Disorders of the conjunctiva

Applied anatomy:

The conjunctiva is a transparent mucous membrane lining the inner surface of the eyelids and the surface of the globe as far as the limbus. It is richly vascular, supplied by the anterior ciliary and palpebral arteries. There is a dense lymphatic network, with drainage to the preauricular and submandibular nodes corresponding to that of the eyelids. It has a key protective role, mediating both passive and active immunity. Clinically, it is subdivided into the following:

1 **The palpebral conjunctiva** starts at the mucocutaneous junction of the lid margins and is firmly attached to the posterior tarsal plates. The underlying tarsal blood vessels can be seen passing vertically from the lid margin and fornix.

2 **The fornical conjunctiva** is loose and redundant and may be thrown into folds.

3 **The bulbar conjunctiva** covers the anterior sclera and is continuous with the corneal epithelium at the limbus.
Histology:
Conjunctiva is consists of two layers:

1. **The epithelium** is non-keratinizing and around five cell layers deep (Fig. 5.1). Basal cuboidal cells evolve into flattened polyhedral cells before they are shed from the surface. Goblet cells are located within the epithelium and are densest inferonasally and in the fornices.

2. **The stroma** (substantia propria) consists of richly vascularized loose connective tissue. The adenoid superficial layer does not develop until about 3 months after birth, hence the inability of the newborn to produce a follicular conjunctival reaction. The deep fibrous layer merges with the tarsal plates. The accessory lacrimal glands of Krause and Wolfring are located deep within the stroma. Mucus from the goblet cells and secretions from the accessory lacrimal glands are essential components of the tear film.

The conjunctiva containing the following secreting glands and cells:

1. **Mucin secretors:** They are of three types:
   - a. Goblet cells.
   - b. Crypts of Henle: Found at upper part of tarsal plate.
   - c. Glands of Manz.

   **Function:** Lubrication.

   In destructive disorders e.g. autoimmune conjunctivitis (cicatricial pemphigoid or Steven Johnson syndrome), there is decrease in number of cells lead to decrease mucin secretion, while chronic inflammatory disorders increases the number of the cells with increase mucin secretion e.g. vernal keratoconjunctivitis.

2. **Accessory lacrimal glands:**
   - b. Wolfring.

   They are found deep in Stroma mainly at fornices.

**Clinical Evaluation of Conjunctival inflammation:**

The differential diagnosis of conjunctival inflammation depends on:

1. **Symptoms:**
Conjunctivitis: Has non-specific symptom such as: lacrimation, irritation, stinging, burning and photophobia (visual acuity is not affected as conjunctiva is away from visual axis and it is not a part of the optical system of the eye).

   If it is associated with keratitis, there will be pain, foreign body sensation and sometimes blurred vision (as the cornea is affected).

   In allergic conditions, the hallmark is *itching*, which also occurs in blepharitis (inflammation of lid margin) and keratoconjunctivitis sicca.
2- discharge:
   It is exudates filtered through conjunctival epithelium from dilated blood vessels with additional epithelial debris, mucus and aqueous tear.
   Discharge can be of the following types:
   a- Watery: Serous exudates and reflexly secreted tear. e.g.
      - Acute viral conjunctivitis.
      - Allergic conjunctivitis.
   b- Mucoid: usually seen in chronic inflammatory conditions when mucin secretion is increased: e.g.
      - Vernal conjunctivitis.
      - Keratoconjunctivitis sicca.
   c- Purulent: e.g. in Severe acute bacterial conjunctivitis.
   d- Mucopurulent: e.g. - Mild bacterial conjunctivitis.
      - Chlamydial infections.

3- Conjunctival Appearance:
   a- Conjunctival injection: Can give a clue in diagnosis although it is a non-specific feature, in which, the beefy-red conjunctiva suggests a bacterial cause (especially in the inferior fornix) while fish meat color suggests allergy.
   b- Subconjunctival haemorrhages: mostly associated with:
      - Viral infection, e.g.: Adenovirus, Acute haemorrhagic conjunctivitis.
      - Bacterial infection, e.g. Streptococcus pneumoniae.
   c- Follicular reaction: It is seen by magnification of slit-lamp. It is consists of hyperplasia of lymphoid tissue within the stroma, commonly occurs in inferior forniceal conjunctiva.
   Clinically: It is seen as multiple, discrete, slightly elevated lesions, reminiscent of small grains of rice. Each follicle is encircled (surrounded) by tiny blood vessels.
The main causes of follicular reaction are (differential diagnosis):
- Viral infections.
- Chlamydial infections.
- Parinaud oculoglandular syndrome.
- Hyper sensitivity to topical medications.

d- Papillary reaction: It is of less diagnostic value than follicular reaction. It is hyperplasia of conjunctival epithelium (surrounding a core of blood vessels) thrown into numerous folds or projections. Commonly occurs in the upper palpebral conjunctiva.
Clinically seen as a fine mosaic-like pattern of elevated polygonal hyperemic areas separated by paler channels.

Main causes are:
- Chronic blepharitis.
- Allergic conjunctivitis.
- Bacterial conjunctivitis.
- Contact lens-related problems.

e- Oedema (chemosis): whenever the conjunctiva is severely inflamed. It is transudation of fibrin and protein-rich fluid through the walls of the damaged blood vessels producing a translucent swelling of the conjunctiva.

f- Scarring: its causes are:
- Trachoma.
- Ocular cicatrical pemphigoid.
- Atopic conjunctivitis.
- Prolonged use of topical medications.

4- **Conjunctival membranes:**
   
a- **Pseudomembranes:**
   Coagulated exudates adherent to the inflamed conjunctival epithelium, peeled off leaving the epithelium intact (or healthy).

   - Severe adenoviral infection.
   - Gonococcal conjunctivitis.
   - Steve-Johnson syndrome.
   - Ligneous conjunctivitis, idiopathic, rare type of conjunctivitis.

b- **True membranes:**
   When inflammatory exudate is permeates the conjunctival epithelium. Removal of membranes may be accompanied tearing of the epithelium and bleeding.
   - Beta-haemolytic Streptococci.
   - Diphtheria.

5- **Lymphadenopathy:**
   The upper and lower lids, the eyeball and other structures drain into the preauricular and submandibular lymph nodes. These lymph nodes are swollen in these cases:
   - Viral infections.
   - Chlamydial infections.
   - Severe Gonococcal infections.
   - Parinaud syndrome.
Laboratory Investigations:
There is no need to do routine investigations for every patient presented with conjunctivitis unless has one of the following indications.

Indications:
- Severe purulent conjunctivitis.
- Follicular conjunctivitis (viral, chlamydial).
- Atypical conjunctivitis.
- Neonatal conjunctivitis.

Investigations:
1- Swabs: done after application of local anesthesia for Gram's stain, Giemsa.
2- Cultures.
3- Cytological: detects characteristic of cellular infiltration by immunological test.
4- Detection of viral or chlamydial antigens in conjunctival specimens.

Bacterial Conjunctivitis

1- Simple bacterial conjunctivitis:
It is a common disease, and usually it is self-limiting condition. Common causative organisms are:
- Staphylococcus epidermidis.
- Staphylococcus aureus.
- Other like Strptococcus pneumoniae, H. influenzae.

Symptoms:
- Acute onset of redness.
- Grittiness.
- Burning.
- Discharge.
- On morning, eyelids are stuck together due to accumulation of exudates during the night.
- Both eyes are usually involved.

Signs:
- The eyelids are crusted and oedematous (mild oedema).
- Mucopurulent discharge.
- Beefy-red injection, maximally in the fornices.
- Pseudoembranes in severe cases.
- Corneal involvement is uncommon.
* Blurred vision may occur due to mucus not due to corneal involvement.

Treatment:
- Usually resolves within 10-14 days and laboratory tests are not routinely performed.
- Bathe all discharge away.
- Topical drops (Antibiotics): Chloramphenicol, ciprofloxacin, ofloxacin, gentamicin, neomycin, tobramycin.
- Antibiotic ointments: it gives higher concentration for long period and usually given at night because it causes blurred vision. e.g. chloramphenicol, gentamicin, tetracydine, framycetin.

2- Neonatal bacterial Keratoconjunctivitis:
* bacterial conjunctivitis in neonate is one cause for Ophthalmia neonatorum (any infection of the conjunctiva within the first month after delivery).
- Usually appears at 1-3 days of life.
- it is rare condition.

**Signs:**
- Hyperacute presentation.
- Chemosis.
- Pseudomembranes.
- Corneal involvement.

**Treatment:** Systemic and tropical.

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**Viral Conjunctivitis**

1- Adenoviral keratoconjunctivitis:
- It is a highly contagious virus.
- Transmission is via respiratory or ocular secretion.
- Dissemination is by contaminated towels or equipments (e.g. tonometer: an instrument used to measure the intraocular pressure).
- Incubation period is 4-10 days; it is an occupational hazard of ophthalmologists (due to contamination of their hands with their patients).

**Conjunctivitis:**

**Presentation:** acute onset of watery discharge, redness, discomfort and photophobia, both eyes are affected in **60%** of cases.

**Signs:**
- Eyelids are oedematous.
- Watery discharge.
- Mild chemosis to moderate.
- Follicular reaction.
- Subconjunctival haemorrhages.
- Pseudomembranes. and - Lymphadenopathy is tender.

**Keratitis:**

Multiple, corneal sub epithelial infiltration and opacification.

**Treatment:**

a- Avoid transmission following examination of patients:
- Washing of hands.
- Meticulous disinfection of ophthalmologic instruments.
- Infected hospital personnel should not be in contact with patients.

b- Medications:

i- For conjunctivitis:
- **Spontaneous** resolution occurs within 2 weeks.
- Antiviral agents are ineffective (has no role).
- Topical steroids are indicated only in very severe inflammations and when Herpes simplex infection has been excluded. The treatment with steroids is symptomatic and supportive (not used routinely).

ii- For keratitis:
- Topical steroids, which are indicated only if the eye is uncomfortable or there is diminishing of the visual acuity by corneal sub epithelial infiltrates and opacifications, Steroids should not be used till exclusion of Herpes simplex infection.

Note: Steroids do not shorten the natural course of the disease but suppress the inflammation and relief symptoms.

2- Herpes simplex conjunctivitis:
   Conjunctivitis may occur in patients with primary Herpes simplex infection.
   - when the person catches the infection for the first time it is primary, after treatment, the virus get dormant in the trigeminal nerve ganglia. If for any reason, the person gets decrease immunity, then secondary herpes infection is developed.

Signs:
   - The eyelids and periorbital skin show unilateral herpetic vesicles, which may be associated with edema.
   - Watery discharge.
   - Ipsilateral follicular reaction.
   - Lymphadenopathy is tender.
   - Keratitis is uncommon.
   - Herpes simplex infection is very severe and it can lead to dendritic ulcer of the cornea.
   - No subconjunctival hemorrhage.

Treatment: Antiviral agent (as Acyclovir "Zovirax™") for 21 days to prevent keratitis.

Chlamydial Conjunctivitis

1- Adult chlamydial Keratoconjunctivitis:
   It is a sexually transmitted disease caused by the obligate intracellular bacterium Chlamydia trachomatis.
   - Patients are usually young and at least 50% have a concomitant genital infection (cervicitis in ♀ or urethritis in ♂).

Mode of transmission:
   - Autoinoculated from genital secretions.
   - Eye to eye spread is rare.

Incubation period: 1 week.

Presentation:
   Subacute onset of unilateral or bilateral mucopurulent discharge.
   * Without treatment conjunctivitis persists for 3-12 months. So, in chronic conjunctivitis we should think about Chlamydial Keratoconjunctivitis.
Signs:
- Eyelids are lightly oedematous.
- Mucopurulent discharge.
- Large follicles are formed at the inferior fornix.
- Lymphadenopathy (not tender).
- Keratitis is uncommon, if it occurs:
  * Epithelial Keratitis.
  * Subepithelial keratitis (opacities).
  * Marginal infiltrates (circumferential, i.e. involvement of the limbus and the periphery of cornea).
- Conjunctival scarring.
- Pannus (subepithelial corneal neovascular or fibrovascular membrane, i.e. affects the cornea not the conjunctiva).

Diagnosis:
  a- Clinical diagnosis.
  b- Laboratory tests, e.g.:
     i- Direct monoclonal fluorescent antibody microscopy.
     ii- Enzyme immunosorbant assay.

Treatment:
  a- Topical therapy: Tetracycline ointment 4 times/day for 6 weeks.
  b- Systemic therapy: One of the following:
     i- Doxycycline: 100mg X 1 for 1-2 weeks.
     ii- Tetracycline: 250mg X 4 for 6 weeks.
     iii- Erythromycin: 250mg X 4 for 6 weeks.

2- Neonatal chlamydial conjunctivitis:
- The most common cause of neonatal conjunctivitis (ophthalmia Neonatorum).
- It may be associated with systemic infection, e.g. otitis, rhinitis or pneumonitis.
- It is transmitted from the mother genital tract during delivery.

Presentation:
The child is usually presented between 5 & 19 days after birth.

Signs:
- Papillary conjunctivitis (there is no follicular reaction as the lymphoid tissue develops 3 months after delivery).
- Mucopurulent discharge.

Complications (if not treated):
There is Conjunctival scarring and superior corneal pannus.

Treatment:
  a- Topical Erythromycin.
  b- Oral Erythromycin, 250mg/kg body weight daily for 14 days.
3- Trachoma:
(Compare it with Adult Chlamydial Keratoconjunctivitis)
- It is an infection caused *Chlamydia trachomatis*.
- It is a disease of underprivileged populations with poor conditions of hygiene (low socioeconomic status).

**Transmission:**
Common fly is the major vector, currently trachoma is the leading cause of preventable blindness in the world.

**Presentation:** is usually during childhood.

**Signs:**
1- Follicular reaction.
2- Chronic conjunctival inflammation causes conjunctival scarring that involves the entire conjunctiva but most prominent on the upper tarsus.
3- Keratitis: either *
   - Superficial epithelial keratitis.
   - Anterior stromal inflammation and pannus formation.

4- Progressive conjunctival scarring: if it is severe lead to:
   * Destruction of lids.
   * Trichiasis: Misdirection of eyelashes towards the cornea causing rubbing of cornea, it is either true Trichiasis (due to affection of hair follicles) or pseudo (due to entropion of lid margin).
   * Entropion: the inward turning of the eyelid.
   * Dry eyes, due to destruction of conjunctival goblet cells, accessory lacrimal cells and lacrimal ducts of main lacrimal duct.

5- End-stage trachoma:
   * Corneal ulceration (due to dry eye and Trichiasis). Superficial corneal ulcers usually heal by regeneration so the cornea remains transparent, while deep ulcers do not regenerate but heal by fibroblasts to fibrous tissue leading to opacification, which lead to diminished visual acuity or even blindness in severe cases.

**World Health Organization (WHO) grading:**

- **TF:** Trachoma follicles (5 or more follicles in the superior tarsal conjunctiva).
- **TI:** Trachomatous intense inflammation diffusely involving the tarsal conjunctiva.
- **TS:** Trachomatous conjunctival scarring.
- **TT:** Trachomatous trichiasis touching the cornea.
- **CO:** Corneal opacity.

**Treatment of trachoma:**
- indicated for stages I & II (TF & TI) only, as there is no benefit from treating stages III, IV & V (there is no active inflammation).
- Preventive measures: strict personal hygiene, especially washing the face of young children (single face wash at the morning is enough to prevent the infection).
- Topical Tetracycline or Erythromycin eye ointment plus Single dose of systemic erythromycin.
Allergic conjunctivitis

1- Acute allergic conjunctivitis (Allergic rhinoconjunctivitis):
   - The most common type of eye allergy.
   - It is a hypersensitivity reaction (type I) to specific airborne antigens.
   - Usually there is associating nasal symptoms (so it is called rhinoconjunctivitis) that is thought to be a result of one or more of the following fact:
     a- Direct effect of the allergen on the nasal mucosa and conjunctiva.
     b- We have nasolacrimal drainage, so the excessive tears produced are drained to the nose.
     c- As both of them (the conjunctiva and nasal mucosa) are supplied by pterygopalatine ganglia, so the stimulation of one of them will lead to stimulation of the other.

Presentation:
   Acute, transient attacks of slightly red, itchy and watery eyes associated with sneezing and a water nasal discharge.

Signs:
   - Mild to moderate lids oedema (as there is inflammation of the palpebral part of conjunctiva that liberates mediators that cause collection of fluids).
   - Periorbital oedema in severe cases.
   - Milky or pinkish appearance of conjunctiva as a result of oedema and injection.
   - Mild papillary reaction in the upper tarsal conjunctiva.

Treatment:
   Is either topical mast cell stabilizer e.g. nedocromil & lodoxamide, or topical antihistamine e.g. levocabastine & azelastine.
   * Only in very rare and severe cases we need topical steroids.

2- Vernal keratoconjunctivitis (spring catarrh):
   - It is a recurrent, bilateral, external, ocular inflammation affecting children and young adults.
   - More common in male than females.
   - Vernal keratoconjunctivitis is an allergic disorder in which IgE and cell-mediated immune mechanisms play an important role (hypersensitivity reactions type I & IV).
   - 3/4 of patients have associated atopy and 2/3 has close family history of atopy.
   - Atopic patients often develop asthma and eczema in infancy.
   - The onset of vernal keratoconjunctivitis is usually after the age of 5 years (5-8y) and the condition eventually resolves around puberty, only rarely persisting beyond the age of 25 years.
   - As its name suggests (seasonal basis), the peak incidence of symptoms occur between April and August but many patients have year-round disease.
   - The condition is more common in warm, dry climate and less frequently in colder climates.
Clinical features:
The main symptoms are: Intense ocular itching, Lacrimation, Photophobia, Foreign body sensation, Burning, Thick mucus discharge and Ptosis which is also occurs (it is a mechanical ptosis as it occurs due to chronic inflammation and oedema that causes heaviness and increased weight of the eyelid).
There are three main types (according to anatomical distribution of vernal disease):
a- Palpebral, b- Limbal and c- mixed.
Limbal vernal keratoconjunctivitis is more common in dark-skinned races, palpebral vernal keratoconjunctivitis is more common in lighter-skinned races and it is usually more severe.

Signs:
* For conjunctivitis:
  * For palpebral vernal keratoconjunctivitis, the signs in chronological order:
    - Conjunctival hyperaemia.
    - Diffuse papillary hypertrophy mostly on the superior tarsus (tarsal conjunctiva).
    - Enlarged of papillae ends in flat-topped polygonal appearance reminiscent of cobblestones.
    - In severe cases, the connective tissue septa rupture, giving rise to giant papillae.

  * For limbal vernal keratoconjunctivitis:
    - Trants dots
      - It is characterized by mucoid nodules that have a smooth round surface.
      - Discrete white superficial spots (Trantas dots); which are composed of collections of inflammatory predominantly eosinophils, are found scattered around the limbus.

  * For mixed vernal keratoconjunctivitis:
    - There are papillary reactions and Trantas dots.

* For keratitis: (in chronological fashion)
  - Punctate keratopathy (epithelial erosions, micro erosions), it is the earliest finding.
  - Macro erosions (result of continued epithelial loss, i.e. small ulcers).
- Plaque (macro erosions coated by layers of mucus which cannot be wetted by tears and resists epithelization).
- Subepithelial scarring (sign of previous severe corneal involvement), it occurs due to persistent inflammation that prevents healing).
- Pseudogerontoxon, which resembles arcus senilis. It is seen in the outline of previously inflamed limbus (occurs if the epithelial scarring and opacification are in the periphery of the cornea).

**Treatment:**

1- Topical steroids: (its use is mandatory)
   - As the patients will not cure until around puberty by any drug, so we should use weak steroids as fluorometholone or Clobetasone. Potent topical steroids likes dexamethasone, betamethasone or prednisolone should be avoided as their corneal penetration and their risk to increase IOP and causing cataract is more than weak steroids.
   - It should be of short course.

2- Mast cell stabilizers:
   - nedocromil 0.1% drops *2 daily
   - lodoxomide 0.1% drops *4 daily.
   - sodium cromoglycate 2% *4 daily
   - They are not effective as steroids in controlling acute exacerbation.

3- Acetylcysine 5% drops *4 daily, as treatment of early plaque formation (mucolytic).

4- Topical cyclosporin A: used in steroids resistant cases.

5- Debridement: of early mucus plaques to get speed repair of persistent epithelial defect, done under topical anesthesia with cotton-tipped applicator.

6- Lamellar keratectomy: For densely adherent plaques or subepithelial scarring, and sometimes we may need corneal replacement (corneal graft).

7- Supratarsal injection of steroids: it is very effective in patients with severe disease and Giant tarsal papillae. It is used to avoid ocular side effect of topical medications.
Conjunctival Degenerations

1- Pinguecula:
It is an extremely common lesion which consists of a yellow-white deposit on the bulbar conjunctiva adjacent to the nasal or temporal aspect of the limbus and it is usually asymptomatic.

Histology: There is degeneration of the collagen fibers of the conjunctival stroma, thinning of the overlying epithelium and occasionally calcification. Some pinguecular may enlarge very slowly but surgical excision is seldom required. (usually, it need no treatment)

2- Concretions (ocular lithiasis):
- They are small yellow-white deposits.
- Commonly present in the palpebral conjunctiva of the elderly.
- Also in patients with chronic meibomian gland disease.
- Usually asymptomatic, but occasionally causes foreign body sensation when erode through the epithelium.

Treatment: They can be easily removed with a needle.

3- Pterygium:
- It is a triangular sheet of conjunctival fibrovascular tissue invades the cornea.
- Occurs in patients who have been living in outdoor, hot climates.
- May represent a response to chronic dryness and exposure to the sun.
Signs:

a- Small, grey, corneal opacities near the nasal limbus.
b- Then, the conjunctiva overgrows these opacities and progressively invades onto the cornea in a triangular fashion.
c- A deposit of iron (Stocker line) may be present in the corneal epithelium anterior to the advancing head of the pterygium.

* Usually asymptomatic.

Treatment:

a- Surgical excision: **indicated only** in the following cases: i- If it is threatening the visual axis. ii- Severe irritation. iii- For cosmetic reason.
b- Lamellar keratoplasty: required if the visual axis is affected by opacification.

Surgical excision, it is an easy procedure but should be avoided unless there is indication because the recurrent rate is high (about 40%) and the recurrent pterygium is uglier, rapidly progress and causing more severe symptoms.