Autoimmune blistering diseases confined to the eye

Pintusorn Kungvalpivat MD,
Kumutnart Chanprapaph MD,
Varintorn Chuckpaiwong MD.

ABSTRACT:

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**DIVISION OF DERMATOLOGY, DEPARTMENT OF MEDICINE, FACULTY OF MEDICINE, RAMATHIBODI HOSPITAL, MAHIDOL UNIVERSITY, BANGKOK, THAILAND.*

***DEPARTMENT OF OPHTHALMOLOGY, FACULTY OF MEDICINE, RAMATHIBODI HOSPITAL, MAHIDOL UNIVERSITY, BANGKOK, THAILAND.*

Ophthalmic involvement in autoimmune bullous diseases (AIBDs) can lead to permanent visual loss and blindness. Ocular manifestation usually parallel to active mucocutaneous disease. Apart from mucous membrane pemphigoid (MMP), pure ocular involvement in other AIBDs is exceedingly rare. We report three cases of AIBDs consisting of immunoglobulin (Ig) A/IgG pemphigus, linear IgA disease (LABD) and pemphigus vulgaris (PV) in which all patients presented with chronic cicatrizing conjunctivitis, mimicking MMP, without skin involvement. Our first patient's conjunctival biopsy revealed separation of the stratified squamous epithelium with acantholysis. Direct immunofluorescence (DIF) demonstrated intercellular IgA deposition. Indirect immunofluorescence (IIF) was also positive for intercellular IgA. IgG enzyme-linked immunosorbent assay was positive for Desmoglein-1 (Dsg1) and negative for Anti-Dsg3. The diagnosis of IgA/IgG pemphigus was made. The second patient's conjunctival biopsy showed fibrosis, chronic inflammation at subepithelial junction with separation. DIF revealed linear basement membrane IgA, leading to the diagnosis of LABD.

From: Division of Dermatology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
Corresponding author: Kumutnart Chanprapaph MD., email: kumutnartp@hotmail.com

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Conjunctival biopsy of the final case showed chronic conjunctivitis with focal suprabasal separation of the stratified squamous epithelium. Immunoperoxidase showed intercellular IgG and C3. IIF was positive for IgG. The final diagnosis was ocular PV. All patients received systemic corticosteroids together with azathioprine or dapsone with satisfactory results. To the best of our knowledge, this is the first reported case for ocular IgA/IgG pemphigus. The presence pure ocular involvement is extremely rare for LABD and PV. We emphasize that AIBDs exclusive to the eye is a diagnostic dilemma. Early recognition and treatment can halt the progression and prevent permanent visual loss.

Key words: Cicatricial conjunctivitis IgA/IgG pemphigus, Linear IgA bullous dermatosis, Pemphigus Vulgaris, Cicatricial conjunctivitis, Anti-Desmoglein

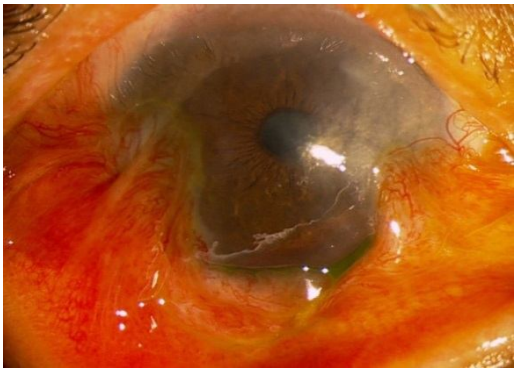

Figure 1 The right eye of patient 1 showing bilateral advance fibrovascular tissue extending from bulbar conjunctiva across the limbus and tightly adhere to corneal surface in both nasal and temporal sides. The surrounding conjunctiva showed marked injection and accompanying by deep corneal stromal vessels.

Introduction

Autoimmune bullous diseases (AIBDs) can involve the ocular mucous membranes. The initial phase of ocular involvement is characterized by conjunctival inflammation, consequence from deposition of immunoglobulin and/or complement at the intercellular junction or basement membrane zone of conjunctival epithelium. Chronic conjunctival inflammation may progress to subepithelial fibrosis and possibly lead to alteration of conjunctival architecture causing chronic cicatrizing conjunctivitis. Major ophthalmic involvement is most commonly seen in mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita, linear IgA bullous dermatosis (LABD), pemphigus vulgaris (PV) and paraneoplastic pemphigus[1, 2] which may lead to permanent reduction of visual function and blindness.

IgA pemphigus is a rare autoimmune intraepidermal blistering disease with circulating IgA autoantibody that targets cell surface component of epidermis. Pure ocular involvement of IgA pemphigus has never been reported in the literature. LABD is an autoimmune subepidermal bullous disorder that affects skin and mucous membranes. The presence of ocular

involvement as an exclusive manifestation of the disease is exceedingly rare[3, 4]. PV is an autoimmune blistering disease of the skin and mucous membranes that is characterized histologically by intraepidermal blisters due to acantholysis. It is rarely associated with ocular involvement[5]. Hence, we report 3 cases of AIBDs consisting of IgA pemphigus, LABD and PV in patients presenting with chronic cicatrizing conjunctivitis without cutaneous or other mucous membrane involvement.

Case Reports

Patient 1

A 54-year-old Thai man came to see the ophthalmologist with complaint of blurred vision and red eyes on both sides for 7 years. He was diagnosed as pterygium and performed surgical excision several times with failure to impede any recurrences. The examination demonstrated bilateral advance fibrovascular tissue which extended from bulbar conjunctiva across the limbus and tightly adhere to corneal surface in both nasal and temporal sides. The tissue precluded both visual axis and lead to visual impairment. The surrounding conjunctiva showed marked injection and accompanied by deep corneal stromal vessels [Figure 1]. Simple fibrovascular excision was done on one eye, followed by rapid recurrence and severe conjunctival inflammation. Intraocular pressure had raised secondary to prolong topical steroid treatment. Neither the skin nor oral mucosa was involved. Conjunctival biopsy was performed and processed for routine histological examination for hematoxylin-eosin stain which revealed acantholysis of the stratified squamous epithelium at 2 levels, the subcorneal and suprabasilar layer, and chronic inflammatory cells infiltration. Direct immunofluorescence (DIF) demonstrated intercellular deposition of IgA throughout the stratified squamous epithelium. Indirect immunofluorescence (IIF) was positive 1:8 for IgA with intercellular pattern. IgG enzyme-linked immunosorbent assay (ELISA) was strongly positive for Desmoglein-1 (Dsg1) with an anti-Dsg1 index of 130 U/ml while IgG Anti-Dsg3 was negative. These results are consistent with IgA pemphigus with dual autoantibody reactivity (IgA/IgG) of the conjunctiva. Due to unfamiliarity of the diagnosis, conjunctival biopsy and immunomorphologic examination were repeated and revealed identical IgA intercellular deposition throughout the entire stratified squamous epithelium, while IgG was constantly negative. Owing to reported association with monoclonal gammopathy with IgA pemphigus, we evaluated the patient's serum and urine electrophoresis and the results were negative. Systemic corticosteroids (prednisolone 40 mg/day), topical steroids and dapsone (100 mg/day) were initiated. After 2 months of treatment, conjunctival

inflammation persisted, hence, dapsone was discharged and azathioprine (100 mg/d) was commenced. To determine the therapeutic response, in addition to recording of patient's conjunctival disease activity, the titer of IgG Anti-Dsg1 was monitored at various intervals. After 4 months of treatment, the patient was clinically stable, and his visual acuity improved to some extent. Anti-Dsg1 titer decreased from 130 to 20.63 U/ml and IIF IgA titer was decreased from 1:8 to 1:2.

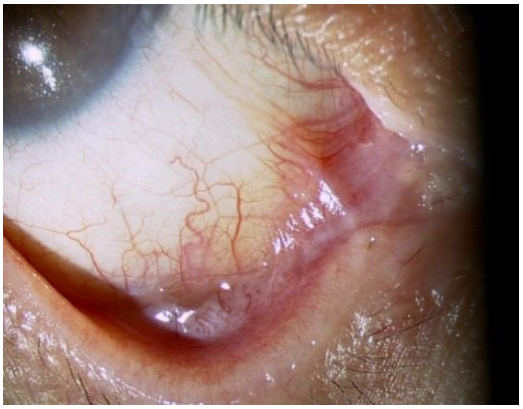

Figure 2 The left eye of patient 2 revealed trichiasis and cicatricial entropion, streak-like epithelial defect with generalized corneal edema and dense scarring. The surrounding conjunctiva showed marked ciliary injection and accompanying by deep corneal stromal vessels.

Patient 2

A 63-year-old Thai man had 1-year history of uncharacterized bilateral chronic conjunctivitis diagnosed with recurrent herpes simplex keratoconjunctivitis. Topical antiviral eye ointment had been ineffective. The review of systems revealed history of cardiac arrest due to coronary artery disease undergone coronary artery bypass grafting 3 years ago, gouty arthritis and mild renal insufficiency. The patient stated that he had experienced redness, pain, and reduction in his visual acuity especially on the left eye during the past year. Ophthalmologic examination revealed bilateral trichiasis and cicatricial entropion, streak-liked epithelial defect with generalized corneal edema and dense scarring of left eye leading to visual impairment. The surrounding conjunctiva showed marked ciliary injection and accompanying by deep corneal stromal vessels [Figure 2]. Symblepharon was apparent at the right lower fornix without conjunctival hyperemia. The patient's skin, oral cavity and genitalia were normal. Conjunctival biopsy showed fibrosis, chronic inflammation at epithelium with minimal separation at subepithelial junction. DIF revealed linear deposition of IgA along the basement membrane zone. IIF was negative. The diagnosis of pure ocular LABD was made. Dapsone (100 mg/day) was initiated as the sole primary systemic therapy in adjunction to topical steroids to control inflammation, which resulted in partial improvement. Four months later, the patient complained of decrease visual acuity, low dose

systemic corticosteroids (prednisolone 15 mg/day) was administered in addition to dapsone, significant improvement of conjunctival symptoms was achieved thereafter.

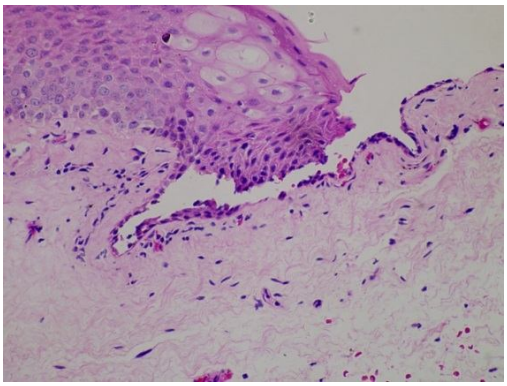

Figure 3 Histologic section of the conjunctiva of patient 3 showing focal suprabasal separation with acantholyis. (Hematoxylin-eosin stain; original magnification:x40)

Patient 3

A 51-year-old woman visited the ophthalmology department for 10-year history of progressive bilateral visual impairment, leading to blindness of the right eye. She denied any underlying medical illness. Ophthalmic examination demonstrated total corneal haziness, conjunctival keratinization, corneal stromal neovascularization and marked injection of conjunctiva with symblepharon of the right eye. The left eye showed corneal scaring, neovascularization, and marked conjunctival injection. At the time of initial consultation, the patient did not have erosion of skin or mucosa. Conjunctival histopathology revealed chronic conjunctivitis with focal suprabasal separation and acantholysis of the stratified squamous epithelium [Figure 3]. Due to technical error and placement of biopsy tissue in formalin, we were unable to perform conventional DIF and we did not justify a new conjunctival biopsy. Conjunctival specimen was sent for immunoperoxidase study instead and showed intercellular deposition of IgG and complement 3. IIF was positive 1:16 for IgG in an intercellular pattern. Anti-Dsg1 and Anti-Dsg3 were both negative. The clinical manifestation and biopsy results were concluded to ocular PV. Moderate dose systemic corticosteroids (prednisolone 40mg/day) with azathioprine (50 mg/day) were commenced which ceased the disease progression on the left eye.

Discussion

Exclusively, all of our patients presented with isolated chronic cicatrizing conjunctivitis, mimicking MMP clinically, without skin or other mucous membrane involvement. They were diagnosed with ocular IgA/IgG pemphigus, LABD and PV, respectively.

The term IgA pemphigus refers to a group of AIBDs with recalcitrant vesiculo-pustular eruption on the trunk, extremities, and intertriginous areas[6]. The involvement of mucous membrane has been rarely described[7, 8]. To the best of our knowledge,

ocular involvement has never been reported. IgA pemphigus is generally classified into 2 subtypes: subcorneal pustular dermatosis (SPD) type and the intraepidermal neutrophilic (IEN) type[9]. In SPD type, histology shows subcorneal pustules. DIF and IIF are positive for IgA, often localized in the superficial epidermis. Desmocollin1 has been identified as the autoantigen. In IEN type, histology of these patients usually demonstrates intraepidermal pustule, with or without acantholysis. DIF and IIF are positive for IgA throughout the epidermis. The targeted antigen is not clearly classified although Dsg1 or Dsg3 was identified in a few cases[10]. Amagai had proposed a classification of four subgroups of IgA pemphigus based on antigen determination: SPD type (Dsc1), IEN type (unknown), pemphigus foliaceous (PF) type (Dsg1), and pemphigus vulgaris (PV) type (Dsg3)[11].

In our first patient, the combination of clinical presentation, histological results, both DIF and IIF findings and ELISA for Dsg1 and Dsg3 indexes caused a diagnostic dilemma. The patient lacked skin and other mucosal involvement in which immunohistopathological findings may guide to the diagnosis. The histological results of the conjunctival specimen showed marked acantholysis, intraepidermal blister of the stratified squamous epithelium at 2 levels, the subcorneal and suprabasal layer, resembling PV and pemphigus foliaceous, respectively. Neutrophilic infiltration, a typical finding of IgA pemphigus, was unidentifiable in this patient's conjunctival biopsy. However, the results of DIF studies, repeated 3 times of 2 conjunctival biopsies, were consistent with IgA pemphigus. IIF microscopy, using normal human skin as substrate, detected IgA depositing with intercellular pattern, confirms the diagnosis of IgA pemphigus. We further investigated IgG ELISA, which was strongly positive for Dsg1, while IgG Anti-Dsg3 was negative. Unfortunately, IgA autoantibody testing to Dsg by ELISA was not available and we did not have a diagnostic tool to detect IgA anti-desmocollin autoantibody. Nevertheless, by constantly identifying IgA deposition in DIF and IIF and a high titer of IgG anti Dsg1, we believed that this patient had ocular IgA/IgG pemphigus, a dual autoantibody reactivity, and possibly pemphigus foliaceous type of IgA pemphigus, with Dsg1 as the target antigen, as described by Amagai[11]. There were several reports of dual IgA/IgG pemphigus in the literature involving skin, oral mucosa, esophagus and colon[7,10,12]. Also, there were cases of IgA pemphigus showing IgG anti Dsg1 and Dsg3, conversely, circulating IgA anti Dsg1 or Dsg3 were also found in patients with classic IgG pemphigus, suggesting that a spectrum of disease may co-exist.[13] The lower expression of Dsg1 in mucosa, together with the higher sensitivity of ELISA compared to DIF, may explain why ELISA result

was strongly positive while IgG in DIF was negative in our first case. Both IgA and IgG antibodies has been demonstrated in keratinocyte cell surface in a unique case of paraneoplastic pemphigus with the presence of ocular mucosal lesion[11]. Never has both IgA and IgG autoantibodies against conjunctival stratified squamous epithelium and IgG against Dsg1 been reported before. Unlike the classical IgA pemphigus with predominant neutrophil infiltration, it is not surprising that this patient was unresponsive to dapsone. The combination of high dose systemic steroids and azathioprine gave promising therapeutic results clinically. Furthermore, anti-Dsg1 titer, a well-recognized predictor to the disease activity, declined significantly corresponding to this patient's clinical improvement.

LABD is a rare autoimmune disease, characterized by subepidermal blistering that may affect the skin and/or mucous membrane. Patients may present with annular or group of papules, vesicles, and bullae, symmetrically distributed on extensor surface. Mucous membrane involvement in LABD is presented in 67% of the patients[14]. The estimate incidence of ocular involvement in LABD is 50-60%[2]. However, pure ocular disease is exceptionally rare, with only a few reports in the literature[3, 4]. Initial symptoms are irritation, redness, dryness, light sensitivity and blurred vision. Unlike skin and oral mucosa, the process may deteriorate consequence in severe and irreversible cicatricial conjunctivitis, indistinguishable from that of cicatricial pemphigoid. The presence of linear IgA deposits along the dermal-epidermal basement membrane is characteristic of this condition. Circulating antibodies are generally absent. In our second patient, DIF revealed linear deposition of IgA along the basement membrane zone. IIF was negative. The results were consistent with LABD. After 10 months of follow up, the patient remained free of skin and other mucosal involvements. We treated our patient with dapsone and prednisolone with considerable improvement. However, prior to treatment, the patient already had corneal scar and decreased visual acuity, indicating that the disease was in a late stage.

PV is an autoimmune vesiculobullous mucocutaneous disease that affects the skin and all stratified squamous epithelium. Histological characteristic of PV is acantholysis, suprabasal separation of the epidermis and by the presence of autoantibodies against Dsg1 and 3. Oral mucosa is the most common affected area in PV. Involvement of the pharynx, larynx, esophagus, anal canal, genital mucosa and the eyes are uncommon. In a recent retrospective study of 167 patients with PV, ocular involvement occurred in 14.3% and was not the solely mucosal manifestation[15]. Most of ocular involvement occurred during flares of mucocutaneous

pemphigus and usually preceded by PV lesions at other sites with mean period of 33.7 months. There was one report which ocular symptoms preceded the other manifestation of PV. The duration of eye symptoms prior to the diagnosis of PV varied from a few days to 9 months[16]. Typical ocular findings of PV are bilateral conjunctivitis and blepharitis[2]. Ocular involvement is usually transient, responds well to systemic immunosuppression without progression to scaring. In our last patient with ocular PV, after the moderate dose systemic corticosteroids and azathioprine, mild clinical improvement was achieved. Despite of treatment, bilateral conjunctival scarring persisted. This was probably due to the presentation at an advance stage of disease. After 18 months of consistent follow up, skin and other mucosal involvement were yet unapparent. Long term assessment is required to determine whether the patient will remain to have pure ocular PV.

Conclusion

We report 3 cases series of patients presenting with exclusively scarring conjunctivitis with the diagnosis of ocular IgA/IgG pemphigus, linear IgA bullous dermatosis and pemphigus vulgaris, respectively. Informatively, this report emphasizes dermatologist, ophthalmologist and physicians to be aware of these rare autoimmune bullous disease causing chronic cicatrizing conjunctivitis.

Disclosure Statement

The authors declare no conflict of interest.

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