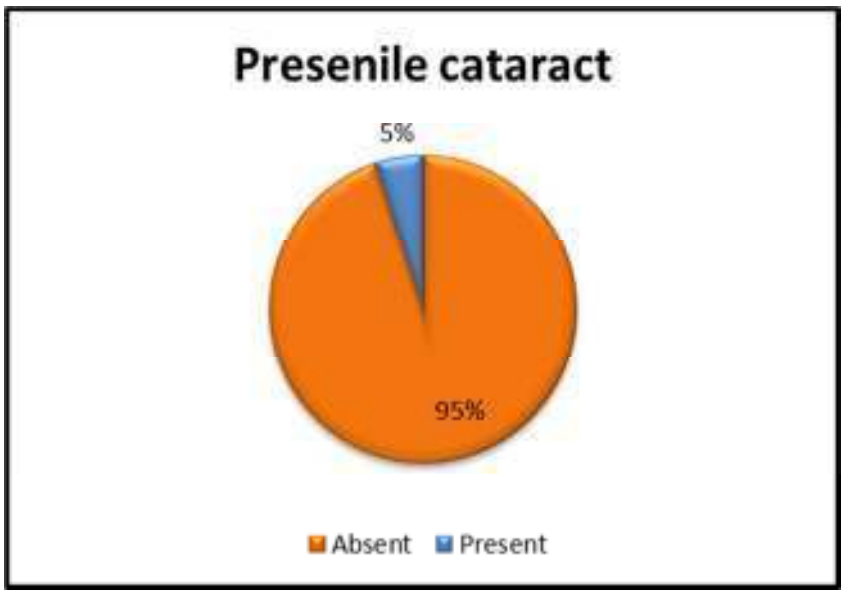


5 of the 100 patients developed presenile posterior subcapsular cataract as a complication of long-term steroid usage. 3 of these had PSCC along with other ocular manifestations of skin disease while 2 did not have any other ocular manifestations.

TABLE 10: FREQUENCY OF PRESENILE PSCC IN PATIENTS ON STEROIDS

		Frequency	Percent
	Absent	95	95.0
	Present	5	5.0
	Total	100	100.0

CHART 9: FREQUENCY OF PRESENILE PSCC IN PATIENTS ON STEROIDS



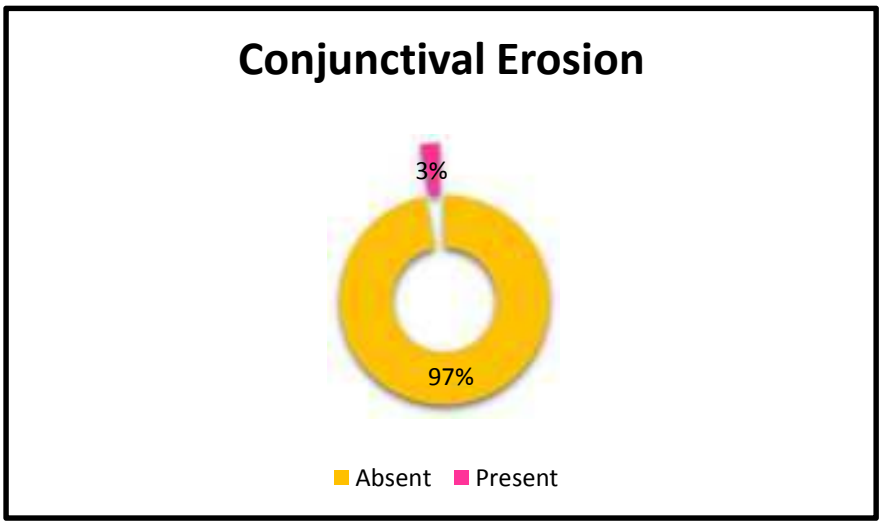
3 of our patients had conjunctival erosions, 2 of them had lid margin erosions, 2 of them had conjunctival scarring and 4 had symblepharon.

2 of the 3 patients with conjunctival erosions had pemphigus vulgaris and 1 had bullous pemphigoid. 2 of the patients with conjunctival erosions also had dry eye; of which one had moderate dry eye and the other had severe dry eye. One patient with erosions did not have associated dry eye.

TABLE 11: FREQUENCY OF CONJUNCTIVAL EROSIONS

		Frequency	Percent
	Absent	97	97.0
	Present	3	3.0
	Total	100	100.0

CHART 10: FREQUENCY OF CONJUNCTIVAL EROSIONS

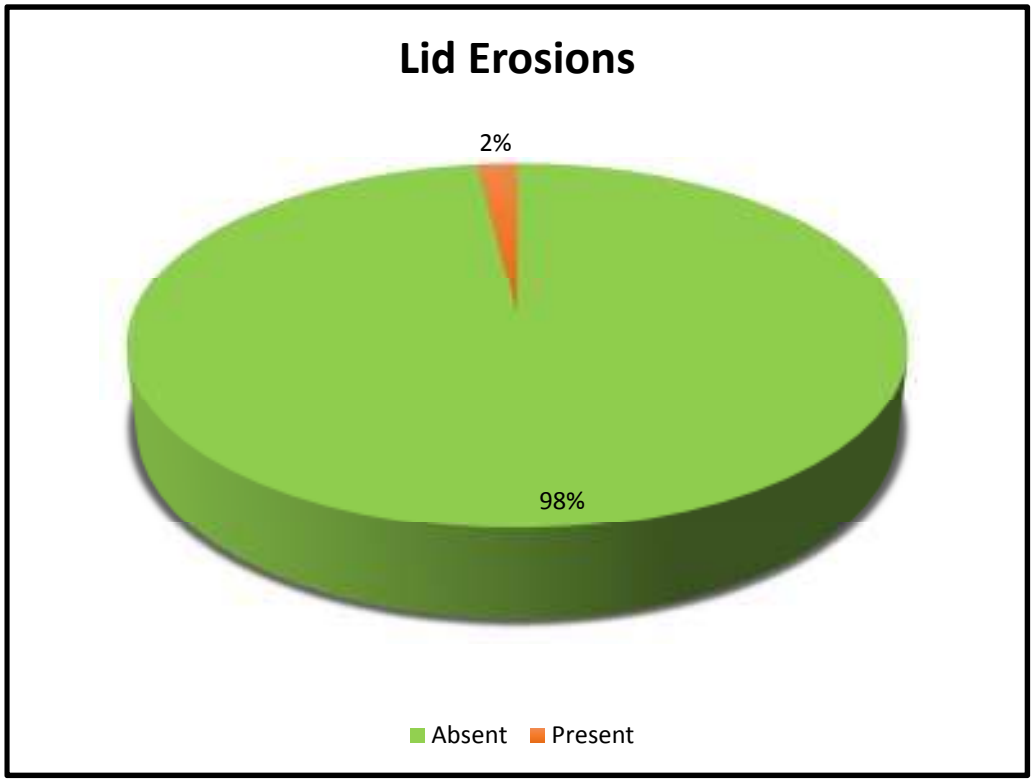


Both the patients with lid margin erosions had a skin diagnosis of pemphigus foliaceous.

TABLE 12: FREQUENCY OF LID MARGIN EROSIONS

		Frequency	Percent
	Absent	98	98.0
	Present	2	2.0
	Total	100	100.0

CHART 11: FREQUENCY OF LID MARGIN EROSIONS

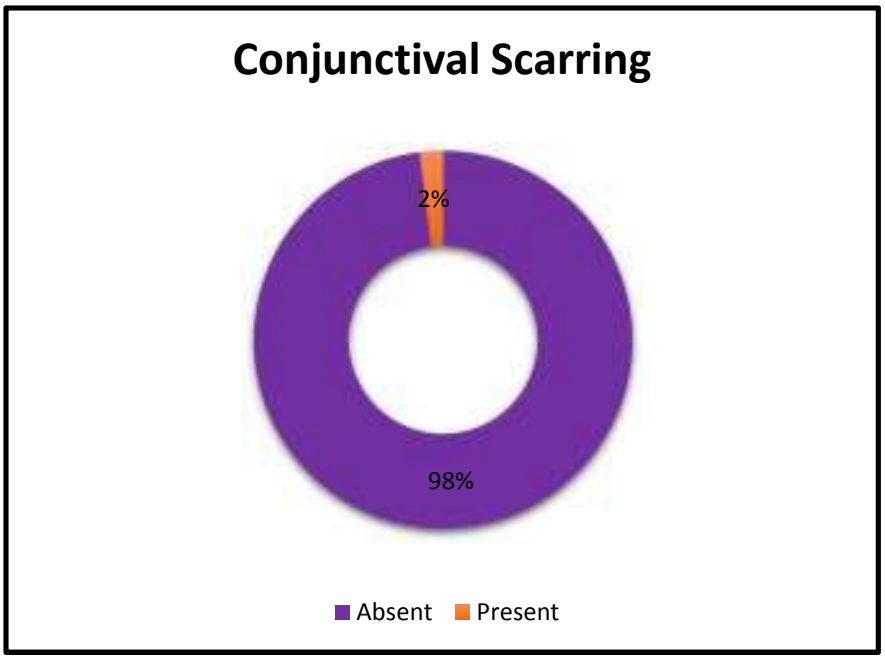


Of the 2 patients who had conjunctival scarring, one had a skin diagnosis of pemphigus vulgaris and the other had linear IgA disease. Both the patients also had associated moderate-severe dry eye.

TABLE 13: FREQUENCY OF CONJUNCTIVAL SCARRING

		Frequency	Percent
	Absent	98	98.0
	Present	2	2.0
	Total	100	100.0

CHART 12: FREQUENCY OF CONJUNCTIVAL SCARRING



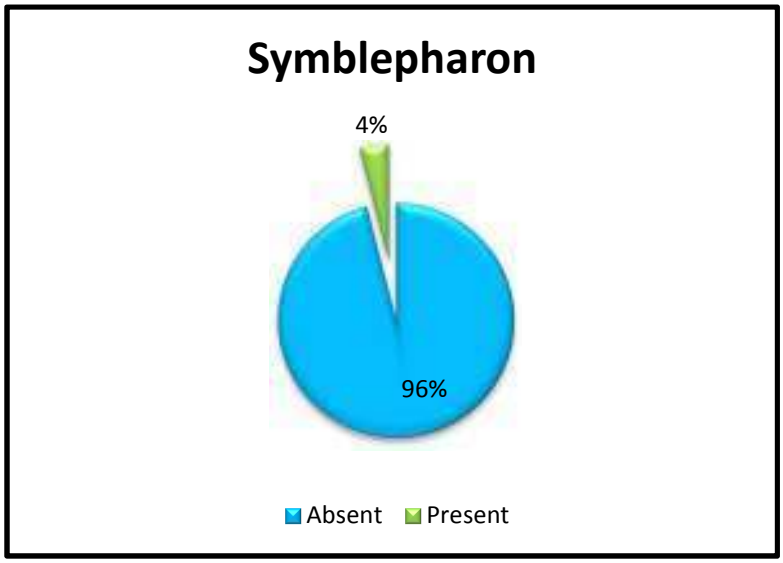
Of the 4 patients who had symblepharon, two had bullous pemphigoid, one had mucous membrane pemphigoid and one had pemphigus vulgaris. All the 4 patients also had severe dry eye, which was a sequela of the cicatrisation.

In our study we encountered only one case of MMP. The patient had severe dry eye with superficial punctate keratitis and symblepharon.

TABLE 14: FREQUENCY OF SYMBLEPHARON

		Frequency	Percent
	Absent	96	96.0
	Present	4	4.0
	Total	100	100.0

CHART 13: FREQUENCY OF SYMBLEPHARON



In the analysis of conjunctivitis as an ocular manifestation of bullous skin diseases, a total of 17 patients had conjunctivitis.

We found that 8 patients of BP had conjunctivitis of which 3 had cicatrizing and 5 had non-cicatrizing.

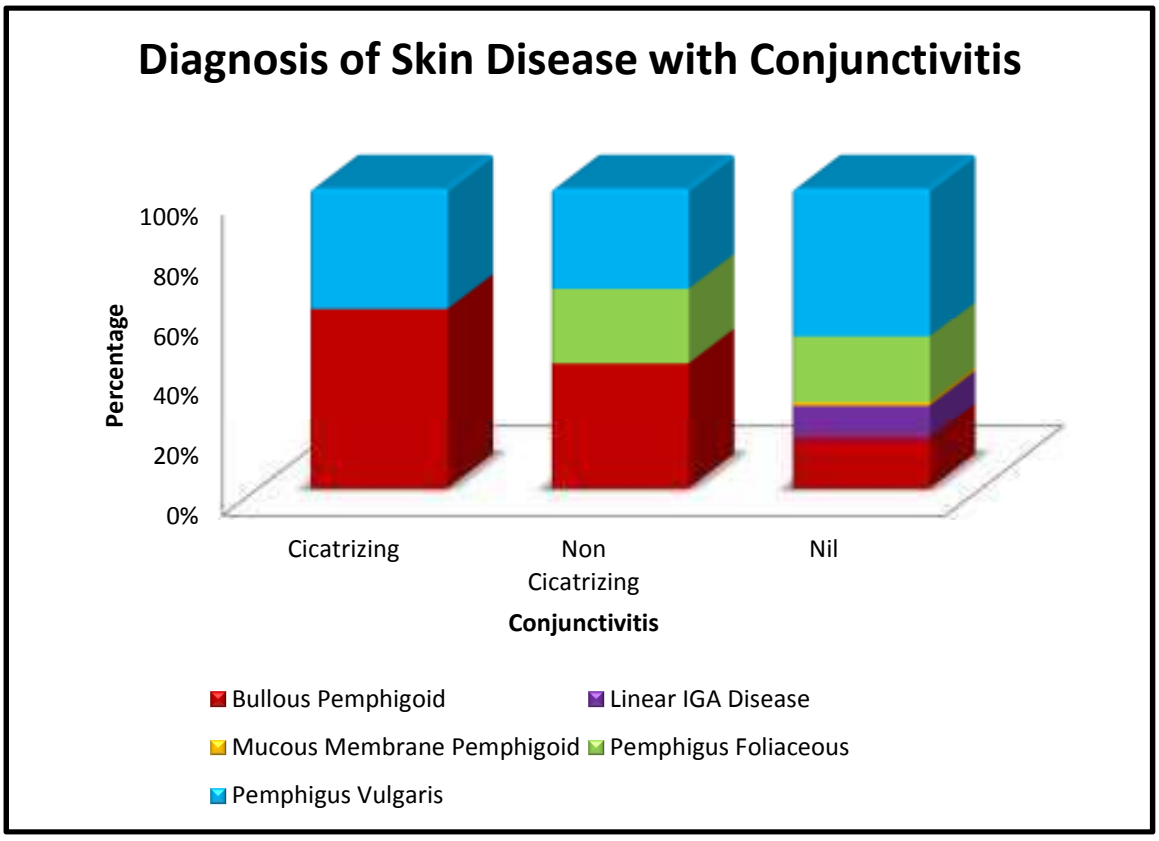
3 patients of pemphigus foliaceous had conjunctivitis; all 3 had the non-cicatrizing form.

6 patients of pemphigus vulgaris had conjunctivitis, of which 2 had cicatrizing and 4 had non-cicatrizing conjunctivitis.

TABLE 15: DIAGNOSIS OF SKIN DISEASE WITH CONJUNCTIVITIS

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%		

CHART 14: DIAGNOSIS OF SKIN DISEASE WITH CONJUNCTIVITIS



In the analysis of dry eye and bullous skin diseases, 37 patients had 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 –

- 6 had bullous pemphigoid
- 4 had linear IgA disease
- 1 had mucous membrane pemphigoid
- 6 had pemphigus foliaceous
- 20 had pemphigus vulgaris

CHART 15: DISTRIBUTION OF DRY EYE AMONG VARIOUS SKIN DISEASES

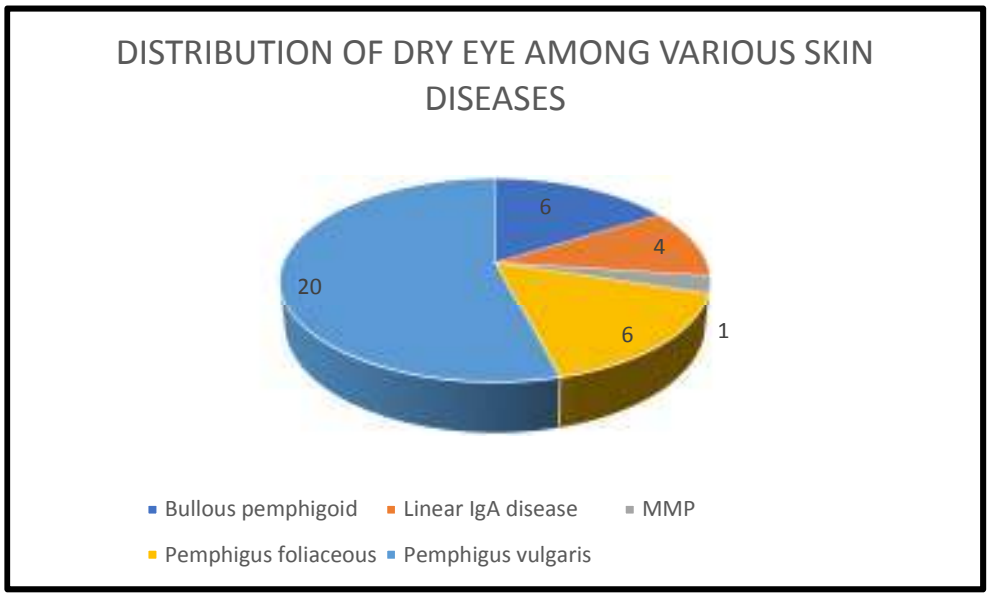
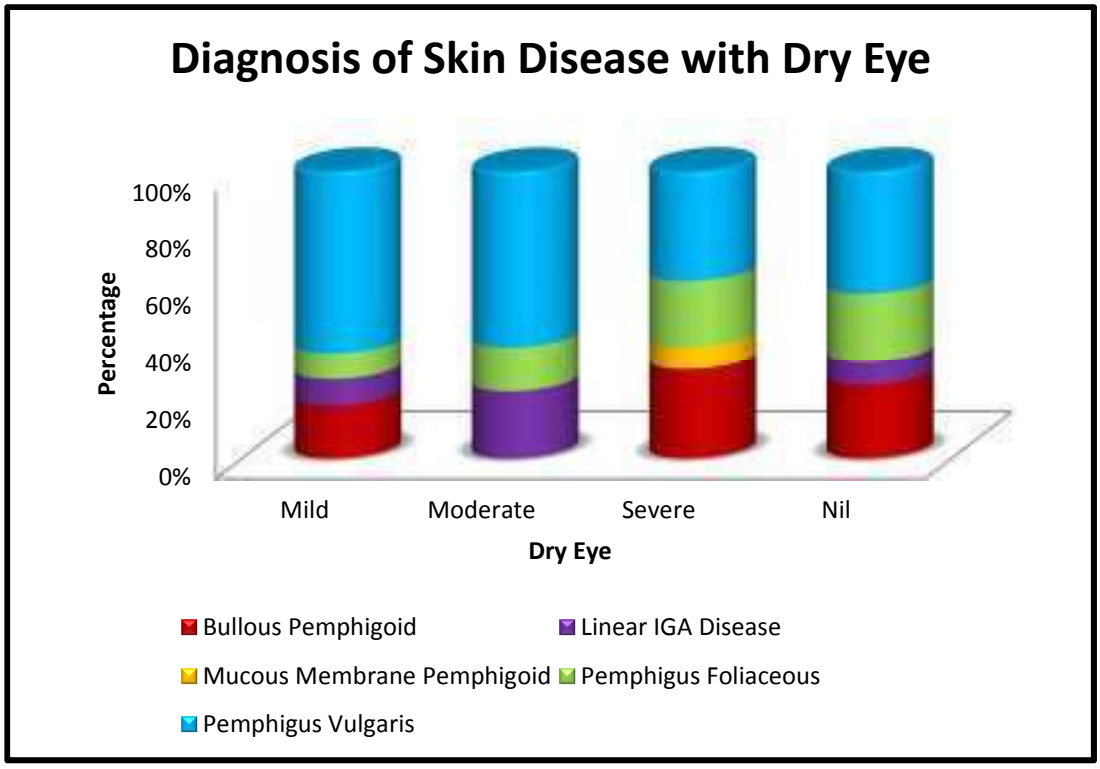


TABLE 16: DIAGNOSIS OF SKIN DISEASE WITH DRY EYE

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%		

CHART 16: DIAGNOSIS OF SKIN DISEASE WITH DRY EYE

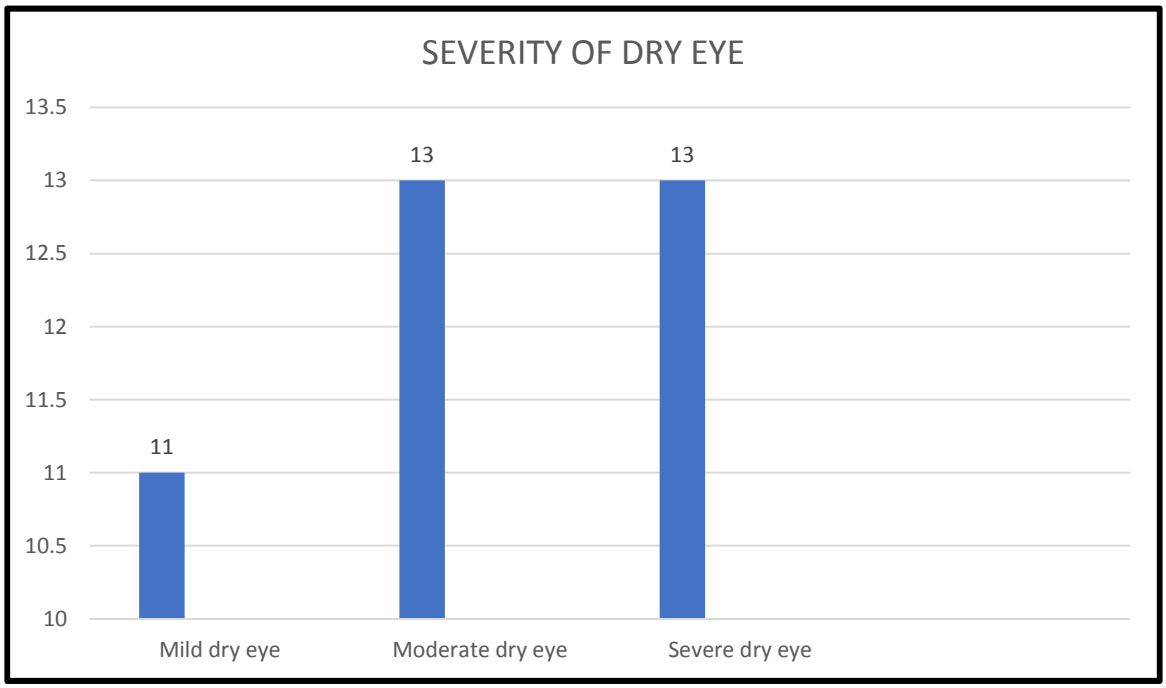


The analysis of the severity of dry eye among the various skin diagnoses revealed the following observations.

Bullous pemphigoid	Linear IgA disease	Mucous membrane pemphigoid	Pemphigus foliaceous	Pemphigus vulgaris
• Mild dry eye - 2 • Moderate - none • Severe - 4	• Mild dry eye - 1 • Moderate - 3 • Severe - none	• Mild dry eye - none • Moderate - none • Severe - 1	•Mild dry eye - 1 •Moderate - 2 •Severe - 3	•Mild dry eye - 7 •Moderate - 8 •Severe - 5

11 patients had mild dry eye, 13 patients had moderate dry eye and 13 patients had severe dry eye.

CHART 17: ANALYSIS OF SEVERITY OF DRY EYE



Moderate to severe dry eye patients also had associated features such as superficial punctate keratitis, symblepharon, conjunctival scarring and conjunctival erosions. Dry eye associated with these features needed to be aggressively managed to prevent complications.

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.

Blistering diseases can be broadly classified into two categories – intraepidermal and subepidermal blistering diseases. The intraepidermal diseases include pemphigus and its variants and the subepidermal diseases are many, the most common of which are bullous pemphigoid, linear IgA disease and mucous membrane pemphigoid.

In our 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%.

This was in accordance to the study published by **Amrinder et al.**(5) who described that among the pemphigus variants, pemphigus vulgaris was the most common followed by pemphigus foliaceous. In our study, we encountered only two variants of pemphigus – vulgaris and

foliaceous, of which vulgaris was the most common followed by foliaceous. This finding was also in accordance to the study by **Ramassamy et al. (3)**

In India, pemphigus was found to be more common among the younger age group. It was found to be more common in individuals less than 40 years of age. In our study too, 23% of patients were between the age group of 31-40 years, which constituted the majority, followed by 51-60 years age group.

In our study, 53% patients were male and 47% were female. The incidence was found to be almost equal. This is in accordance to the various studies like the study by **Bose et al. (70)** which reported equal incidence rate among men and women.

In our study, the incidence of ocular manifestations in pemphigus vulgaris was found to be 46%. Other studies have reported a slightly lower incidence of the condition such as the study by **Omeed Memar et al. (68)** reported the incidence to be between 7 and 16%. Other studies have also reported the incidence to be around 16-20%.

The incidence of ocular manifestations in bullous pemphigoid in our study was 26%. Other studies have reported a higher incidence of ocular manifestations in bullous pemphigoid ranging from around 40-

55%. A study by **Peggy A Frith et al. (24)** reported the incidence to be approximately 56%. **Eftekhari H et al. (23)** reported the incidence to be around 40%. The lower incidence in our study was probably due to the smaller number of patients examined.

Clape et al. (22) in their analysis of 97 patients of BP, found that 18 patients had mucosal involvement but none of them had conjunctival involvement.

The incidence of ocular manifestations in linear IgA disease has been reported to be around 50%. **Brendon W H Lee et al. (69)** reported the incidence in their study to be 50-60%. The incidence in our study was only 8%. This is because of the very small number of patients with linear IgA disease encountered in our study.

The most common ocular manifestations encountered among patients of autoimmune bullous skin diseases in our 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 in our study were confined to the lids, conjunctiva and cornea i.e. the ocular surface. The most common ocular manifestation in our study was dry eye followed by conjunctivitis.

Figure 15: Schirmer's test

Figure 16: Appearance of dry spot in T-BUT

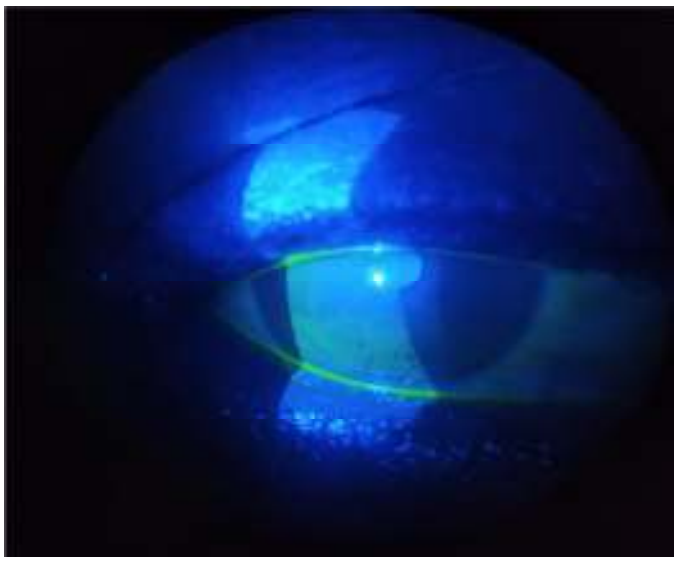
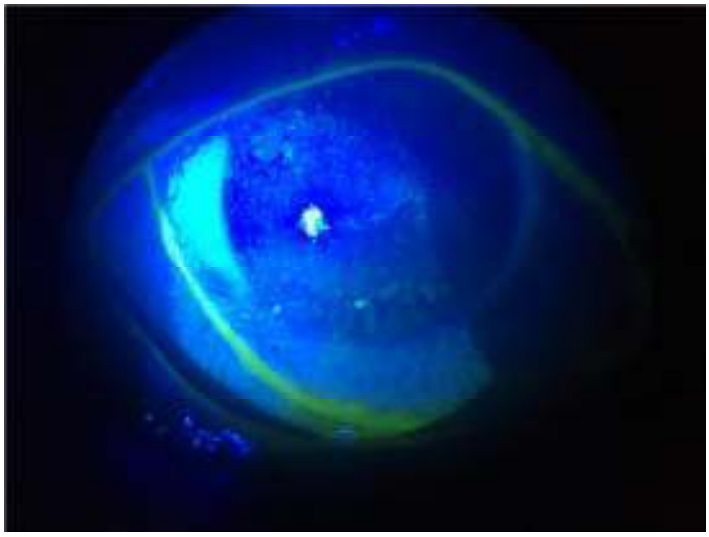


Figure 17: SPK stained with fluorescein in a patient with dry eye



In a study by **Jeremy C K Tan et al. (20)** the reported incidence of dry eye was 77%. The most common symptom reported was photophobia. In our study 26 patients of the 68 patients with pemphigus had dry eye which approximated to 40% and the most common symptom reported was chronic irritation.

Omeed Memar et al. (68), Sehgal et al. (71), Brendon W H Lee et al. (69) all reported conjunctivitis as commonly occurring in pemphigus. In our study 9 of the 68 patients had conjunctivitis as the ocular manifestation accounting for approximately 15%. Of the 9 patients with conjunctivitis, 2 had cicatrizing conjunctivitis and 7 had non cicatrizing conjunctivitis.

Daoud YJ et al. (74) reported a case of pemphigus foliaceous who had severe involvement of the eyelids with sparing of the conjunctiva. In

our study too we encountered two patients with PF who had eye lid margin erosions and blepharitis. One patient had associated involvement of the conjunctiva (non- cicatrizing conjunctivitis) whereas the other patient had isolated involvement of the eyelid margins.

Akhyani et al. (18), Palleschi et al. (72), reported that there was no correlation between the severity and activity of skin disease and ocular manifestations. In our study also, we found no correlation between the duration, activity, and severity of skin disease and ocular manifestations.

We also did not encounter vision threatening manifestations in our study in accordance to various studies like that by **Omeed Mennar et al.** who reported that vision loss is rare in pemphigus.

None of the patients included in our study had ocular involvement as the presenting manifestation of the disease.

Among the 100 patients in our 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.

Of the 8 patients with conjunctivitis, 3 had cicatrizing and 5 had non-cicatrizing conjunctivitis.

Among those with dry eye, 2 had mild dry eye and 4 had severe dry eye. Severe dry eye was also associated with other manifestations such as superficial punctate keratitis, conjunctival scarring and symblepharon.

In our study only one patient had mucous membrane pemphigoid and he manifested with severe dry eye, superficial punctate keratitis and symblepharon.

Venning V A et al. (54), Peggy A Frith et al. (26), reported that there was considerable overlap of manifestations between bullous pemphigoid and mucous membrane pemphigoid. Both of them can cause cicatrizing lesions of the ocular surface. In our study, we encountered conjunctival scarring and symblepharon as a result of the cicatrisation.

None of our patients had posterior segment ocular manifestations, which is in accordance to various studies, which have reported posterior segment manifestations to be very rare.

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 the 100 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.

43% of patients in our study were being treated with intravenous dexamethasone. According to the study by **R Mohan et al. (64)** on steroid induced glaucoma and cataract, it was reported that dexamethasone and betamethasone, both topical and systemic were more potent in inducing cataract and glaucoma than prednisolone.

It was observed in our study that all the 5 patients who developed steroid induced cataract were being treated with intravenous dexamethasone and the type of cataract observed was PSCC in all the 5, in accordance with the study by **Eric R James et al. (66)** who reported that PSCC was the most common type of steroid induced cataract.

The absence of steroid induced glaucoma in our study was probably due to the fact that glaucoma occurs more commonly in patients using long-term topical steroids; and patients who had received treatment with periocular or intraocular steroids. None of our patients had received any form of long-term topical steroids; intraocular or periocular steroid treatment in the past.

The complications of therapy too contributed to the visual dysfunction of the patients in addition to the ocular manifestations of the skin disorder per se.

SUMMARY

This study titled **"An analytical study on the ocular manifestations in patients with autoimmune blistering skin disorders in a tertiary care hospital"** is a hospital based analytical study.

The aim of the study was to find out the spectrum of ocular manifestations occurring in patients with autoimmune bullous skin diseases and to analyse whether early ophthalmological examination will be beneficial in reducing the visual morbidity associated with these conditions.

In our study of 100 patients with autoimmune blistering skin disorders, 54 patients had ocular manifestations. The most common bullous skin disease encountered was pemphigus and its variants accounting for 68 patients; of which pemphigus vulgaris was the most common, seen in 47 patients.

The most common ocular manifestation in this study was dry eye which was seen in 37 patients followed by conjunctivitis, seen in 17. Among patients with dry eye, 26 patients had moderate – severe dry eye and 11 had mild dry eye. Among patients with conjunctivitis, 5 had cicatrizing and 12 had non-cicatrizing conjunctivitis. The most common ocular symptom reported by these patients was chronic ocular irritation.

We also encountered 5 patients with presenile posterior subcapsular cataract, a complication of long-term steroid treatment.

CONCLUSION

Autoimmune bullous skin diseases were associated with a significant proportion of ocular manifestations of which dry eye and conjunctivitis were the most common in this study.

Dry eye results from breakdown of the tear film, resulting in dysfunction of the ocular surface, thereby interfering with the optics of the eye and ultimately leading to decreased quality of vision. Dry eye can range in severity from mild irritation to debilitating manifestations.

In this study, majority of the patients had moderate-severe dry eye and some of them had ocular surface staining, cicatrisation and scarring of conjunctiva.

Though none of the patients in our study had vision threatening manifestations, it is important to do a comprehensive ophthalmological examination and follow up these patients, to monitor the improvement / progression of the condition,

An early and periodical ophthalmological evaluation will thereby help in the early diagnosis and management of the ocular symptoms and signs, and will help in preventing visually debilitating sequelae. This requires the combined effort of the ophthalmologist and the dermatologist.

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DATA SHEET

Name Op/Pin no-

Age /sex Date

Ocular complaints

Duration of illness

Diagnosis of skin disease

Duration of skin disease

Treatment history

Co morbid conditions (if any)

Ocular Examination

1. Anterior segment: RE LE

    Lids

    Conjunctiva

    Cornea

    Anterior chamber

    Iris

    Pupil

    Lens

    Extra ocular movements

RE LE

2. Visual acuity

    Uncorrected visual acuity

    Best corrected visual acuity

3. Intra ocular pressure
4. Schirmer's test
5. T-BUT
6. Slit lamp examination
7. Fundus examination
8. Investigations

    Complete blood count

    ESR

    Blood sugar

    Blood urea, serum creatinine

    Lipid profile

    Blood pressure

    Specific investigations (where necessary)

CONSENT FORM

I hereby volunteer and consent to participate in this study **"AN ANALYTICAL STUDY ON THE OCULAR MANIFESTATIONS IN PATIENTS WITH AUTOIMMUNE BLISTERING SKIN DISORDERS"**. I was fully explained about the nature of this study by the doctor; knowing which I Mr/Ms/Mrs……. fully consent to volunteer in this study.

Date: Signature of the volunteer

Place:

Signature of the witness

CONSENT FORM

I **Dr. ANUPAMA VINUPAL** am carrying out a study on the topic, **"AN ANALYTICAL STUDY ON THE OCULAR MANIFESTATIONS IN PATIENTS WITH AUTOIMMUNE BLISTERING SKIN DISORDERS".**

My research project guide is **Dr.S.PADMANABAN M.S.,D.O**

My research project is being carried out in the Department of Ophthalmology, Coimbatore Medical College Hospital, Coimbatore.

RESEARCH BEING DONE:

AN ANALYTICAL STUDY ON THE OCULAR MANIFESTATIONS IN PATIENTS WITH AUTOIMMUNE BLISTERING SKIN DISORDERS

PURPOSE OF RESEARCH:

To find out the incidence and spectrum of the various ocular manifestations occurring in patients with autoimmune blistering skin disorders.

PROCEDURE INVOLVED:

Patients diagnosed as a case of autoimmune blistering skin disease are selected and evaluated for the presence of ocular manifestations by a comprehensive ophthalmological examination that includes vision and IOP assessment, anterior segment examination by slit lamp, tests for dry eye, and fundus examination.

You, Shri./Smt./Kum. _____, aged_____ years

S/o/ W/o/D/o_____, residing at_____

_____ are requested to be a participant in the research study titled **"AN ANALYTICAL STUDY ON THE OCULAR MANIFESTATIONS IN PATIENTS WITH AUTOIMMUNE BLISTERING SKIN DISORDERS"** done in Government Coimbatore Medical College Hospital, Coimbatore. You satisfy eligibility criteria as per the inclusion criteria. You can ask any questions or seek any clarifications on the study that you might have before agreeing to participate.

DECLINATION FROM PARTICIPATION

You are hereby made aware that participation in this study is purely voluntary and honorary and that you have the option and the right to decline from participation in the study.

PRIVACY AND CONFIDENTIALITY

You are hereby assured about your privacy of subject will be respected and any information about you or provided by you during the study will be kept strictly confidential.

AUTHORIZATION TO PUBLISH RESULTS

Results of the study may be published for scientific purposes and/or presented to scientific groups; however, you will not be identified; neither will your privacy be breached.

STATEMENT OF CONSENT

I, _____, do hereby volunteer and consent to participate in this study being conducted by Dr ANUPAMA VINUPAL. I have read and understood the consent form/or it has been read and explained to me in my own language. The study has been fully explained to me and clarifications have been cleared whenever I ask questions.

Date: Signature/Left Thumb Impression of the Volunteer

Date: Signature and Name of witness

ஒப்புதல் படிவம்

பெயர் :

வயது : பாலினம் :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் கண் மருத்துவத் துறையில் பட்டமேற்படிப்பு பயிலும் மாணவி மரு. அனுபமா வினுபால் அவர்கள் மேற்கொள்ளும் "தன்னுடல் தாங்குதிறன் கொப்புள தோல் நோய்களில் உண்டாகும் கண் கோளாறுகளைப் பற்றிய்" ஆய்வின் செய்முறை தொடர்பான அனைத்து விபரங்களையும் கேட்டு எனது சந்தேங்களைத் தெளிவுபடுத்திக் கொண்டேன்.

நான் இந்த ஆய்வில் என்னை பரிசோதனை செய்ய முழு மனதுடனும், சுய சிந்தனையுடனும் சம்மதிக்கிறேன்.

எனது நோய் பற்றிய இந்த ஆய்வில் எங்களது அனைத்து விபரங்களும் பாதுகாக்கப்படுவதுடன் நோய் பகுதியின் புகைப்படம் மற்றும் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதைத் தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம்

தேதி நோயாளியின் கையொப்பம்

NAME	AGE (in years)	SEX	DIAGNOSIS OF SKIN DISEASE	DURATION OF SKIN DISEASE	TREATMENT OF SKIN DISEASE	VISUAL ACUITY		IOP (mm Hg)		SCHIRMER'S TEST (in mm of		T-BUT (in seconds)		OCULAR DIAGNOSIS	CONJUNCTIVITIS		DRY EYE			PRE SENILE CATARACT	SUPERFICIAL PUNCTATE KERATITIS	LID EROSIONS	SYMBLEPHARON	CONJUNCTIVAL SCARRING	CONJUNCTIVAL EROSIONS
						RE	LE	RE	LE	RE	LE	RE	LE		Cicatrizing	Non cicatrizing	Mild	Moderate	Severe						
Chitra	50	female	Pemphigus foliaceous	13 years	systemic steroids	6/12	6/12	17	12	4	4	3	4	(BE) Severe dry eye					+					
Selvi	42	female	Pemphigus vulgaris	1 year	systemic steroids	6/9	6/9	12	14	17	19	9	9	(BE) Conjunctivitis		+								
Prakash	23	male	Pemphigus vulgaris	6 months	systemic steroids	6/6	6/6	11	11	10	9	8	9	(BE) moderate dry eye				+						
Kavitha	33	female	Pemphigus vulgaris	2 years	systemic steroids	6/60	6/36	14	16	1	1	3	2	(BE) Severe dry eye					+					
Parthiban	55	male	Pemphigus vulgaris	1 year	systemic steroids	6/12	6/12	14.5	14.5	25	25	>10	>10	(BE) Normal										
Vasanthi	42	female	Pemphigus vulgaris	5 years	systemic steroids	6/60	6/24	13	15	2	2	3	3	(BE) Normal										
Sathyapriya	16	female	Linear IgA disease	1 year	systemic steroids, Tab.Dapsone, Tab.Azathioprine	6/6	6/6	16	17	26	30	>10	>10	(BE) Normal										
Manoharan	57	male	Pemphigus vulgaris	3 years	Dexamethasone + Cyclophosphamide pulse therapy	6/18	6/24	15	16	25	20	>10	>10	(BE) Normal										
Ramarao	30	male	Pemphigus vulgaris	8 months	Dexamethasone only pulse therapy	6/9	6/9	16	17	>35	>35	>10	>10	(BE) Normal										
Jaimul Abdeen	27	male	Pemphigus foliaceous	7 months	systemic steroids	6/6	6/6	19	19	25	26	>10	>10	(BE) Conjunctivitis		+								
Chinnammal	65	female	Bullous pemphigoid	4 months	Dexamethasone + Cyclophosphamide pulse therapy	4/60	5/60	15	12	13	11	7	8	(BE) mild dry eye			+							
Krishnammal	65	female	Pemphigus vulgaris	5 years	Dexamethasone + Cyclophosphamide pulse therapy	6/60	6/60	12	12	11	10	9	9	(BE) mild dry eye			+							
Manoharan	55	male	Bullous pemphigoid	2 years	systemic steroids	6/18	6/9	17	14	26	26	>10	>10	(BE) Normal										
Ramasami	33	male	Pemphigus vulgaris	1 month	systemic steroids, Tab.Azathioprine	6/6	6/6	13	14	9	9	5	4	(BE) moderate dry eye				+						
Kavitha	35	female	Pemphigus foliaceous	2 years	Dexamethasone + Cyclophosphamide pulse therapy	6/6	6/6	12	12	>35	>35	>10	>10	(BE) Normal										
Dhanalakshmi	57	female	Pemphigus vulgaris	1 month	Tab.Azathioprine and Inj.Dexamethasone	6/9	6/9	20	20	10	10	8	8	(BE) moderate dry eye				+						
Velayutham	76	male	Bullous pemphigoid	1 year	systemic steroids	6/12	6/12	18	19	19	20	>10	>10	(BE) Normal										
Mohammed Ali	55	male	Pemphigus vulgaris	3 months	systemic steroids	6/9	6/9	15	13	23	24	>10	>10	(BE) Normal										
Nagappan	60	male	Linear IgA disease	1 year	systemic steroids	6/60	6/24	17	19	9	8	7	8	(BE) moderate dry eye				+						
Sinthamani	40	female	Bullous pemphigoid	12 years	Dexamethasone only pulse therapy	6/24	6/24	13	14	5	5	4	4	(BE) presenile cataract (steroid induced) with severe dry eye					+	+				
Krishnaveni	63	female	Pemphigus vulgaris	5 years	systemic steroids	6/12	6/18	14	16	23	24	>10	>10	(BE) Normal										
Ramaprakash	31	male	Pemphigus vulgaris	10 months	Dexamethasone only pulse therapy	6/6	6/6	13	15	26	28	>10	>10	(BE) Normal										
Ammasai	75	female	Bullous pemphigoid	15 years	systemic steroids	1/60	1/60	14	16	8	7	6	7	(BE) Normal										
Govindammal	75	female	Bullous pemphigoid	6 months	Dexamethasone + Methotrexate pulse therapy	5/60	5/60	20	20	27	30	>10	>10	(BE) severe dry eye with conjunctival erosions and symblepharon					+				+	+
Kavipriya	33	female	Pemphigus foliaceous	2 years	Dexamethasone + cyclophosphamide pulse therapy	6/6	6/6	20	18	8	9	6	7	(BE) moderate dry eye				+						
Krishnammal	62	female	Pemphigus vulgaris	5 years	Dexamethasone + cyclophosphamide pulse therapy	6/60	5/60	13	14	32	30	>10	>10	(BE) conjunctivitis		+								
Ganeshan	30	male	Pemphigus vulgaris	2 years	Dexamethasone only pulse therapy	6/6	6/6	15	16	20	21	>10	>10	(BE) Normal										
Rathinasamy	72	male	Bullous pemphigoid	2 months	systemic steroids	6/12	6/12	14	15	22	23	>10	>10	(BE) Normal										
Rangammal	77	female	Bullous pemphigoid	5 years	systemic steroids	1/60	1/60	14	13	19	18	>10	>10	(BE)cicatrizing conjunctivitis	+									
Kittan	50	male	Pemphigus foliaceous	3 months	systemic steroids	6/24	6/24	18	18	no wetting	no wetting	2	2	(BE) Severe dry eye with superficial punctate keratitis					+		+			
Natarajan	65	male	Bullous pemphigoid	1 month	systemic steroids	6/24	6/24	12	13	19	21	>10	>10	(BE) Conjunctivitis		+								
Kandhasamy	66	male	Bullous pemphigoid	1 year	systemic steroids	6/12	6/12	15	16	26	28	>10	>10	(BE) conjunctivitis		+								
Visalatchi	67	female	Pemphigus foliaceous	1 year	Dexamethasone + Methotrexate pulse	6/60	6/60	16	19	4	4	2	3	(BE) severe dry eye					+					
Ramathal	45	female	Pemphigus vulgaris	2 years	Dexamethasone only pulse therapy	6/6	6/6	12	11	6	6	4	4	(BE) moderate dry eye				+						
Ramalakshmi	52	female	Pemphigus foliaceous	12 years	systemic steroids	6/12	1/60	17	13	16	17	>10	>10	(RE) Normal										
Selvam	45	male	Pemphigus vulgaris	1.5 years	systemic steroids	6/12	6/12	12	13	25	24	>10	>10	(BE) Conjunctivitis		+								
Satheesh	23	male	Pemphigus vulgaris	9 months	systemic steroids	6/9	6/9	15	16	12	12	8	8	(BE) Mild dry eye			+							
Karthigha	38	female	Pemphigus vulgaris	3 years	Dexamethasone + cyclophosphamide pulse therapy	6/36	6/36	12	12	24	23	>10	>10	(BE) Presenile cataract (steroid induced) with conjunctival erosions						+				+
Pandiarajan	60	male	Pemphigus vulgaris	5 years	Dexamethasone + cyclophosphamide pulse therapy	6/9	6/18	12	14	25	28	>10	>10	(BE) Normal										
Varalakshmi	43	female	Pemphigus vulgaris	6 years	Systemic steroids	6/12	6/12	13	15	4	4	3	3	(BE) Severe dry eye with superficial punctate keratitis					+		+			
Vetrimaran	59	male	Pemphigus vulgaris	3.5 years	Dexamethasone + cyclophosphamide pulse therapy	5/60	6/36	15	16	30	>35	>10	>10	(BE)Normal										

Mahendran	60	male	Pemphigus vulgaris	4 years	Dexamethasone + cyclophosphamide pulse therapy	6/60	6/60	13	14	28	29	>10	>10	(BE) Normal											
Ramaraj	32	male	Pemphigus vulgaris	8 months	Dexamethasone only pulse therapy	6/6	6/6	12	13	13	12	9	9	(BE) Mild dry eye			+								
Chandra	65	female	Bullous pemphigoid	4 months	Dexamethasone + cyclophosphamide pulse therapy	6/12	6/12	16	17	33	32	>10	>10	(BE) Normal											
Mohammed Nawaz	29	male	Pemphigus foliaceous	7 months	Systemic steroids	6/6	6/6	12	13	>35	>35	>10	>10	(BE) Normal											
Rasathi	75	female	Bullous pemphigoid	5 years	systemic steroids	6/60	6/60	12	13	19	18	>10	>10	(BE) Normal											
Krishnan	54	male	Pemphigus foliaceous	6 months	systemic steroids	6/24	6/24	18	18	7	7	5	5	(BE)Normal											
Nagasivam	66	male	Bullous pemphigoid	2 months	systemic steroids	5/60	4/60	19	12	30	30	>10	>10	(BE) conjunctivitis		+									
Kalidasan	60	male	Pemphigus foliaceous	1 year	Dexamethasone + Methotrexate pulse therapy	6/9	6/9	12	14	34	32	>10	>10	(BE) Normal											
Seetha	46	female	Pemphigus vulgaris	2.5 years	Dexamethasone only pulse therapy	6/9	6/9	13	16	>35	>35	>10	>10	(BE) Normal											
Vilasini	53	female	Pemphigus vulgaris	5 years	Dexamethasone + Cyclophosphamide pulse therapy	6/12	6/18	13	16	30	28	>10	>10	(BE) Moderate dry eye with conjunctival erosions				+							+
Sivaraman	35	male	Pemphigus vulgaris	4 years	Systemic steroids	6/6	6/6	14	16	13	12	8	8	(BE) Mild dry eye			+								
Seeniammmal	65	female	Bullous pemphigoid	7 years	Systemic steroids	6/12	6/18	18	19	5	5	6	6	(BE) severe dry eye with superficial punctate keratitis					+		+				
Vijayasanthi	54	female	Pemphigus vulgaris	3 years	Systemic steroids	6/12	6/18	15	17	3	3	2	2	(BE) Severe dry eye with superficial punctate keratitis with conjunctival scarring					+		+			+	
Senthil	23	male	Pemphigus foliaceous	2 years	Systemic steroids	6/6	6/6	12	13	>35	>35	>10	>10	(BE) Normal											
Prema	40	female	Pemphigus vulgaris	5 years	Dexamethasone + Cyclophosphamide pulse therapy	6/6	6/6	14	15	25	28	>10	>10	(BE) Normal											
Vasantha	49	female	Pemphigus vulgaris	3 years	Dexamethasone + cyclophosphamide pulse therapy	6/24	6/18	13	12	8	9	6	7	(BE) Presenile cataract (steroid induced) with moderate dry eye				+		+				
Lakshmanan	54	male	Bullous pemphigoid	7 years	systemic steroids	6/60	6/36	11	10	17	18	>10	>10	(BE)cicatrizing conjunctivitis	+										
Vidya	23	female	Linear IgA disease	2 years	systemic steroids	6/6	6/6	12	13	12	12	8	8	(BE) Moderate dry eye with conjunctival scarring				+						+	
Mohammed Farooq	25	male	Linear IgA disease	4 years	systemic steroids	6/6	6/6	14	15	10	10	7	7	(BE) Moderate dry eye with superficial punctate keratitis				+			+				
Moorthi	54	male	Pemphigus vulgaris	8 years	systemic steroids	6/18	6/18	12	13	14	13	9	9	(BE) Mild dry eye			+								
Balakumar	35	male	Pemphius foliaceous	2 years	Dexamethasone + cyclophosphamide pulse therapy	6/6	6/6	15	17	30	30	>10	>10	(BE) Blepharitis with eyelid margin erosions								+			
Mookayi	65	female	Pemphigus vulgaris	5 years	Systemic steroids	5/60	5/60	12	14	32	32	>10	>10	(BE) Normal											
Sabarimani	49	male	Bullous pemphigoid	2 years	systemic steroids	6/18	6/18	13	16	>35	>35	>10	>10	(BE) Conjunctivitis		+									
Masilamani	36	male	Pemphigus vulgaris	3 years	Dexamethasone + cyclophosphamide pusle therapy	6/9	6/9	15	17	10	10	5	5	(BE) Moderate dry eye with cicatrizing conjunctivitis	+			+							
Senniappan	65	male	Bullous pemphigoid	2 years	Systemic steroids	4/60	3/60	12	13	20	23	>10	>10	(BE) Conjunctivitis		+									
Swarnalatha	25	female	Linear IgA disease	3 years	systemic steroids	6/6	6/6	14	15	>35	>35	>10	>10	(BE) Normal											
Shanmugham	47	male	Pemphigus vulgaris	6 years	Dexamethasone + cyclophosphamide pulse therapy	6/12	6/18	13	16	14	13	6	7	(BE) Mild dry eye			+								
Venkatachalam	50	male	Pemphigus vulgaris	7 years	Dexamethasone only pulse therapy	6/24	6/24	16	17	12	12	6	6	(BE) mild dry eye			+			+					
Rajendran	60	male	Pemphigus foliaceous	4 years	Dexamethasone + cyclophosphamide pulse therapy	6/60	6/12	13	14	26	27	>10	>10	(BE) conjunctivitis		+									
Vimala	36	female	Pemphigus vulgaris	5 years	Dexamethasone + cyclophosphamide pulse therapy	6/9	6/9	15	16	2	2	3	3	(BE) Severe dry eye with symblepharon					+				+		
Kamalam	50	female	Bullous pemphigoid	3 years	systemic steroids	6/9	6/12	14	16	25	24	>10	>10	(BE) cicatrizing conjunctivitis	+										
Chandrasekharan	32	male	Pemphigus foliaceous	2 months	systemic steroids	6/6	6/6	12	13	>35	30	>10	>10	(BE) Normal											
Swarnam	47	female	Pemphigus vulgaris	6 months	Dexamethasone + cyclophosphamide pulse therapy	6/18	6/18	15	16	6	7	5	4	(BE) Moderate dry eye with superficial punctate keratitis				+			+				
Vijayan	27	male	Linear IgA disease	7 months	systemic steroids	6/6	6/6	17	18	>35	>35	>10	>10	(BE) Normal											
Kala	65	female	Bullous pemphigoid	3.5 years	Dexamethasone only pulse therapy	6/9	6/9	17	19	17	19	>10	>10	(BE) Normal											
Somasundaram	35	male	Pemphigus foliaceous	9 months	Tab.Azathioprine and Inj.Dexamethasone	6/6	6/6	19	20	34	32	>10	>10	(BE) Eyelid margin erosions with conjunctivitis		+						+			
Vinayagam	40	male	Mucous membrane pemhigoid	7 months	Systemic steroids and Tab.Azathioprine	6/60	6/60	15	16	3	3	2	2	(BE) Severe dry eye with symblepharon and superficial punctate keratitis					+		+		+		
Prathap	39	male	Pemphigus vulgaris	4 years	Dexamethasone only pulse therapy	6/6	6/6	17	18	>35	>35	>10	>10	(BE) Normal											
Padmavathi	53	female	Pemphigus vulgaris	6 years	Dexamethasone only pulse therapy	6/18	6/24	19	20	30	29	>10	>10	(BE)Normal											
Sakunthala	45	female	Pemphigus vulgaris	4 months	Systemic steroids	6/6	6/6	13	14	32	34	>10	>10	(BE) Normal											
Santhanamani	50	male	Pemphigus vulgaris	8 years	Systemic steroids	6/9	6/9	15	12	30	32	>10	>10	(BE) Normal											
Mahalingam	35	male	Pemphigus foliaceous	4 years	Dexamethasone + cyclophosphamide pulse therapy	6/6	6/6	13	14	9	9	5	5	(BE) Moderate dry eye				+							
Valli	60	female	Bullous pemphigoid	7 years	systemic steroids	6/12	6/12	17	18	1	1	2	2	(BE)severe dry eye with symblepharon and keratinization					+				+		

Sarojini	40	female	Pemphigus foliaceous	3 months	Tab.Azathioprine and Inj.Dexamethasone	6/6	6/6	19	20	11	10	7	8	(BE) Mild dry eye			+								
Sathyavathi	39	female	Linear IgA disease	1 month	Systemic steroids	6/6	6/9	12	13	12	13	8	8	(BE) Normal											
Leelavathiammal	64	female	Bullous pemphigoid	5 years	Systemic steroids	6/18	6/18	17	18	15	16	>10	>10	(BE) Normal											
Palani	28	male	Pemphigus vulgaris	7 months	Systemic steroids	6/6	6/6	14	15	>35	>35	>10	>10	(BE) Normal											
Varadarajan	43	male	Pemphigus foliaceous	4 years	Dexamethasone + cyclophosphamide pulse therapy	6/24	6/18	17	18	27	28	>10	>10	(BE) Normal											
Sathyabhama	23	female	Linear IgA disease	8 months	Systemic steroids	6/6	6/6	13	15	12	12	7	7	(BE) Mild dry eye			+								
Meena	44	female	Pemphigus foliaceous	5 years	Dexamethasone + Cyclophosphamide pulse therapy	6/18	6/24	15	18	>35	>35	>10	>10	(BE) Presenile cataract (steroid induced)						+					
Manikandan	37	male	Pemhigus vulgaris	2 years	Systemic steroids	6/6	6/6	14	17	>35	>35	>10	>10	(BE) normal											
Sakthivel	67	male	Bullous pemphigoid	4 years	Tab.Azathioprine and Inj.Dexamethasone	4/60	5/60	11	12	16	17	9	9	(BE) mild dry eye			+								
Rajathiammal	70	female	Pemphigus vulgaris	9 years	systemic steroids	6/24	6/24	12	16	29	20	>10	>10	(BE) cicatrizing conjunctivitis	+										
Prabhakaran	41	male	Pemphigus vulgaris	3 years	Dexamethsone + cyclophosphamide pulse therapy	6/18	6/18	14	15	3	3	2	2	(BE) Severe dry eye with superficial punctate keratitis					+		+				
Rajasekharan	57	male	Pemphigus foliaceous	1 year	Dexamethsone + cyclophosphamide pulse therapy	6/24	6/24	17	18	20	21	>10	>10	(BE) Normal											
Vedhanayaki	39	female	Linear IgA disease	5 months	systemic steroids	6/6	6/6	14	15	29	28	>10	>10	(BE) Normal											
Jasmine Priyanka	25	female	Pemphigus vulgaris	6 months	Dexamethasone only pulse therapy	6/6	6/6	17	18	30	32	>10	>10	(BE) conjunctivitis		+									
Anwar Rasheed	51	male	Pemphigus foliaceous	6 years	Systemic steroids	6/18	6/36	12	15	25	26	>10	>10	(BE) normal											
Chinnasamy	37	male	Pemhigus vulgaris	3 months	Dexamethasone + Cyclophosphamide pulse therapy	6/6	6/6	17	20	28	30	>10	>10	(BE) Normal											