REVIEW

Pseudopemphigoid as caused by topical drugs and pemphigus disease

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Abstract

Pseudopemphigoid can cause a chronic cicatricial conjunctivitis that is clinically identical to the manifestations seen in mucous membrane pemphigoid, a disorder with a common clinical phenotype and multiple autoimmune links. For the purpose of this review, we will describe pseudopemphigoid as caused by topical drugs, the most common etiology with ocular manifestations, and as caused by the pemphigus disease, a more rare etiology. Specifically, we will discuss the ophthalmological features of drug-induced cicatricial conjunctivitis, pemphigus vulgaris, and paraneoplastic pemphigus. Other etiologies of pseudopemphigoid exist that will not be described in this review including autoimmune or inflammatory conditions such as lichen planus, sarcoidosis, granulomatosis with polyangiitis (Wegener's granulomatosis), erythema multiforme (minor, major, and Stevens-Johnson syndrome), bullous pemphigoid, skin-dominated linear IgA bullous dermatosis, and skin-dominated epidermolysis bullosa acquisita. Prompt diagnosis of the underlying etiology in pseudopemphigoid is paramount to the patient's outcome as certain diseases are associated with a more severe clinical course, increased ocular involvement, and differential response to treatment. A complete

history and ocular examination may find early cicatricial changes in the conjunctiva that are important to note and evaluate to avoid progression to more severe disease manifestations. When such cicatricial changes are noted, proper diagnostic techniques are needed to help elucidate a diagnosis. Lastly, collaboration between ophthalmologists and subspecialists such as dermatologists, pathologists, immunologists, and others involved in the care of the patient is needed to ensure optimal management of disease.

Core tip: Pseudopemphigoid in the context of chronic cicatricial conjunctivitis mimicking mucous membrane pemphigoid is a disease with terminology that has continuously evolved since its inception. Recent understanding of the ophthalmological and systemic manifestations of pseudopemphigoid as caused by topical drugs and the pemphigus disease demonstrates that significantly decreased vision and/or increased mortality due to paraneoplastic associations may result. Proper diagnosis and treatment of the underlying disease is therefore critical in order to provide maximal care to the patient.

INTRODUCTION

The first use of the term pseudopemphigoid referred to a non-progressive, unilateral cicatricial conjunctivitis that developed in response to certain aggravating topical medications[1]. Pseudopemphigoid was originally named due to its clinical similarity to mucous membrane pemphigoid (MMP) - an autoimmune blistering disease characterized by subepithelial deposition of antigen-antibody complexes at the basement membrane zone. Subepithelial deposition of autoantibody complexes seen in pemphigoid disease differentiates it from pemphigus that is characterized by intraepithelial deposition of autoantibody complexes. If clinical manifestations of pemphigus produce conjunctival cicatrization identical to MMP, then pemphigus may therefore be characterized as "pseudopemphigoid" and the modern terminology of pseudopemphigoid now includes any etiology that mimics MMP in clinical presentation.

The purpose of this review is to elaborate on the epidemiology, clinical features, diagnosis, and treatment options available for patients with pseudopemphigoid. This paper will review the ocular manifestations associated with three etiologies of pseudopemphigoid including the most common cause, drug-induced cicatricial conjunctivitis[2], and two rare causes from the pemphigus family, pemphigus vulgaris and paraneoplastic pemphigus. Pemphigus foliaceus, a third subset of the pemphigus family, does not involve the conjunctiva and will not be discussed in this review.

Pseudopemphigoid may be caused by a variety of other conditions not included in this review article such as sarcoidosis, granulomatosis with polyangiitis (Wegener's granulomatosis), bullous pemphigoid, skin-dominated linear IgA bullous dermatosis, and skin-dominated epidermolysis bullosa acquisita[3]. Additionally, inflammatory and/or autoimmune disease associated cicatricial conjunctivitis characterized by an interface/lichenoid lymphocytic infiltrate such as lichen planus[4], graft *vs* host disease, erythema multiforme spectrum, and discoid lupus erythematosis[5] are not included in this review article.

PSEUDOPEMPHIGOID

How pseudopemphigoid differs from mucous membrane pemphigoid

Historically, pseudopemphigoid referred to a unilateral drug-induced cicatricial reaction identical to MMP that did not progress upon removal of the inciting drug. The term has since evolved and for the purposes of this review, pseudopemphigoid will be characterized according to the criteria proposed by Thorne *et al*[2]: (1) Chronic cicatricial conjunctivitis; (2) A biopsy that rules out MMP; and (3) The existence of an alternate cause for cicatrization.

MMP refers to a group of autoimmune, subepithelial, blistering diseases that predominantly affect the mucous membranes and are notable for linear deposition of autoantibodies (IgG, IgA, or C3) along the epithelial basement membrane zone on biopsy. The primary distinction between MMP and pseudopemphigoid is that MMP consists exclusively of autoimmune blistering diseases with subepidermal deposition of autoantibodies as opposed to pseudopemphigoid that simply mimics MMP in clinical presentation but does not involve subepidermal deposition of autoantibodies.

How pseudopemphigoid mimics mucous membrane pemphigoid

Clinical features: Pseudopemphigoid, similarly to MMP, may produce a chronic cicatricial conjunctivitis in patients characterized by the presence of scarring. The clinical presentation of a patient with cicatricial conjunctivitis includes irritation, burning, a foreign body sensation, photophobia, tearing, dryness, redness or blurry vision and hyperemic conjunctiva, misalignment of eyelashes, cicatricial entropion, and trichiasis[6].

The Foster[7] staging system developed for MMP may be utilized to characterize the severity of chronic cicatricial conjunctivitis secondary to pseudopemphigoid

Table 1 Staging for severity of cicatricial conjunctivitis

Staging for severity of cicatricial conjunctivitis
Foster Staging[7]
I Subepithelial fibrosis, positive rose-bengal staining in conjunctiva, conjunctival "shrinkage" from abnormal connective tissue due to small white striae that form around the superficial vessels in substantia propria
II Marked foreshortening of inferior conjunctiva described by (1) 0%-25%; (2) 25%-50%; (3) 50%-75%; and (4) 75%-100%
III Corneal neovascularization, trichiasis, dystichiasis, keratopathy, subepithelial bands of connective tissue resulting in symblepharon (conjunctival adhesions) formation that is described by (1) 0%-25%; (2) 25%-50%; (3) 50%-75%; and (4) 75%-100%
IV Severe sicca syndrome, keratinization, ankyloblepharon
Mondino Staging[134]
I 0%-25% loss of inferior conjunctival fornix depth
II 25%-50% loss of inferior conjunctival fornix depth
III 50%-75% loss of inferior conjunctival fornix depth
IV 75%-100% loss of inferior conjunctival fornix depth

Table 2 Conditions associated with cicatricial conjunctivitis

Trauma
Physical trauma
Chemical burn
Thermal burn
Radiation burn
Infection
Trachoma
Membranous conjunctivitis
Allergic
Chronic atopic keratoconjunctivitis
Mucocutaneous disease
Erythema multiforme
Stevens-Johnson Syndrome
Toxic epidermal necrolysis
Immunobullous disorders
Mucous membrane pemphigoid
Bullous pemphigoid
Pemphigus vulgaris
Paraneoplastic pemphigus
Lichen planus
Dermatitis herpetiformis
Systemic lupus erythematosus
Systemic disorders
Rosacea
Sjogren's syndrome
Graft-*vs*-host disease
Sarcoidosis
Ectodermal dysplasia
Erythroderma ichthyosiform congenital
Drug-induced
Systemic
Topical

as well. In Stage I, conjunctival inflammation develops with mucous discharge, subepithelial fibrosis, and areas of degenerated cells in the conjunctival epithelium. Abnormal connective tissue and small white striae develop around the superficial vessels of the substantia propria, producing conjunctival "shrinkage." In Stage II, inferior conjunctival foreshortening occurs. In Stage III, subepithelial bands of connective tissue create symblepharon (conjunctival adhesions), corneal neovascularization, trichiasis (misdirected eyelash growth), dystichiasis (eyelash growth arising from meibomian glands), and keratopathy due to scarring of the conjunctival goblet cells, lacrimal gland ducts, and meibomian gland orifices. In Stage IV, severe sicca syndrome, keratinization, and ankyloblepharon (lid adhesions) develop (Table 1).

Despite a severe end-stage presentation, early cicatrization secondary to pseudopemphigoid and MMP is often nonspecific and subtle which causes patients to present with disease that is already erosive and scarring[8]. Additionally, more than 65% of patients may have cicatricial conjunctivitis develop without any symptoms[9]. In a prospective study of 163 eyes with cicatricial change, a diagnostic delay of a median 225 d after symptom onset was noted causing 59% of patients to present as Stage III at diagnosis[10]. Therefore, it is paramount to have etiologies such as MMP and pseudopemphigoid on the differential diagnosis for any patient who presents with cicatrization to best optimize management.

Diagnosis: The first step to discovering the etiology of chronic cicatricial conjunctivitis involves the history. The patient should be asked about any past medical history of chemical or thermal burns; membranous conjunctivitis caused by infectious organisms such as adenovirus; mucocutaneous disorders such as erythema multiforme (minor, major, and Stevens-Johnson syndrome), Sjogren's syndrome; systemic allergic disease such as chronic atopic conjunctivitis or rosacea; chronic graft-*vs*-host disease following organ transplantation; history of trachoma if from endemic areas;

previous eyelid surgery; or previous use of any aggravating topical or systemic medications (Table 2). Additionally, because many etiologies of pseudopemphigoid include systemic autoimmune bullous disease, the physician should inquire about new onset cutaneous or oral mucosal lesions. Most patients presenting with cicatricial conjunctivitis will have a history that makes the diagnosis simple. If inconclusive evidence is found from the history, then other methods of diagnosis are needed including a conjunctival biopsy.

ETIOLOGIES OF PSEUDOPEMPHIGOID

Drug-induced cicatrization
Epidemiology: Drug-induced conjunctival cicatrization (DICC), also known as drug-induced ocular pseudopemphigoid, produces clinical findings identical to MMP in response to varying offending topical and systemic drugs[11]. The incidence of DICC remains unknown, but has been documented to occur most often in patients who require long-term use of glaucoma medications[11]. In a retrospective cohort study of 145 pseudopemphigoid patients, DICC was the most common cause of pseudopemphigoid in this population occurring in 28.3% of patients[2].

Pathophysiology: DICC can develop as a non-progressive, self-limiting "toxic" reaction to an offending topical drug or as a progressive, immunological process that continues

despite cessation of the offending drug[12-14]. Although increased activity of fibroblasts has been implicated as a possible effect on the local immune system, the exact mechanism by which offending topical drugs directly induce cicatricial conjunctivitis remains unknown[15].

When IgG localized to the ocular epithelial basement membrane zone are found, then autoimmune phenomenon are suggested[15,16]. Practolol, an oral beta-blocker, and its derivative metipranolol, a topical beta-blocker that treats glaucoma, have been implicated to induce immunologically mediated DICC[17-20]. This is related to the chemical structure and pharmacologic metabolism in the body - both compounds require deacetylation for metabolic activation, which produces a toxic aniline derivative in practolol and a slightly less toxic phenol derivative in metipranolol[17]. When oxidized, these derivatives become highly reactive and are normally neutralized in the body by the addition of glucuronic acid or sulfate. However, this mechanism is insufficient in patients that have a lower capacity for enzymatic detoxification[17]. When this occurs, proteins can bind these reactive oxidative products to create antigens[17]. Therefore, the toxicity potential of practolol and metipranolol to produce immunologically mediated cicatricial conjunctivitis occurs in patients who are susceptible to these reactions required for metabolic activation of the drug due to its pharmacologic structure. Drug chemical structure has not been implicated in the mechanism of cicatricial conjunctivitis induced by other offending topical drugs and in many cases of DICC, a toxic or immune-mediated reaction cannot be further defined.

Epitope spreading is one possible theory that may elucidate the mechanism behind autoimmune phenomenon as induced by topical drugs. Epitope spreading[21,22] refers to the phenomenon of autoimmune reactivity not only against one protein, but also against other epitopes on the same protein or other proteins in the same tissue. Intramolecular epitope spreading that occurs between different epitopes on the same protein is often used to explain the molecular pathogenesis and severity of disease in bullous pemphigoid[23]. Additionally, epitope spreading may occur due to tissue damage that causes certain antigens to become newly exposed to autoreactive T or B cells, thus producing an autoimmune disease in predisposed individuals[21,24]. This mechanism of epitope spreading can be promoted by injury that exposes previously sequestered antigens, causing activation of antigen presenting cells that attract autoreactive lymphocytes in these individuals[22]. Intermolecular epitope spreading that occurs between two different proteins has been cited to explain the conversion of one autoimmune disease into another. Pemphigus autoimmune disease converting into pemphigoid disease, or conversions between other autoimmune blistering diseases either simultaneously or separated by a few years, is hypothesized to occur when tissue damage exposes protein parts that are normally undetected by the immune system[25,26]. In a similar manner, ocular mucosal injury due to Stevens-Johnson syndrome, Lyell Syndrome, or direct chemical injury from drugs may be implicated to expose normally hidden antigens to processing and presentation by activated T-cells, resulting in the formation of MMP[12,21,24].

Incidences of MMP developing in uninvolved eyes of patients that did not receive the inciting drug may indicate an immunological etiology[12]. On the other hand, instances of unilateral changes histologically and immunologically identical to MMP that occur in only the eye that received an offending drug is considered to be drug-induced[16]. The absence of bilateral ocular involvement, other mucosal or cutaneous manifestations, and disease that is non-progressive after cessation of the offending drug suggests a drug-induced reaction. Therefore, DICC may involve either a toxic mechanism of damage or an autoimmune etiology where inciting topical medications sensitize predisposed individuals to developing a more rapid onset of ocular MMP.

Clinical findings: DICC produces symptoms of cicatrization clinically identical to MMP. Two distinguishing factors that differentiate DICC from MMP include unilaterality of symptoms localized to the eye that received the topical therapy as well as non-progression of disease after cessation of the drug. However, reports of progressive DICC have occurred in the literature[13,14].

A total of 7 studies comprising 63 cases of drug-induced conjunctival cicatrization were found in the literature[1,2,14,16,27-29]. The most commonly used inciting topical drugs and the average duration of utilization before onset of DICC symptoms consisted of: timolol (73% or 46/63) for an average 10.5 years, pilocarpine (51% or 32/63) for an average 9 years, dipivefrin (49% or 31/63) for an average 7 years, latanoprost (13% or 8/63) for an average 8 years, echothiophate iodide (11% or 7/63) for an average 8 years, epinephrine (10% or 6/63) for an average 2 years, acetazolamide (6% or 4/63) for an average 9 years, betaxolol (3% or 2/63) for an average 6 years, idoxuridine (6% or 4/63) for an average 2 years, dichlorphenamide (5% or 3/63) for an average 3 years, and bromonidine (8% or 5/63) and other beta blocker antiglaucomatous medications for an unknown duration of time (48% or 30/63).

Of 7 studies comprising 23 patients with drug-induced conjunctival cicatrization found in the literature, the most common clinical findings included: forniceal foreshortening (57% or 13/23), symblepharon formation (48% or 11/23), trichiasis (48% or 11/23), corneal epithelial defects (35% or 8/23), entropion (30% or 7/23), corneal pannus (30% or 7/23), pseudopterygium formation (4% or 1/23), and corneal perforation (4% or 1/23)[1,14,16,27-30].

Diagnostic studies: There are no specific changes associated with medications that induce cicatrization nor is there a favored location of conjunctival involvement to distinguish DICC from idiopathic MMP[11]. Histopathological features seen on conjunctival biopsy can vary according to whether cicatrization is mild or severe[31]. When histopathological changes are seen, biopsy specimens can be identical to that of MMP and include subepithelial fibrosis, subepithelial infiltration with inflammatory cells,

reduction or loss of goblet cells, and basement membrane thickening[1,12,19,28]. Conjunctival biopsy with the use of direct immunofluorescence (DIF) is often not helpful as the findings are usually absent or nonspecific. However, IgG and complement staining to the epithelial basement membrane zone have been reported[1,15]. Although it is more common for immunofluorescent testing to lack positive findings, patients who present with both DICC and positive basement membrane zone autoantibody deposition should be considered to have MMP[3]. Otherwise, if the patient presents with a unilateral, non-progressive cicatrization of the conjunctiva, lacks other cutaneous or oral mucosal lesions, has a history of topical medication use for a prolonged amount of time, and other causes of conjunctival shrinkage have been excluded, then DICC should be considered.

Treatment: Management of DICC involves withdrawing the causative drug as early as possible and monitoring the patient carefully for the progressive type of disease. As topical intraocular lowering pressure therapies are commonly implicated in the pathogenesis of DICC, therapy involves a dual approach that includes controlling intraocular pressure and treating the signs of cicatrization. The primary management to resolve or inhibit the progression of fibrosis is cessation of intraocular lowering pressure medication[12]. The treatment to control intraocular pressure includes systemic carbonic anhydrase inhibitors followed by early surgical trabeculectomy[14,16]. If there are no other treatment options for the topical preparation suspected to be the offending drug, then re-introducing the medication in an unpreserved preparation may help. The patient should be followed closely for progressive disease and if progression occurs, then one must consider that the patient has developed ocular MMP and begin the patient on therapy.

A total of 7 studies comprising 63 cases of DICC or drug-induced pseudopemphigoid were found in the literature[1,2,14,16,27-29]. Aside from cessation of the inciting drug, management to control signs of cicatrization included medical treatment involving dapsone (10% or 2/21) or steroids (10% or 2/21). Procedural treatments to control sequelae of cicatrization include electrolysis and cryotherapy. Surgical treatments to control sequelae of cicatrization included anterior lamellar repositioning, tarsectomy, mucous membrane grafting, lower lid retractor tightening, lamellar keratoplasty, conjunctival transplant, terminal tarsal rotation procedure, and everting sutures. When switching to a different anti-glaucomatous medication, acetazolamide (14% or 3/21) or methazolamide (14% or 3/21) were utilized. Surgical treatment to manage uncontrolled intraocular pressure included trabeculectomy.

Prognosis: Clinical outcomes after procedural and/or medical treatment included persistence of ocular lesions without progression (48% or 10/21), remission of ocular lesions defined as regression (33% or 7/21), progression of ocular lesions (10% or 2/21), and recurrence of ocular lesions (5% or 1/21). Overall, average follow up time was 25 mo. If cicatrization is non-progressive upon withdrawal of inciting drug, then prognosis is favorable and management should treat the signs of scarring. If cicatrization is progressive upon withdrawal of inciting drug, then management and prognosis should be according to that of MMP.

Pemphigus vulgaris

Epidemiology: Pemphigus vulgaris (PV) is an intraepithelial blistering disease with a reported incidence of 4 to 4.7 cases per one million individuals[32,33]. PV most often affects patients in the fourth to fifth decade of life with equal occurrence in both sexes[34,35]. This differs from MMP that occurs less commonly at an incidence of 1.13 cases per one million individuals and presents in older individuals with a female predominance[8,36-41]. PV affects all races, but a higher predilection is associated with certain HLA subtypes such as the HLA-DRB1*0402 in Ashkenazi Jews and DRB1*1401/04 and DQB1*0503 in patients of European or Asian origin[42-44].

Pathophysiology: PV is an autoimmune disease characterized by suprabasal acantholysis (loss of cell-to-cell adhesions in epidermal cells that occurs just above the basal layer) induced by IgG binding to target antigens desmoglein 1 and 3 of the cadherin family[45-47]. Acantholysis leads to formation of a cleft which subsequently develops into an intraepithelial bulla[48]. This differs from MMP that is characterized by subepithelial lesions due to autoantibodies directed against various target antigens identified in the basement membrane zone.

PV antigens, desmoglein 1 and 3, are part of desmosome complexes that anchor intermediate filaments for adhesion between adjacent cells. These complexes consist of plakoglobin, plakophilin, desmoplakin, and desmosomal cadherins[45]. Desmoglein 1 (160 kDa) is located more superficially just below the stratum corneum whereas desmoglein 3 (130 kDa) is confined to the lower levels just above the basal cell layer[45,48].

Ocular involvement in PV is rare and its low incidence in the literature may be related to the course of disease or due to underreporting. Desmoglein 3 is heavily expressed in the basal layer of conjunctival epithelium along with strong expression of desmocollin 3, and desmoplakin 1 and 2, throughout the conjunctiva[49,50]. The mechanism on why ocular involvement in PV is rare despite the presence of anti-desmoglein 3 autoantibodies in disease is unclear. Suggestions include that the ocular surface is less exposed to trauma than other tissues normally affected by PV[51]; that there is inactivation of desmoglein 3 in ocular epithelium that is readily compensated by other desmosomal proteins thereby leaving only a minority of patients susceptible to disease if compensation cannot be attained[49]; or that conjunctival involvement in PV is simply underreported.

Clinical findings: PV is characterized by the development of large, flaccid cutaneous blisters and mucosal surface

Figure 1 Clinical manifestations of ocular pemphigus vulgaris. A: Lid margin erosions of the medial aspect on the lower lid and blisters of the upper lid; B: Higher magnification of eyelid demonstrating erosions and crusting of the upper eyelid with superficial blisters; C: Conjunctival hyperemia, crusting from lid margin erosions, and mucoid discharge.

involvement including the oral mucosa, conjunctiva, esophagus, larynx, and genitalia. Cutaneous lesions are fragile blisters that bleed easily and are characteristic for demonstrating Nikolsky's sign (rubbing of the perilesional skin with slight pressure produces exfoliation of the outer layer) and the indirect Nikolsky sign (moving an intact blister laterally and enlarging it with pressure)[52].

Mucosal involvement is the most common manifestation of PV and painful, chronic erosions of mucus membranes are often the initial presentation[39,53,54]. Ocular involvement in PV is rare and typically benign - ocular lesions do not usually progress to scarring and patients often fully recover without sequelae[51,55]. If ocular involvement occurs, it typically induces bilateral conjunctivitis without fibrosis (Figure 1)[56]. Lid margin erosions in the medial aspect of the lower eyelid can be characteristic of ocular pemphigus vulgaris (OPV)[57]. This differs from MMP that most commonly presents ophthalmologically with signs of overt cicatrization including symblepharon, trichiasis, punctate keratitis, and entropion[10].

A total of 10 studies comprising 36 OPV patients were found in the literature[34,49,51,55,58-63]. The most common ocular symptoms included the following: conjunctival hyperemia (49% or 17/35), conjunctivitis (46% or 16/35), conjunctival ulceration (14% or 5/35), lid margin erosions (14% or 5/35), corneal erosions (6% or 2/35), erosions of the medial canthus (3% or 1/35), and pseudomembrane formation (3% or 1/35). Concomitant systemic manifestations most commonly included oral involvement (80% or 28/35) followed by cutaneous lesions (54% or 19/35). The initial presentation of disease included ocular involvement in 41% (14/34) of cases.

Despite the seemingly benign nature of OPV, other studies suggest that ocular involvement in PV may be a sign of severe or recurrent disease that can occur in conjunction with exacerbation of systemic disease or in patients who have previously failed conventional immunosuppressive therapy[34,51,58]. Although fibrosis is very uncommon in PV, a subset of patients characterized by ocular involvement as the first manifestation of disease can produce a progressive cicatricial conjunctivitis in a similar manner to MMP[35].

In the largest series in the literature regarding OPV

patients, Chirinos-Saldaña *et al*[35] described 15 patients whose presentation included the following: conjunctival hyperemia (100% or 15/15), cicatrization (100% or 15/15), subconjunctival scarring (100% or 15/15), conjunctival cul-de-sac shortening (73% or 11/15), symblepharon formation (40% or 6/15), eyelid involvement including trichiasis or entropion (33% or 5/15), corneal perforation (27% or 4/15), and ankyloblepharon formation (7% or 1/15). Concomitant systemic manifestations included oral (20% or 3/15) and cutaneous involvement (7% or 1/15). The initial presentation of disease included ocular involvement in 100% (15/15) of cases. These results, alongside other reports in the literature involving progressive keratolysis with secondary corneal perforation[64,65], have led authors to conclude that a subset of patients exist with atypical pemphigus characterized by severe ocular involvement as the primary manifestation of disease[35]. Although all patients in this series had immunopathological diagnoses of PV, additional serology studies and/or secondary confirmatory biopsies were not performed to determine the coexistence of MMP. Dual diagnoses of MMP and PV have been previously reported in the literature[66,67] and therefore remain a possibility in this series.

Diagnostic studies: Histopathological studies utilizing hematoxylineosin staining of conjunctival biopsies in OPV demonstrate suprabasal and intraepithelial acantholysis that is characteristic of the pemphigus disease with splitting that occurs above the basal layer[51,61]. This differentiates OPV from MMP where most changes occur at the basement membrane zone with subepithelial conjunctival shrinkage; inflammatory infiltrate involving lymphocytes, macrophages, and plasma cells; and squamous metaplasia progressing to parakeratosis and keratinization of conjunctival epithelium[56,68].

The initial laboratory method to diagnose PV includes a conjunctival biopsy with subsequent DIF to IgG deposits in the intercellular space (Figure 2). This demonstrates antibodies directed against pemphigus antigens including desmosomal proteins desmoglein 3 and 1. This differs from MMP that demonstrates IgG deposits in the subepithelial space with antibodies directed against a variety of antigens not including desmoglein 3 and 1.
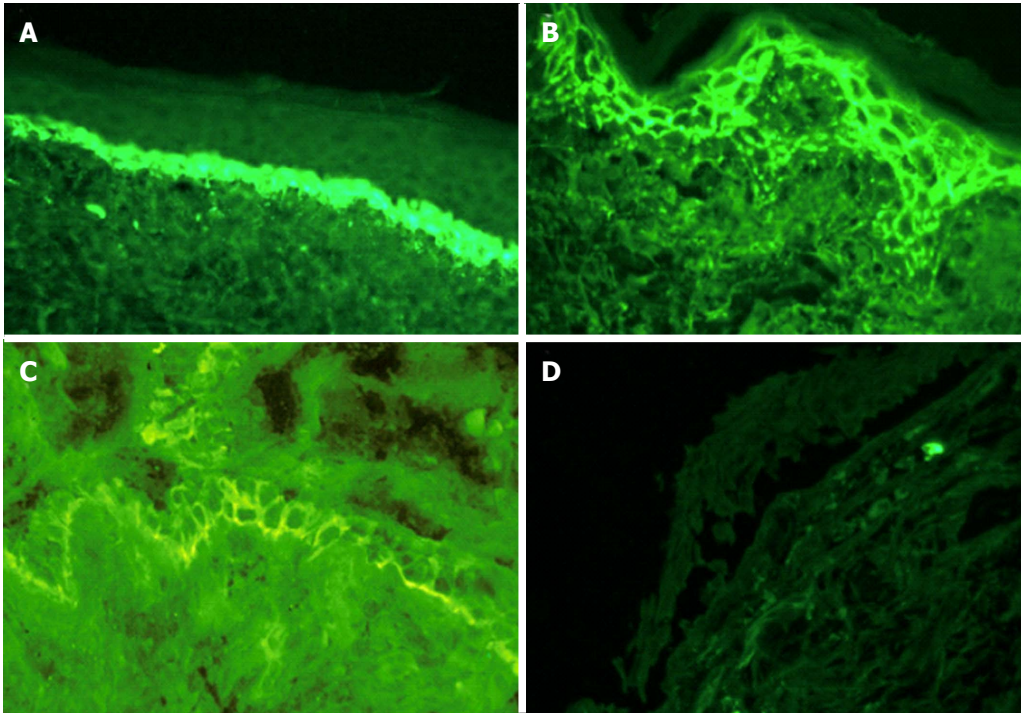
Figure 2 Direct immunofluorescence studies of conjunctival biopsies. A: Conjunctival mucous membrane pemphigoid showing thick linear IgG along the lamina propria in a background of squamous metaplasia; B: Conjunctival pemphigus vulgaris showing linear IgG deposition on desmosomal areas of epithelial cell surfaces displaying a classic "chicken-wire" pattern; C: Conjunctival paraneoplastic pemphigus (PNP) showing linear IgG along the lamina propria with a hemidesmosomal pemphigoid-like in conjunction with a desmosomal pemphigus vulgaris-type epithelial cell surface "chicken-wire" type pattern. The pattern in PNP is due to the presence of IgG autoantibodies against hemidesmosomal antigens (plakin proteins: BP230/BPAG1 and plectin) as well as desmosomal antigens (plakin proteins: desmoplakin, envoplakin, periplakin, and desmogleins 3 and 1); D: Conjunctival pseudopemphigoid (most likely drug-induced) showing negative IgG deposition along the lamina propria in a background of subepithelial clefting, mild submucosal fibrosis, and incipient epithelial metaplasia.

Indirect immunofluorescence (IIF) is utilized to detect a titer of circulating autoantibodies through serologic assays. IIF in PV will have serum positive for anti-intercellular substance antibodies in greater than 80%-90% of untreated cases which can be correlated with disease activity[68,69]. This differs from MMP where circulating antibodies are found less commonly than in PV, but may also be utilized to monitor disease activity[3,15,70].

Direct immunoelectron microscopy (IEM) detects peroxidase-labeled antibodies attached to autoantigens in tissue that react with various agents to form electron-dense material[71]. Indirect IEM localizes pemphigus-associated antigens to the extracellular hemidesmosomes in the upper portion of the lamina lucida. This differs from MMP where IEM localizes immune deposits to the lower lamina lucida and lamina densa[56].

The detection of target antigen in OPV can be accomplished through immunoblotting and immunoprecipitation techniques, which identify unknown target antigens bound to autoantibodies. Although immunoprecipitation is less available and more difficult to perform, it is more sensitive than immunoblotting because it utilizes native protein as opposed to denatured protein substrates[52]. A standardized enzyme-linked immunosorbent assay can be utilized to measure autoantibody titers to both desmoglein 3 and desmoglein 1 with higher sensitivity compared to IIF[72]. This differs from MMP that demonstrates immunoprecipitation of various target antigens not including desmoglein 3 and 1.

Treatment: Before the availability of immunosuppressive therapy, mortality for PV reached up to 90% but has now dropped to 3.3% with the use of corticosteroids, cytotoxic drugs, and other biologic agents with immunomodulatory effects[68,73]. Ocular lesions appear to be more responsive to treatment compared to other sites of mucosal involvement[51].

First line therapy for PV includes corticosteroids. Corticosteroids may be used alone or in conjunction with corticosteroid-sparing immunosuppressive agents to allow gradual weaning of steroids to decreased doses or alternate-day therapeutic regimens[60,74,75]. Side effects of corticosteroid treatment most commonly seen include weight gain, cushingoid features, infection, gastrointestinal bleeding, hypertension, hyperglycemia, osteoporosis, and acne[73]. To avoid the occurrence of these side effects, corticosteroids may be used concurrently with sulfone derivatives, immunosuppressive agents, antimetabolites, alkylating agents, and biologic agents.

A total of 10 studies encompassing 39 OPV patients and treatments with multi-drug systemic regimens were found in the literature[34,35,49,55,58-63]. These regimens most commonly consisted of: systemic steroids (82% or 32/39), dapsone (18% or 7/39), azathioprine (13% or 5/39), cyclophosphamide (13% or 5/39), mycophenolate mofetil (10% or 4/39), methotrexate (10% or 4/39), and

rituximab (5% or 2/39). Additionally, adjunctive topical drops were utilized in 40% (4/10) studies, of which the most commonly used were topical steroids (8% or 3/39) followed by topical diclofenac, naphazolin, zinc sulphate, chloramphenicol, cyclosporine, and tacrolimus (each 3% or 1/39). Surgical procedures for treatment consisted of penetrating keratoplasty (8% or 3/39) and manual removal of pseudomembranes (3% or 1/39). Overall, the average duration of treatment was 42.1 d.

Prognosis: Factors associated with worse prognosis in PV include ethnicities such as Indo-Asian and Jewish origin, younger age of onset, higher initial intercellular antibody titer, and higher initial desmoglein 3 titer[76,77]. If left untreated, the spread of erosions and bullae leads to severe infection and eventually death with 50% mortality at 2 years and almost 100% mortality at 5 years[78]. If treated, cutaneous lesions heal with re-epithelialization leaving residual hyperpigmentation without scarring.

Of 10 studies encompassing 39 OPV patients treated with multi-drug systemic regimens, outcomes of treatment included remission defined as regression of ocular lesions (54% or 21/39), remission of ocular lesions with persistence of other systemic manifestation of disease (13% or 5/39), persistence of ocular lesions without progression (8% or 3/39), progression of ocular lesions (18% or 7/39), and recurrence of ocular lesions (8% or 3/39). Overall, average follow-up time was 26.6 mo[34,35,49,55,58-63].

Paraneoplastic pemphigus

Epidemiology: Paraneoplastic pemphigus (PNP), also known as paraneoplastic autoimmune multiorgan syndrome, is a rare intraepithelial blistering disease that occurs less commonly than MMP. PNP occurs at an unknown incidence although approximately 250 cases have been reported in the literature[79]. PNP typically affects patients aged 45-70 years old although cases have occurred in children[80] and males appear to be more commonly affected compared to females[81]. The disease affects all races, but a higher predilection is associated with certain HLA subtypes such as the DRB1*03 allele in Caucasian patients and HLA Cw*14 in Chinese patients[82,83]. Additionally, PNP is strongly associated with underlying malignancy, more often lymphoproliferative neoplasms (chronic lymphocytic leukemia and non-Hodgkin Lymphoma), and the type of malignancy may be related to the ethnic background of the patient. A high prevalence of PNP associated with Castleman's disease and follicular dendritic cell sarcomas in Chinese and Korean patients has been documented[84].

Pathophysiology: PNP is an intraepithelial blistering disease characterized by autoantibodies that bind desmoglein 3, similarly to the pathogenic mechanism seen in PV. However, in PNP, the autoantibodies bind to epitopes distributed throughout the extracellular domain of desmoglein 3 as opposed to solely the N-terminal extracellular domain in PV[85]. Additionally, PNP has multiple other target antigens including the plakin protein

family that connects cytoskeletal networks. These target antigens include desmoplakin I (250 kDa), desmoplakin II (210 kDa), bullous pemphigoid antigen 1 (BPAG1, 230 kDa), envoplakin (210 kDa), periplakin (190 kDa), plectin (500 kDa), desmocollin 2 (105 kDa), desmocollin 3, α2-macroglobulin-like-1 (A2LM1, 170 kDa), desmoglein 1 (160 kDa), and desmoglein 3 (130 kDa)[85-93]. This differs from MMP that is characterized by subepithelial lesions due to autoantibodies directed against various target antigens not including the plakin protein family.

Clinical features: PNP is a systemic autoimmune disease that occurs mostly in the setting of lymphoproliferative malignancies. PNP manifests as persistent painful erosions of mucous membranes and chronic cicatricial conjunctivitis clinically identical to MMP. Anhalt *et al*[94] termed paraneoplastic pemphigus to refer to a distinct clinical, histopathologic, and immunopathologic condition that included 5 criteria, of which Camisa *et al*[95] later revised these into major and minor criteria (Table 3)[69,94,95].

The distinguishing clinical manifestations that differentiate PNP include a painful and intractable ulcerating stomatitis that extends to the vermillion surface of the lips[45,96,97] and tense bullae that develop on the palms and/or soles[98]. Cutaneous manifestations of PNP are widely variable and can include superficial vesicles and flaccid blisters (pemphigus-like); scaly erythematous papules with or without tense blisters (bullous pemphigoid-like); polymorphic lesions (erythema multiforme-like); disseminated red scaly papules (graft *vs* host disease-like); or small violaceous papules with predominant mucosal membrane involvement (lichen planus-like)[99].

A total of 12 studies comprising 23 PNP patients with ocular involvement were found in the literature[84,94,100-109]. The most common ocular symptoms included the following: conjunctival erosions (68% or 15/22), conjunctivitis (45% or 10/22), pseudomembrane formation (27% or 6/22), conjunctival scarring (23% or 5/22), symblepharon formation (18% or 4/22), conjunctival shrinkage (14% or 3/22), forniceal foreshortening (9% or 2/22), corneal epithelial defect (5% or 1/22), and corneal perforation (5% or 1/22). Concomitant systemic manifestations included oral involvement (100% or 23/23) and cutaneous involvement (96% or 22/23). The most common initial presentation of disease was oral involvement (94% or 17/18) followed by ocular (17% or 3/18) and cutaneous (11% or 2/18) lesions.

Additionally, PNP is associated with malignant neoplasms. PNP may be the initial manifestation of a previously undetected malignancy in up to 33% of cases[81,102,110] or PNP may arise years after a patient has already undergone treatment for a previously known malignancy[111]. Of 12 studies comprising 23 PNP patients with ocular involvement, associated malignancies included the following: non-Hodgkin lymphoma (43% or 10/23), Castleman's disease (22% or 5/23), follicular dendritic cell sarcoma (22% or 5/23), peripheral T cell lymphoma (4% or 1/23), thymoma (4% or 1/23), and squamous cell lung carcinoma (4% or 1/23)[84,94,100-109]. Others have reported

Table 3 Diagnostic criteria for paraneoplastic pemphigus

Diagnostic criteria for paraneoplastic pemphigus	
Anhalt *et al*[94]	Camisa *et al*[95]
Painful mucosal and polymorphous skin erosions that involves the trunk, extremities, palms, and soles of a patient with a neoplasm	Major criteria
	Polymorphous mucocutaneous eruption
Histological changes including intraepidermal acantholysis, keratinocyte necrosis, and vacuolar interface dermatitis)	Concurrent internal neoplasia
	Specific serum immunoprecipitation pattern
Direct immunofluorescence findings of IgG and complement localized to the intercellular regions of the epithelium in a linear or granular fashion at the basement membrane zone	Minor criteria
	Histology demonstrating acantholysis
	Direct immunofluorescence demonstrating intercellular and basement membrane staining
Circulating autoantibodies that bind to stratified squamous epithelium as well as simple, columnar, and transitional epithelium	Indirect immunofluorescence staining with rat murine epithelium
Immunoprecipitation studies that demonstrate the presence of autoantibodies directed against a complex of five proteins of 250, 230, 210, 190, and 170 kDa	Diagnosis: All three major or two major and two minor required to diagnosis paraneoplastic pemphigus

the occurrence of chronic lymphocytic leukemia in up to 18%-29% of cases[97,108] as well as adenocarcinoma of various solid organs including the pancreas, colon, breast, prostate, and liver and squamous cell carcinoma of the tongue, cervix, and kidney[107,108,112-116].

Diagnostic studies: Histopathological studies utilizing hematoxylin-eosin staining in conjunctival biopsies from patients with PNP include the characteristic feature of pemphigus - vacuolization of basal cells and suprabasilar intraepithelial acantholysis[109]. Specimens taken from cutaneous biopsy may be widely variable and reflect the clinical polymorphisms present in this disease. Histopathologic features that are unique to PNP and are not found in other pemphigus subsets include vacuolar degeneration of basal keratinocytes with lichenoid or lymphohistiocytic infiltration as well as apoptotic keratinocytes located throughout the epidermis[84,94]. These changes differentiate PNP from MMP where changes occur exclusively at the basement membrane zone with subepithelial conjunctival shrinkage; inflammatory infiltrate involving lymphocytes, macrophages, and plasma cells; and squamous metaplasia progressing to parakeratosis and keratinization of conjunctival epithelium[56,68].

DIF studies show IgG and complement (C3) distributed both intercellularly and at the basement membrane zone in a linear or granular distribution[98]. This differentiates PNP from other types of pemphigus where only intercellular deposits are found and from MMP where only subepithelial deposits are found. Histological examination of biopsy parallels the clinical phenotype categorization and may demonstrate suprabasal acantholysis; keratinocytic dyskeratosis, apoptosis, and necrosis; vacuolization of the basal layer; or a lichenoid appearance seen along the dermal-epidermal junction[117,118].

IIF in PNP demonstrates autoantibodies binding to a variety of epithelium including simple columnar, transitional, respiratory, gastrointestinal, and myocardium[88]. This differentiates PNP from PV where autoantibodies against desmoglein 3 are restricted to stratified squamous epithelial tissues and from MMP where autoantibodies are found only in the epidermal basement membrane zone.

Additionally, IIF using murine bladder and tongue or monkey esophagus distinguishes PNP because these tissues express desmoplakin 1 without desmoglein 3[81,119]. When IIF results are indeterminate, western blotting and immunoprecipitation may provide more sensitive techniques. Detection of autoantibodies to envoplakin and periplakin is most specific followed by desmoplakin I and II[79].

Utilization of IEM enables visualization of autoantibodies binding to desmosomes, hemidesmosomes, and spreading along the keratinocyte cell surface including the lamina lucida[120,121].

Immunoprecipitation demonstrating polyclonal autoantibodies that target a complex of plakin proteins is best for diagnosis and is a major criterion for diagnosis of PNP[95,122]. The combination of rat bladder IIF and immunoblotting has equally sensitive results that are highly specific; this can be utilized as an alternative approach to immunoprecipitation for serologic diagnosis[122].

Treatment: Treatment for PNP is directed towards relieving symptoms of PNP as well as treating the underlying neoplasm. Resection of benign neoplasms may lead to improvement or remission of cutaneous lesions in 6-11 wk[86,105,118]. However, the disease often progresses despite surgical excision and chemotherapy[118]. Aside from treating the associated neoplasm, management of PNP includes corticosteroids and adjunctive corticosteroid-sparing agents to decrease the incidence of side effects. Concurrent use of corticosteroids with sulfone derivatives, immunosuppressive agents, antimetabolites, alkylating agents, and biologic agents may occur although PNP is much less responsive to therapy compared to other forms of pemphigus[123]. In general, skin lesions are usually more responsive whereas mucosal lesions are highly refractory to treatment and recover more slowly[57,86,124].

A total of 12 studies encompassing 23 PNP patients with ocular involvement were found in the literature[84,94,100-109]. Treatment regimens most commonly consisted of: systemic steroids (81% or 13/16), rituximab (31% or 5/16), cyclophosphamide (31% or 5/16), cyclosporine (25% or 4/16), azathioprine (25% or 4/16), IVIG (25% or 4/16), vincristine (25% or 4/16), chlorambucil (19% or 3/16), and fludarabine, doxorubicin, bleomycin, double filtration

Table 4 Overview of mucous membrane pemphigoid and pseudopemphigoid as caused by the pemphigus disease

	MMP	Pseudopemphigoid	
		PNP	OPV
Location	Subepidermal	Intraepidermal	Intraepidermal
DIF	IgG/IgA/IgM/C3	IgG/C3	IgG/C3
IIF on salt-split skin	Dermal, epidermal, or combined depending on antigen	Not applicable	Not applicable
IEM: ultrastructural location of antigen	Lamina lucida	Hemidesmosomes	Desmosomes
	Lamina densa	Desmosomal plaques	
	Sublamina densa (anchoring fibrils)	Lamina lucida	
Immunoblot: determination of antigen	Bullous pemphigoid antigen 1 (Bullous Pemphigoid 230)	Plakin protein family:	Desmoglein 1 (160 kDa)
	Bullous pemphigoid antigen 2 (Bullous Pemphigoid 180, type XVII collagen)	Desmoplakin I (250 kDa)	Desmoglein 3 (130 kDa)
	Type VII collagen (290 kDa)	Bullous pemphigoid antigen 1 (230 kDa)	
	Laminin332, epiligrin, or laminin 5 $\alpha 3\beta 3\gamma 2$ (165, 145, 140, 105 kDa)	Desmoplakin II and envoplakin (210 kDa)	
	Laminin 6 (α3)	Periplakin (190 kDa)	
	Integrin beta 4	Plectin (500 kDa)	
	45 kDa epithelial protein	Desmocollin 2 (105 kDa)	
	130 kDa epithelial protein	Desmocollin 3	
	140 kDa epithelial protein	α2-macroglobulin-like-1	
	205 kDa epithelial protein	(A2LM1, 170 kDa)	
	168 kDa epithelial protein	Desmoglein 1 (160 kDa)	
	Uncein	Desmoglein 3 (130 kDa)	
	LAD-1 (97/120 kDa)		
Increased malignancy	Yes - solid malignancies (laminin 332 subtype)	Yes - lymphoproliferative malignancies	--

MMP: Mucous membrane pemphigoid; PNP: Paraneoplastic pemphigus; OPV: Ocular pemphigus vulgaris; DIF: Direct immunofluorescence; IIF: Indirect immunofluorescence; IEM: Immunoelectron microscopy; LAD-1: Linear IgA bullous dermatosis autoantigen 1.

membrane plasmapheresis, methotrexate, and daclizumab (each 6% or 1/16). Additionally, adjunctive topical drops were utilized in 27% (3/11) of studies, of which the most commonly used were topical steroids (13% or 2/16) followed by topical tacrolimus (6% or 1/16). Surgical procedures consisting of resection of primary tumor occurred in 48% (11/23) of cases. Discontinuation of treatment due to side effects occurred in 13% of cases (3/23) and included plasmapheresis secondary to hypogammaglobulinemia and hypoalbuminemia; cyclosporine secondary to renal dysfunction; and cyclophosphamide, vincristine, prednisone, and rituximab regimen secondary to chemotherapy related side effects.

Prognosis: Of 12 studies encompassing 23 PNP patients with ocular involvement treated medically and/or surgically, outcomes included remission defined as regression of ocular lesions (30% or 7/23), remission of ocular lesions but persistence of other systemic manifestations (9% or 2/23), persistence of ocular lesions without progression (22% or 5/23), progression of ocular lesions (22%, 5/23), and recurrence of ocular lesions (4% or 1/23). Prognosis including death as final outcome occurred in 61% of cases (14/23) at an average 26 mo after onset of symptoms due to PNP[84,94,100-109]. Although reports of long-term survival have been described in the literature[104,125-128], others indicate that mortality rates may reach up to 90% with a mean survival of less than 1 year[128-130].

Death most commonly occurs secondary to malignancy, sepsis, or respiratory failure due to pulmonary involvement producing bronchiolitis obliterans[131,132]. Pulmonary involvement may occur and can continue to progress despite treatment with immunosuppressants, resection of malignancy, and improvement of other mucocutaneous symptoms[133]. Factors associated with worse prognosis in PNP include presence of erythema multiforme-like lesions, keratinocyte necrosis on biopsy specimens, and non-Hodgkin lymphoma patients with an increased risk of infection due to systemic chemotherapy and corticosteroids[128].

CONCLUSION

Pseudopemphigoid as caused by topical drugs and pemphigus disease may produce a chronic cicatricial conjunctivitis that can present clinically identical to MMP. In these cases, a vigilant history and examination combined with thorough diagnostic methods are needed to differentiate these diseases (Table 4). Distinguishing between the different causes of pseudopemphigoid that includes but is not limited to drug-induced cicatricial conjunctivitis, pemphigus vulgaris, and paraneoplastic pemphigus is paramount as there may be a poorer prognosis or a more severe clinical course unresponsive to medical management. Collaboration of the ophthalmologist with subspecialists such as the dermatologist, immunologist, and others involved in care of the patient is critical to prevent progression of the disease.

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