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# **Advances in Non-neoplastic Conjunctival Disease - Inflammation, Degenerations and Deposits**

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### ***I. INTRODUCTION***

Significant advances have been made in the understanding of the genetic, molecular and immunologic aspects of various conjunctival disorders. The following conjunctival conditions have been selected because these advances translate into the ophthalmic pathology practice.

### ***II. IMMUNOLOGIC DISORDERS OF THE CONJUNCTIVA***

Numerous immunologic disorders can affect conjunctiva, including Stevens-Johnson syndrome and toxic epidermal necrolysis, ocular cicatricial pemphigoid, drug-induced pemphigoid, linear IgA bullous dermatosis, graft-vs-host disease, dermatitis herpetiformis, epidermolysis bullosa, lichen planus, paraneoplastic pemphigus, pemphigus vulgaris, pemphigus foliaceus, discoid lupus erythematosus, and phlyctenular conjunctivitis.

#### ***A. Mucous membrane pemphigoid (ocular cicatricial pemphigoid)***

**Definition.** Mucous membrane pemphigoid (MMP) and its subset, ocular cicatricial pemphigoid (OCP), is a type II immune-mediated hypersensitivity disorder, characterized by deposition of autoantibodies or complement to the components of basement membrane zone (BMZ) at the epithelial-subepithelial junction of mucous membranes and

occasionally at the dermo-epidermal junction of the skin. MMP is associated most frequently with autoantibodies against bullous pemphigoid (BP) antigen 180 (BP180) and less often with autoantibodies against BP230, laminin 5/epiligrin, laminin 6, uncein, type VII collagen and integrin subunits  $\beta 4$  and  $\alpha 6$ . OCP is associated mainly with autoantibodies against laminin 5 or  $\beta 4$  integrin.

**General features.** Binding of the antibodies to the target antigens at BMZ leads to complement activation, deposition, and inflammatory cell infiltration, manifesting clinically by sub-epithelial bullae formation and eventual cicatrization. Approximately 10 – 30% of patients with OCP demonstrate circulating IgG and IgA autoantibodies and display serologic activity against classical bullous pemphigoid antigens. Environmental triggers, such as topical medications, have been occasionally implicated in pathogenesis of OCP in genetically predisposed individuals (pseudopemphigoid). Rarely, cicatricial pemphigoid with its representative pathologic findings is observed as a sequela of SJS.

Recent research has focused on elucidating the reasons why despite similar immunopathology of BP and MMP, the MMP is associated with disabling scarring while BP is not. Some studies have found high levels of TGF- $\beta$  in OCP conjunctiva and implicated this cytokine in fibrogenesis. Other studies have suggested that high levels of expression of vascular cellular adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM-1) on endothelial cells in MMP leads to IL-4 mediated stimulation of perivascular fibroblasts to lay down scar tissue.

**Clinical features.** The disease most commonly begins in the sixth or seventh decade of life and has a slight female predominance. The mucous membrane affected are most frequently oral (85%) and conjunctival (60 – 80%), followed by nasal, nasopharyngeal, anogenital, skin (20%), larynx and esophagus. Patients with extraocular MMP have approximately 4% per year risk of developing ocular involvement. The conjunctival lesions begin in one eye, but bilateral involvement eventually occurs. The clinical course of OCP is characterized by slow relapsing-remitting progression from chronic conjunctivitis to sub-epithelial fibrosis, fornix foreshortening, symblepharon and ankyloblepharon formation, corneal ulceration and opacification, and ocular surface keratinization.

**Microscopic findings.** Histopathology of the conjunctiva in acute stage of OCP shows subepithelial bullae with predominantly subepithelial inflammatory infiltrate, composed mostly of T-lymphocytes, and to a lesser extent of macrophages, dendritic cells, and neutrophils. Later in the course of disease, squamous metaplasia and loss of goblet cells are observed within the epithelium. Activation of fibroblasts leads to abnormal deposition of extracellular matrix and collagen in the substantia propria in the cicatrizing stages of OCP.

**Immunohistologic findings.** Direct immunofluorescence, immunoperoxidase technique, and immunoelectron microscopy demonstrate deposition of IgA, IgG, IgM, and C3 along the BMZ, but negative conjunctival biopsy does not exclude the diagnosis of OCP.

*Positive predictive value of conjunctival biopsy with direct immunofluorescence is 60 – 80%. Repeat biopsy from extraocular site increases the chance of confirming a diagnosis of MMP.*

An antilaminin 5 ELISA with high specificity and sensitivity has been developed for circulating antilaminin 5 autoantibodies. Its role in pure OCP has yet to be determined.

#### **Differential diagnosis.**

1. Other causes of cicatrizing conjunctivitis: infectious (adenovirus, streptococcus, chlamydia, diphtheria, gonococcus), inflammatory (rosacea blepharoconjunctivitis) atopic keratoconjunctivitis, immune (Stevens-Johnson, toxic epidermal necrolysis, lichen planus, graft-versus-host disease), trauma (chemical, radiation), drug-induced pseudopemphigoid (topical ocular medications, systemic proctolol), post-surgical changes, sarcoidosis, lupus erythematosus.
2. Other bullous disorders: subepithelial (linear IgA disease, epidermolysis bullosa) and intraepithelial (paraneoplastic pemphigus, pemphigus vulgaris).
3. Ocular surface neoplasia.

**Treatment and prognosis.** Systemic immunosuppressive therapy is a mainstay of treatment and includes methotrexate, cyclophosphamide, dapsone, azathioprine, mycophenolate, and possibly IVIg. Topical corticosteroids may suppress the inflammatory response during acute exacerbations. Topical Vitamin A has been shown to reverse, to some extent, keratinization. Surgical therapies include correction of eyelid deformities, mucosal grafting for fornix reconstruction, cultivated corneal/limbal epithelial cell transplantation with amniotic membrane grafting, and keratoprosthesis.

### ***B. Linear IgA bullous disease***

**Definition and general/clinical features.** Linear IgA bullous disease (LABD) is an autoimmune sub-epithelial and sub-epidermal blistering disorder, which typically affects middle age adults, but has also been reported in children. Purely ocular form can occur, which is difficult to distinguish clinically and pathologically from OCP.

**Microscopic/immunohistologic findings.** Histopathology is similar to OCP. Immunofluorescence demonstrates linear deposition of IgA along BMZ. Deposits of IgG/C3 may also be present. Circulating IgA antibodies to BMZ, epidermal (epithelial), and dermal (stromal) sites can occur in some patients and are helpful in establishing the diagnosis of LABD.

**Treatment.** Treatment is similar to OCP.

### ***III. MEMBRANOUS AND PSEUDOMEMBRANOUS CONJUNCTIVITIS***

Membranous and pseudomembranous conjunctivitis occurs when the inflammatory discharge rich in fibrin coagulates on the conjunctival surface. A pseudomembrane lies superficially on the epithelial surface and can be peeled away without bleeding. In contrast, a true membrane incorporates conjunctival epithelium and/or granulation tissue

and peels away with bleeding. The formation of pseudomembrane or a membrane often reflects the difference in the intensity of an inflammatory process, and both membranes and pseudomembranes may be present at the same time.

The components of the exudate in membranes and pseudomembranes may point to an etiology of conjunctivitis. For example, acute membranes in immunologic and infectious disorders are composed of fibrinous exudate, neutrophils, and necrotic epithelial cells, while in ligneous conjunctivitis, lymphocytes, plasma cells, mast cells, and immunoglobulins predominate, with the background of extensive fibrin deposition and granulation tissue formation.

### ***Ligneous conjunctivitis***

**Definition.** Ligneous conjunctivitis is a rare, chronic, pseudomembranous disease, characterized by wood-like (pseudo)membranes developing on the ocular and extraocular mucosa.

*Although the term pseudomembrane is typically applied to ligneous lesion in clinical literature, it behaves as a true membrane by strict clinical and pathologic terminology.*

**General features.** Ligneous conjunctivitis typically presents in childhood as a chronic, bilateral, recurrent conjunctivitis, the hallmark of which is the formation of firm, wood-like, yellowish (pseudo)membranes. These are usually located on the superior tarsal conjunctiva, and less frequently on bulbar and inferior tarsal conjunctiva. Other mucous membranes can be less frequently involved, including oral cavity, respiratory tract, middle ear, and genital tract. Other conditions rarely associated with ligneous conjunctivitis include juvenile colloid milium and congenital occlusive hydrocephalus.

Affected patients have homozygous and compound-heterozygous mutations in the type-1 plasminogen gene. Although mostly sporadic, familial cases with autosomal recessive inheritance pattern have been reported. While many reports describe spontaneous onset of disease, ligneous-like conjunctival changes can occasionally occur after ocular surgery. The condition has also been described in patients without plasminogen deficiency, who have been treated with antifibrinolytic medications, such as tranexamic acid.

It is believed that mechanical injury or exposure to external irritants of mucosal tissues is followed by exudation of plasma proteins and immediate coagulation of fibrin(ogen), the main constituent of (pseudo)membranes. This fibrin(ogen)-rich clot provides local hemostasis at the site of tissue injury, but also provides the substrate for the generation of fibrin matrix, which in turn is replaced by granulation tissue. Normally, fibrinolysis and remodeling of granulation tissue complete wound healing. Plasminogen deficiency results in defective fibrinolysis, thus manifesting in arrest of wound healing at the stage of extensive fibrin deposition and granulation tissue formation.

### **Microscopic findings.**

1. Abundant subepithelial deposits of amorphous, acellular, eosinophilic, periodic acid-Schiff (PAS)-positive material, which consists of fibrin, immunoglobulin deposit (usually IgG), and mucopolysaccharides
2. Granulation tissue
3. Inflammatory infiltrate, which is rich in T-lymphocytes, although B-lymphocytes, plasma cells, and mast cells can also be observed
4. Occasionally, foreign material and bacteria have been demonstrated in the ligneous membranes, possibly providing the inciting stimulus for inflammatory response followed by ligneous membrane formation (debatable)
5. The surface of the ligneous membrane can lack normal epithelium and contains instead a collection of fibrin and inflammatory cells. This superficial layer may be scraped without bleeding, thus imparting a “pseudomembrane” characteristics to the superficial layer of the ligneous membrane.

**Treatment and prognosis.** Ligneous conjunctivitis is usually a self limited disorder. Serious ocular complications can result, however, including secondary infection and corneal ulceration with perforation. Treatment modalities include surgical excision of the membranes with or without adjunctive cryotherapy and amniotic membrane grafting, although recurrences are frequent. Anecdotal successes with topical corticosteroids, cyclosporine, heparin, purified plasminogen, and with intravenously administered purified plasminogen concentrate have been described.

## ***IV. DEGENERATIONS***

### ***A. Conjunctivochalasis (“chalasis” = relaxing, slackening in Greek)***

**Definition.** Isolated bilateral, condition in which redundant, non-edematous bulbar conjunctival tissue interposes between the globe and the lower eyelid, and protrudes over the lid margin.

**General features.** Conjunctivochalasis typically presents after 5<sup>th</sup> decade (average age ~70 years). The patients may be asymptomatic, or complain of dry eye, pleolacrimal or epiphora. Few reported cases have been associated with nasolacrimal duct obstruction. In severe forms, exposure keratopathy and marginal corneal ulceration may occur.

It is hypothesized that aging and actinic damage induce structural changes in the collagen and elastic fibers leading to conjunctival redundancy. Another theory postulates that inflammatory mediators and matrix metalloproteinases may contribute to the collagen and elastic fiber degradation leading to conjunctivochalasis. Increased levels of

metalloproteinases could be induced by poor tear clearance, particularly in the patients with nasolacrimal duct obstruction.

**Microscopic findings.** Several reports have identified varying histopathologic findings:

1. Fragmentation of elastic fibers and sparsely assembled collagen fibers in substantia propria; lymphangiectasis; no increased inflammation or epithelial changes\*\*\*
2. Increased chronic inflammatory infiltrate in the substantia propria
3. Actinic elastosis
4. Normal histology

\*\*\* The first observation is consistent with our experience with conjunctivas bearing a clinical diagnosis of conjunctivochalasis.

**Treatment and prognosis.** The condition is treated with resection of inferior limbal and bulbar conjunctiva.

## ***B. Pinguecula and pterygium***

**Definition.** Pingueculae and pterygia are common conjunctival lesions which typically occur in the temporal and nasal bulbar conjunctiva. Pinguecula appears as a yellow-white, often vascularized nodule, while a pterygium presents as a wing-shaped vascularized fold of conjunctival tissue, which has invaded the superficial cornea.

**General features.** Although pingueculae and pterygia traditionally have been viewed as conjunctival degenerations, this concept has been challenged by recent scientific evidence, which suggests that these lesions are non-malignant neoplasms. The pathogenesis of pingueculae and pterygia has been strongly correlated with environmental exposure (sunlight, wind, dust). Ultraviolet (UV) light (actinic exposure), in particular, is believed to be a strong inducer of these lesions. It is hypothesized that the optics of the anterior eye cause focusing of the scattered light at nasal or temporal limbus, accounting for the observed location of pingueculae and pterygia. The mechanisms proposed to explain growth of pterygia include UV-induced alteration of basal stem cells and resultant breakdown of limbal barrier, UV-induced loss of heterozygosity and loss of expression or function of tumor suppressor genes (e.g., P53), overexpression of cytokines (e. g., fibroblast growth factor, transforming growth factor- $\beta$ , tumor necrosis factor- $\alpha$ , vascular endothelial growth factor) which may lead to upregulation of matrix metalloproteinases, and viral (HSV, HPV) infection.

**Microscopic findings.** Histopathologically, pingueculae and pterygia display actinic elastosis, increased vascularity and inflammatory infiltrate within the substantia propria. Involvement of the superficial cornea and destruction of Bowman's layer distinguish pterygia from pingueculae. Actinic elastosis is recognized by gray or basophilic amorphous, vermiform, or hyalin degeneration of collagen fibers. These regions stain

with elastin (Verhoeff-van Giesen) stains, but the staining is not abolished by pre-digestion with elastase, supporting the conclusion that the material does not consist of true elastin fibers, but, rather, is elastin-like or elastotic. The conjunctival epithelium overlying pterygia or pingueculae may be normal or hyperplastic. Occasionally, pterygia and pingueculae can harbor ocular squamous surface neoplasia and benign and malignant melanocytic lesions, advocating for careful histopathological examinations of these lesions.

**Treatment and prognosis.** Treatment for pterygia and pingueculae ranges from symptomatic relief with topical lubricants and nonsteroidal anti-inflammatory drugs, to surgical excision with limbal conjunctival autograft and/or amniotic membrane grafts. Adjuvant mitomycin-C,  $\beta$ -irradiation, and anti-vascular endothelial growth factor agents are also occasionally used, particularly in pterygia with high risk of recurrence, and in recurrent pterygia. With sophisticated current surgical techniques the recurrence rate for primary pterygia is <10%.

## ***V. DEPOSITS***

The conjunctiva can be damaged by the use of topical and parenteral medications. Direct toxicity from active drug ingredients, drug metabolites, preservatives in drug vehicles, and deposition of drugs and their metabolites into the conjunctiva can occur. Compounds known to be actively accumulated in the conjunctiva include silver (basement membrane deposits), gold (all epithelial layers), mercury, amiodarone (epithelium), tetracycline and minocycline (within cystic inclusions), epinephrine (pigmented adrenochrome within cystic inclusions), quinacrine, and chorapromazine. Pigmentation of the conjunctiva has also been observed after long-term or high-dose therapy with antimalarial drugs and psychotropic medications. Several of drug-induced conjunctival deposits are discussed below.

### ***A. Tetracycline and minocycline-induced pigmentation***

**Definition and general features.** Tetracycline and tetracycline derivatives (especially minocycline) have been frequently associated with pigmentation of bones, teeth, skin, thyroid, and less frequently, of oral mucosa. Ocular manifestations of tetracycline and tetracycline derivatives-induced pigmentation are rare, and include scleral, retinal, and conjunctival pigmented deposits. Ocular manifestations usually appear after prolonged antibiotic use, but can be dose and duration independent.

The mechanisms of pigmentation in various tissues differ, but typically include chelation with calcium or iron and oxidation of antibiotic to melanin-like pigment. Conjunctival deposits accumulate in pseudoglands of Henle possibly from degenerated conjunctival cells or their secretions.

**Microscopic findings.** Pigmented and non-pigmented lamellated concretions are observed in pseudoglands of Henle. These concretions demonstrate yellow-green autofluorescence with blue light in unstained sections. Conjunctival concretions do not

bleach or stain with Fontana-Mason stain for melanin, do not stain with Perl's iron stain, and occasionally stain with Von Kossa stain for calcium

### **Differential diagnosis.**

1. Clinical: melanocytic conjunctival lesions and other deposits
2. Histopathologic: adrenochrome deposits

**Treatment and prognosis.** Conjunctival pigmentation is not reversible, but the deposits can be surgically removed. Pigmentation of non-ocular tissues is occasionally reversible after discontinuation of therapy. Screening of patients after 1 year of administration of minocycline is recommended, with discontinuation of therapy at the first sign of tissue pigmentation.

### ***B. Adrenochrome deposits***

**Definition and general features.** Long-standing administration of epinephrine compounds can lead to black or dark brown deposits in the conjunctiva and cornea composed of oxidized epinephrine, or adrenochrome.

**Microscopic findings.** Histopathologically, an amorphous pink material that stains positively with the Fontana Masson silver stain for melanin and bleaches with potassium permanganate is found within the conjunctival cysts.

**Differential diagnosis.** Melanocytic conjunctival lesions and other pigmented deposits, particularly tetracycline/minocycline.

**Treatment and prognosis.** Conjunctival pigmentation is not reversible by discontinuation of medication, but the deposits can be removed surgically.

### ***C. Mascara deposits***

**Definition and general features.** Gray subepithelial pigmentation in inferior conjunctival fornices, after use of certain brands of mascara. Deposits consist of ferritin particles, and possibly iron oxide and carbon

**Microscopic findings.** Granular, black, mostly extracellular particles in substantia propria. Demonstrate staining with Perl's iron stain. Do not bleach or stain with Fontana-Mason for melanin.

**Differential diagnosis.** Melanocytic conjunctival lesions and other pigmented deposits, particularly argyrosis, kohl deposits, or blood pigment.

**Treatment and prognosis.** Deposits are not reversed by discontinuation of mascara application.

#### ***D. Silver pigmentation: argyrosis (argyriasis)***

**Definition and general features.** Argyrosis results from prolonged environmental exposure to silver compounds in certain industries, ingestion of silver-containing solutions, topical administration of Argyrol eye drops, or after long-term application of eyelash tint. Gray-brown discoloration of the conjunctiva and deep cornea is observed clinically.

**Microscopic findings.** Histopathologically, stippled, granular, dark deposits are noted along the basilar epithelial cell basement membrane and in the superficial substantia propria.

**Differential diagnosis.** Melanocytic conjunctival lesions and other pigmented deposits, particularly mascara deposits, kohl deposits, or blood pigment.

**Treatment and prognosis.** Deposits are not reversed by discontinuation of medication.

#### ***E. Alkaptonuria (ochronosis)***

**Definition and general features.** Alkaptonuria is an autosomal recessive metabolic disorder caused by the deficiency of homogentisic acid 1,2-dioxygenase enzyme, which results in an increased level of homogentisic acid in serum. Oxidized homogentisic acid gives a characteristic bluish-black color to urine. Oxidized and polymerized homogentisic acid accumulates within the connective tissues (cartilage, skin, nails, and in the interpalpebral sclera, conjunctiva, and cornea), causing bluish-brown discoloration, referred to as ochronosis.

**Microscopic findings.** Ochronotic pigment is seen by light microscopy as variably sized, homogenous, amber globules or fiber-like structures in the cornea, conjunctiva, and sclera combined with degenerated stromal collagen. Similar to melanin, ochronotic deposits are bleached by potassium permanganate, but unlike melanin do not reduce silver substances. The deposits can be stained with elastic (Verhoeff-van Gieson's), crystal violet, rhodamine B, toluidine blue O, and Luxol fast blue stains.

**Differential diagnosis.** Melanocytic conjunctival lesions and other pigmented deposits, particularly adrenochrome deposits and tetracycline/minocycline-induced pigmentation.

**Treatment and prognosis.** Deposits are irreversible, but can be removed surgically. Treatment of underlying disease.

#### ***F. Amyloidosis***

**Definition.** Amyloidosis is a group of disorders caused by extracellular deposition of proteinaceous insoluble fibrils with a  $\beta$ -sheet structure derived from aggregation of misfolded proteins.

**General features.** Conjunctival amyloidosis typically presents in middle-aged and elderly patients as unilateral, diffuse, yellow-pink, vascular mass in palpebral/forniceal conjunctiva, frequently associated with hemorrhage. Bulbar conjunctival location and bilateral involvement are less frequently reported.

*Conjunctival involvement by amyloid deposits can be classified into the following broad categories:*

1. *Primary localized amyloidosis (localized amyloid light chain amyloidosis, AL)* – most common etiology of conjunctival amyloidosis; no association with systemic disease; caused by local deposition of monoclonal immunoglobulin light chains by usually benign B-cell or plasma-cell clone.
2. *Secondary localized amyloidosis* – less frequent; associated with antecedent local conjunctival trauma or inflammation (such as trachoma), and occasionally with localized conjunctival malignancy (plasmacytoma, B-cell lymphoma)
3. *Primary systemic amyloidosis (systemic amyloid light chain amyloidosis, AL)* – rarely involves conjunctiva – usually associated with light chain producing monoclonal gammopathy
4. *Hereditary amyloidosis* – rarely involves conjunctiva, A $\beta$ <sub>2</sub>M amyloidosis and ATTR amyloidosis
5. *Secondary systemic amyloidosis (reactive systemic amyloid A protein amyloidosis)* – rarely involves conjunctiva; associated with inflammatory/infectious diseases (such as rheumatoid arthritis, syphilis); of note, although systemic association can be found in the patients with conjunctival amyloidosis, no systemic amyloidosis is usually demonstrated

**Microscopic and immunohistochemical evaluation.** Homogenous, amorphous, eosinophilic material, which stains with Congo red stain and demonstrates apple-green birefringence and dichroism. Immunohistochemical evaluation of localized conjunctival amyloidosis shows monoclonal light chain deposits of IgD, IgA, or IgG. Rarely, a lymphoproliferative process or atypical plasma cell proliferation (such as plasmacytoma) can be observed in the adjacent conjunctival substantia propria and have to be worked-up appropriately.

**Differential diagnosis.** Clinical misdiagnosis of lymphoid tumor is frequent.

**Treatment and prognosis.** Systemic work-up to exclude systemic etiologies of amyloidosis is recommended, although it is typically negative. The risk of systemic amyloidosis in patients with conjunctival amyloidosis is approximately 6%. Treatment for primary localized conjunctival amyloidosis includes observation and conservative management with ocular lubricants, and excision of localized lesions or debulking of diffuse lesions in symptomatic patients.

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