Ocular Pathology Review

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INFLAMMATION

A reaction of the microcirculation characterized by movement of fluid and white blood cells from the blood into extravascular tissues. This is frequently an expression of the host's attempt to localize and eliminate metabolically altered cells, foreign particles, microorganisms or antigens

Cardinal manifestions of Inflammation, i.e. **redness, heat, pain and diminished function** reflect increases vascular permeability, movement of fluid into extracellular space and effect of inflammatory mediators.

Categories of Inflammation- Classified by type of cells in tissue or exudate

Acute (exudative)
Polymorphonuclear leukocytes
Mast cells and eosinophils

Chronic (proliferative)
Nongranulomatous
Lymphocytes and plasma cells
Granulomatous
Epithelioid histiocytes, giant cells

Inflammatory Cells
Polymorphonuclear leukocyte
Primary cell in **acute inflammation (polys = pus)**
Multilobed nucleus, pink cytoplasm
First line of cellular defense
Phagocytizes bacteria and foreign material
Digestive enzymes can destroy ocular tissues (e.g. retina)
Abscess: a focal collection of polys
Suppurative inflammation: numerous polys and tissue destruction (pus)

Endophthalmitis: Definitions:
Endophthalmitis: An inflammation of one or more ocular coats and adjacent cavities. Sclera not involved. Clinically, usually connotes vitreous involvement.
Panophthalmitis:
Usually a suppurative endophthalmitis that spreads to involve the sclera and orbital tissues
Exogenous:
Due to entrance of organisms from external environment, e.g., bacteria introduced by perforating corneal wound, foreign bodies.
Common organisms: staph, strep, gram negative rods, fungi
Endogenous:

Organisms gains entrance by vascular channels or nerves
Common organisms
Bacteria: (Meningococcus, Nocardia)
Fungus: (Candida, Aspergillus)
Protozoans: (Toxoplasmosis)
Viruses: (CMV, herpes simplex, varicella zoster)

Bacterial endophthalmitis- large vitreous abscess; relatively acute onset
Fungal endophthalmitis- **vitreous microabcesses**; more indolent; not as "hot"

Eosinophil
Bilobed nucleus, orange granular cytoplasm
Allergic reactions
Modulates mast cell-mediated reactions
Phagocytizes antigen-antibody complexes
Parasite-associated inflammatory reactions
Many EOSINOPHILS = parasites or allergy

Eosinophilic Granuloma
superior lateral orbit, bone destruction,
localized variant of Langerhans cell histiocytosis, histiocytes with nuclear folds, CD1a, Langerin (CD207), S-100 positive, clonal proliferation, EM shows Birbeck granules or racket bodies, role of chemotherapy controversial

Lymphocyte
Round blue nucleus with scanty cytoplasm
Key cell in humoral and cell-mediated immune responses
Multiple subtypes :
B cells
Effector T cells (Delayed hypersensitivity, mixed lymphocyte reactivity)
Cytotoxic killer cells
Regulator T cells (Helper T cells, Suppressor T cells)
Cytotoxic Natural Killer (NK) cells
Null cells

Plasma Cell
Eccentric "cartwheel" nucleus
Basophilia of cytoplasm reflects RNA in RER
Perinuclear "hof"- Golgi apparatus
Activated "B" lymphocyte
Antibody synthesis and secretion, antibody "factory"
Plasmacytoid cell
Plasma cell with granular eosinophilic cytoplasm (or lymphocyte with plasma cell-like nucleus)
Russell body
Round immunoglobulin crystal formed in "constipated" plasma cells
Morula cell (of Mott)
Contains multiple grape-like Russell bodies
Mast Cell
Called tissue basophil, but probably from other BM precursor
Superficially resembles plasma cell, but stains + for MPS

Binds IgE to surface, contact with antigen causes degranulation and release of histamine and heparin
Cause of acute anaphylaxis, allergic conjunctivitis, etc.

Chronic Nongranulomatous Inflammation:

Inflammatory infiltrate composed of lymphocytes and plasma cells;
Usually denotes activation of immune system, e.g., "endogenous iridocyclitis"
(occasionally, lymphocytes and plasma cells may represent the acute response to certain viruses)

Macrophage (histiocyte, monocyte)

Large mononuclear cell with eccentric reniform nucleus
Second line of cellular defense
Body's primary phagocytic cell
Enormous phagocytic capacity with little tissue damage
Regulate lymphocytic responses
Antigen presentation (process antigens, present to T helper cells in association with class II MHC molecules)
Produce lymphokine IL-1, monokines
Transform into epithelioid cells, inflammatory giant cells
In eye, frequently contain phagocytized substances, e.g., lens material, melanin, lipid, blood breakdown products

Epithelioid Histiocyte (activated macrophage)

Activation caused by large quantities of relatively insoluble or indigestible antigen, or organisms that proliferate intracellularly
Abundant eosinophilic cytoplasm, large vesicular nucleus with nucleolus
Groups of cells superficially resemble epithelium, hence name.
Necessary for diagnosis of granulomatous inflammation!!!
Fuse to form inflammatory giant cells.

Inflammatory giant cells

Langhan's giant cell
Peripheral rim of nuclei, homogenous cytoplasm

Foreign body giant cell
Contains or surrounds foreign material, nuclei random
If foreign body is too large, body "walls it off" with “insulation” of foreign body giant cells (e.g.., precipitates on IOL's)

Touton giant cell
Peripheral wreath of foamy lipid surrounds ring of nuclei
Characteristic finding in JXG, also seen in other lipid disorders such as necrobiotic xanthogranuloma, Erdheim-Chester disease , orbital xanthogranuloma with adult onset asthma (see appendix)

Chronic Granulomatous Inflammation:

Infiltrate contains **epithelioid cells and/or giant cells**. Generally a response to large quantities of insoluble antigen or organisms that grow intracellularly.
Eyes with granulomatous inflammation may harbor organisms (bacteria, fungi, acid fast bacteria) or foreign matter
May be a response to endogenous material acting as a "foreign body", e.g., lipid in chalazion, cholesterolosis; keratin in ruptured dermoid cyst.
Clinically, large, greasy "mutton fat" keratic precipitates denote granulomatous inflammation

Work-up!! Clinical work-up, special stains (Gram, AFB, GMS, polarization etc.

may reveal causative organisms, foreign bodies, specific diagnosis, etc.

Patterns of Granulomatous Inflammation

Diffuse:
Borders ill-defined, epithelioid cells and giant cells randomly distributed against background of lymphocytes and plasma cells. "Salt and pepper" pattern.
Examples: sympathetic uveitis, lepromatous leprosy

Discrete (sarcoidal):
Discrete nodule or aggregate of epithelioid cells surrounded by rim of lymphocytes.
Examples: sarcoidosis, miliary tuberculosis, tuberculoid leprosy.

Sarcoidosis
Discrete noncaseating granulomas
Retinal perivascular candle wax drippings (taches de bougie) = potential for CNS Involvement
Uveitis; granulomas; Busacca and Koeppe nodules

Zonal:
Palisade of granulomatous inflammation surrounds central antigenic nidus.
Concentric zones of lymphocytes and plasma cells surround first zone.
Examples: rheumatoid scleritis, pseudorheumatoid nodule

Phacoanaphylactic endophthalmitis (phacoantigenic uveitis)
Rare autoimmune inflammatory response to lens protein
An **immune complex disease** that develops when normal tolerance to lens protein is lost, not a cell-mediated rejection of "foreign tissue"
(Contrary to prior teachings lens proteins are not totally sequestered or organ specific. They are normally found in aqueous and expressed in other extraocular tissues. Anti-lens antibodies are found in some normal individuals).
Zonal chronic granulomatous inflammation: polys infiltrate central lens material, then epithelioid histiocytes, nonspecific mononuclear cell infiltrate
Zonal pattern caused by antibody/antigen ratio in immune complexes
No penetrating wound or history of trauma in 20%
Concurrence with sympathetic ophthalmia (3-7%), unrelated immunologically

Granulation tissue
Seen in reparative phase of chronic inflammation.
Components: polys, lymphocytes, plasma cells, macrophages, proliferating capillaries, myofibroblasts.
Pyogenic Granuloma: an ***exuberant proliferation of granulation tissue***
Typically follows surgery or trauma, drainage of chalazion
Note: granulation tissue usually is **nongranulomatous**.
Term derives from granular appearance of healing wounds noted in premicroscopic era. Smooth surface, radiating vessels

Specific ocular inflammatory diseases

Necrotizing Retinitides

Cytomegalovirus Retinitis
CMV is a Herpesvirus

Necrotizing retinitis with hemorrhage in immuno-incompetent patients. Frequent ocular manifestation of HIV/AIDS before HAART (28-45% of patients developed CMV retiniitis)
"Mustard and catsup fundus", enlarged cells with "owl's eye" Cowdry type A intranuclear and intracytoplasmic inclusions.

Toxoplasmosis

Classically was congenital and acquired *in utero*; acquired cases more common than previously thought
Retinochoroiditis, primary retinal infection by crescentic tachyzoites with coagulative necrosis, secondary granulomatous choroiditis, vitritis
Intraretinal cysts (bradyzoites) cause recurrent disease

ARN, BARN syndromes (acute retinal necrosis syndrome)

Acute necrotizing viral retinitis in presumably healthy individuals
Herpesviruses H. simplex and varicella-zoster have been isolated

PORN Syndrome (progressive outer retinal necrosis) varicella-zoster

TRAUMA AND WOUND HEALING

Basic principles of ocular trauma

Destruction

Prolapse, incarceration and loss of intraocular tissues

e.g., anterior uvea, lens, vitreous, retina

Trauma opens up new surfaces and substrates for cellular proliferation- *In vivo* "tissue culture"

e.g., epithelial downgrowth (through wound or by implantation), fibrous ingrowth (along scaffold of incarcerated vitreous), preretinal gliosis (on ILM after PVD)

Hemorrhage-expulsive choroidal hemorrhage (not only surgical complication, common with trauma, infectious corneal perforation);vitreous hemorrhage, hemorrhagic retinal detachment

Penetrating and perforating injuries

Penetration: partial thickness wound **(into)**

Perforation: full thickness wound **(through)**

You must specify structure. A ***perforating*** wound of the cornea is a ***penetrating*** wound of the globe!!!

Sympathetic uveitis (ophthalmia)

Bilateral granulomatous uveitis (autoimmune disorder) after unilateral injury
Classically follows injury or surgery with uveal incarceration (? YAG cyclodestruction, association with Behçet Disease, proton beam irradiation for melanoma).
Time period for safe prophylactic enucleation 1-2 weeks
Classic histopathological features:

Diffuse granulomatous infiltrate thickens uveal tract
Sparing of choriocapillaris, retina
Dalen-Fuchs nodules (not pathognomonic, also in sarcoidosis)
Pigment phagocytosis by epithelioid cells
Plasma cells uncommon

Cases have developed after evisceration (antigen in emissarial canals)
Association with phacoanaphylaxis (3-7%) – both diseases share traumatic etiology
Enucleation of inciting eye may decrease severity of inflammation in sympathizing eye, contrary to prior teachings

Uveal thickening more pronounced in blacks, eosinophilia
Sparing of choriocapillaris may reflect prompt enucleation

Contusion Injuries
Iridodialysis- thinnest part of iris avulsed from ciliary body
Cyclodialysis- disinsertion of ciliary body from scleral spur. Frequently associated with **hyphema** due to proximity of greater arterial circle of iris.
Angle Recession (post-contusion angle deformity)
During contusion, lens acts as "ball valve"
Tear into anterior face of ciliary body, or cyclodialysis, hyphema
Post-hyphema, 60% incidence of angle recession
Late glaucoma in small percentage of patients caused by scarring, endothelialization and Descemetization of trabecular meshwork
Secondary synechial closure can hide recession clinically
Fusiform configuration of ciliary muscle results from ischemic atrophy of its inner part
Drop line parallel to optic axis through scleral spur to evaluate angle

Chemical injuries
Acid burns: acid precipitates tissue proteins
Histology: superficial coagulative necrosis of conjunctival and corneal epithelium
Alkali burns: alkali denatures proteins and can penetrate deeply; fat saponified
Vascular endothelial cells and fibroblasts necessary for repair are killed
Ischemic “porcelain conjunctiva”, Histology: corneal and conjunctival necrosis; cataract; glaucoma; uveitis, late symblepharon, entropion

Intraocular foreign bodies
Vegetable matter: violent inflammatory response, often contaminated, fungus, etc.
Glass and plastic: usually inert (IOLs)
Iron: deposits in neuroepithelial structures; **siderosis-** cataract, heterochromia, glaucoma, retinal degeneration, **ferrous (Fe+2) more toxic (“ferrous is furious”)**
Copper: deposits in basement membranes (Descemet, lens capsule); Pure copper-purulent endophthalmitis; <85% copper-**Chalcosis**: Kayser-Fleischer ring, sunflower cataract, retinal degeneration

Hyphema- Corneal blood staining
Hemoglobin particles in corneal stroma, *not rbc’s*; keratocytes contain hemosiderin
Development depends on duration, IOP, health of endothelium
Healthy endothelium, high IOP, 48 hrs = blood staining
Organization of hyphema-fibrosis, anterior synechias
Vitreous hemorrhage
Complications include:
Cholesterolosis bulbi- blood breakdown major source of intraocular cholesterol crystals, "Synchisis scintillans"
Hemosiderosis (liberation of iron with toxic effects)
Iron deposits in neuroepithelial structures
Hemolytic glaucoma, ghost cell glaucoma
Tractional retinal detachment due to organization, vitreous bands

Atrophia bulbi
Atrophia bulbi with shrinkage (clinical **"phthisis bulbi")**

Rectus muscle traction on hypotonous globe causes "squared-off" appearance.
Lacks disorganization seen below
Atrophia bulbi with shrinkage and disorganization
(Pathological phthisis bulbi)
Globe small (16-18mm), hypotonous, sclera thickened and folded
General disorganization of intraocular contents
Cyclitic membrane and total retinal detachment common
Numerous large drusen and osseous metaplasia of RPE
Intraocular bone- osseous metaplasia of the RPE- located on inner surface of Bruch's membrane

CONGENITAL ANOMALIES

Cryptophthalmos
Intact layer of skin covers eye, poor eyelid development, partial or complete
Some have **Fraser Syndrome** (cryptophthalmos-syndactyly syndrome): cryptophthalmos, renal agenesis, laryngeal stenosis, syndactyly, aural and genital anomalies

Uveal Coloboma - defect caused by faulty closure of embryonic fissure
May involve iris, ciliary body, choroid, optic nerve and retina
Located inferonasally, bilateral
Usually sporadic, may be inherited (usually autosomal dominant) with no associated systemic anomalies
Syndromes with Colobomas: CHARGE, Cat-Eye, Kabuki, Wolf-Hirschhorn (4p-)
Compatible with useful vision (absolute scotoma with choroidal coloboma)
Within the coloboma:
Adjacent uvea does not differentiate. It may undergo dysplasia or metaplasia with formation of cartilage, muscle or fat
Overlying retina may be absent or dysplastic
Microphthalmos with cyst (colobomatous cyst) – cyst lined by neuroectoderm

Trisomy 21 (Syndrome of Langdon Down)-most common chromosomal syndrome
"Mongoloid appearance with up and outward slanting palpebral fissures; almond shaped eyes, epicanthal folds, refractive errors, cataract, strabismus, congenital ectropion, Brushfield spots, keratoconus with hydrops, increased number of vessels crossing disc rim

Trisomy 13 (Patau syndrome)- formerly 13-15 or D trisomy
Chromosomal anomaly with most severe ocular involvement
Anophthalmos, synophthalmos, microphthalmos,
Coloboma with intraocular cartilage (usually in eyes <10mm)
PHPV/PFV, retinal dysplasia
Cleft lip and palate, holoprosencephaly, arrhinencephaly

Cyclopia-Synophthalmia
True cyclopia is rare, most cases are synophthalmia
Not fusion anomaly; rather, failure of bilateral differentiation
Single optic nerve, anterolateral structures most differentiated
Nasal proboscis above single midline orbit
Holoprosencephaly (brain not divided into two hemispheres)
Mutations in human sonic hedgehog gene (7q36), SIX3 sine oculo homeobox gene (2p21); association with 13 trisomy; toxic effect of veratrum alkaloid cyclopamine in lambs

Lowe Syndrome
Oculocerebrorenal syndrome of Lowe

X-linked, aminoaciduria, renal rickets
Congenital cataract and glaucoma, lens increscences
Corneal keloids, lens changes in female carriers

Aniridia (iris hypoplasia)
Caused by mutations in PAX6 (homeobox) gene

Categories

AN1- 85%
Familial aniridia (most cases in this category)
Autosomal dominant with incomplete penetrance and expression
Isolated ocular defect, foveal hypoplasia, corneal "dystrophy", glaucoma, etc.

AN2- 13% (**Miller Syndrome,** WAGR)
Sporadic nonfamilial aniridia and Wilms tumor
Deletion or mutation in short arm of chromosome 11 **(11p-)**
Associations include:
Wilms tumor of kidney (nephroblastoma), genitourinary abnormalities, mental retardation, craniofacial dysmorphism, hemihypertrophy
Incidence of aniridia in patients with Wilms tumor is 1/73 (1.4%)
Incidence of Wilms' tumor in sporadic aniridia is 34%

AN3- 2% (Gillespie Syndrome)
Autosomal recessive aniridia, Mental retardation, cerebellar ataxia
Structural defects in cerebellum and brain
Do not develop Wilms' tumor

Congenital Rubella Embryopathy (Gregg syndrome)
Congenital cataracts, deafness, cardiac defects (patent ductus)
Retention of lens nuclei in embryonic nucleus (not pathognomonic)
Virus remains viable in lens for several years
"Salt and pepper" retinopathy
May have congenital glaucoma, inflammation

Phakomatoses (disseminated hereditary hamartomas; neurocutaneous hamartoses, Familial Tumor Syndromes (WHO))

Hamartoma: a congenital tumor composed of tissues normally found in an area, e.g., choroidal hemangioma

Choristoma: a congenital tumor composed of tissues NOT normally found in an area, e.g., choroidal osteoma; phakomatous choristoma (Zimmerman tumor), eyelid odontogenic choristoma, conjunctival osseous choristoma

Phakomatous choristoma (Zimmerman tumor)
Lower nasal eyelid or anterior orbital tumor of infants, probably congenital
A choristoma of lenticular anlage composed of cells resembling lens epithelium surrounded by thick PAS + lens capsule-like basement membrane, cells express lens proteins

Neurofibromatosis (NF-1, VRNF (von Recklinghausen neurofibromatosis)
Autosomal dominant, 1/3-4000 live births; proliferation of Schwann cells
Plexiform neurofibromas of eyelid and orbit -"bag of worms", enlarged nerves, "S"-shaped lid fissure
Congenital glaucoma if upper lid involved
Skin lesions- fibroma molluscum, elephantiasis neuromatosa
Cafe-au-lait spots- (six or more >1.5 cm diameter in patients over age 5 yrs, five or more >0.5 cm diameter in patients less than age 5 yrs are diagnostic)
Hamartomatous thickening of uvea, ovoid bodies resemble tactile corpuscles

Lisch nodules- melanocytic hamartomas of iris (92% > age 5 yr., 100% > age 20
Sphenoid bone dysplasia- "Orphan Annie sign", pulsating exophthalmos
Orbital Schwannomas
Optic nerve gliomas [25% have NF (15-70%)], other CNS tumors
Gene on chromosome 17 **(17q11.2)**, 50% of cases are new mutations
NF gene product neurofibromin interacts with protein product of **ras** oncogene, dampens growth stimulatory signals.

Neurofibromatosis, **Type II, NF-2 -**
Merlin gene on chromosome 22 (22q12.2)
Bilateral acoustic neuromas (schwannomas), presenile PSC cataract, epiretinal membranes, combined hamartoma of RPE and retina (25%), optic nerve sheath meningiomas, oculomotor paresis (12%)

Sturge Weber Syndrome (encephalotrigeminal angiomatosis)
Nonhereditary, congenital (mosaicism for somatic R183Q mutations in GNAQ gene in port wine marks)
Nevus flammeus ("port wine mark"), facial venous angiomatosis
Glaucoma if upper lid involved
Diffuse choroidal hemangioma, "tomato catsup" fundus
Ipsilateral hemangioma of meninges and brain, seizures (80%); MR
"Train track" intracranial calcification
Klippel-Trénaunay-Weber Syndrome (port wine mark, hypertrophy of bones and soft tissues, local gigantism)
Phacomatosis pigmentovascularis: nevus flammeus and melanocytosis; MM risk

Tuberous Sclerosis Complex (TSC, Bourneville's Syndrome)
Autosomal dominant, variable penetrance, high rate of new mutations, TSC1 suppressor gene on chromosomes 9 (9q34 hamartin) and TSC2 on chromosome 16 (16p13 tuberin)
Hamartin and tuberin form complex- suppresses mTOR signaling
Seizures in 80-90%;
Facial adenoma sebaceum (angiofibromas, not sebaceous lesions)
Astrocytic hamartomas of retina ("mulberry nodules")- 50%- rarely progressive
Rare progressive retinal tumors resemble giant cell astrocytomas of brain
Astrocytic hamartomas of optic disk (giant drusen of optic nerve)
Astrocytic hamartomas of brain (calcify forming "brain stones")
Subependymal giant cell astrocytomas (SEGA)
Before calcospherites form, retinal lesions can resemble small retinoblastomas
"Ash leaf" skin lesions, shagreen patch, subungual fibromas
Visceral tumors: renal angiomyolipomas, cardiac rhabdomyomas (43%), subpleural cysts, spontaneous pneumothorax,

Von Hippel-Lindau (VHL, Angiomatosis Retinae)
Autosomal dominant with incomplete penetrance; VHL tumor suppressor gene on chromosome 3 - 3p26-p25); VHL protein targets hypoxia inducible factor 1a (HIF1a) for degredation. Genetic testing important
Retinal hemangioblastomas with large feeder vessels, in 50%, 50% bilateral
Only 5% diagnosed before age 10; new lesions at 2 year intervals- monitor
Tumors may involve optic disk or nerve
Hemangioblastoma with foamy lipid-laden stromal cells and capillary-caliber vessels. Stromal cells show loss of heterozygosity c/w true neoplastic component, Upregulation of VEGF stimulates capillary proliferation
Coats' disease-like exudative maculopathy common
Cerebellar Hemangioblastoma in 35-75%% (Lindau was a neurologist)

Most common cause of death, posterolateral in cerebellum, 80% cystic

Pheochromocytoma (<10%); polycythemia 10-25%

Endolymphatic sac tumor- deafness, vertigo, tinnitus – 11%

Renal Cell Carcinoma- 1/3 of patients; increasing incidence with age

Wyburn-Mason Syndrome - nonhereditary

Retinal and systemic arteriovenous malformations (AVM's); 86% supratentorial 23-30% % have associated midbrain vascular malformation

Ataxia-Telangiectasia (Louis-Bar)- autosomal recessive; ATM gene, 11q23

Conjunctival telangiectases, oculomotor disturbances

Hypoplastic thymus, deficient cell mediated immunity, deficient IgA, increased incidence of lymphoma. elevated alpha fetoprotein

Multiple Endocrine Neoplasia Syndrome IIB (RET proto-oncogene, 10q11.2) AD, 50% sporadic. Enlarged corneal nerves, typical faces, Marfanoid habitus, submucosal neuromas, dry eyes. Pheochromocytomas (45%), neuroendocrine medullary thyroid carcinoma (100%): c-cells, elevated calcitonin, early metastases

Cavernous Hemangioma of the Retina

Light bulbs with fluid level, some patients have CNS and skin lesions

KRIT1/CCM1 gene (7q21-q22)ß

Iris pigment epitheiial flocculi or cysts and aortic dissecting aneurysms (ACTA2 gene encoding vascular smooth muscle actin 10q23.3)

FYI: Phakomatosis is an outdated term and concept and term. Neither the AAO's monograph on Inherited Diseases and the Eye (Traboulsi) nor the WHO's text on CNS Tumors includes the term in the index. The WHO lists the disorders as familial cancer syndromes

Abusive Head Trauma (AHT, shaken baby syndrome)

Massive hemorrhagic retinopathy including hemorrhagic detachments of ILM (and schisis of ILM), paramacular retinal folds, optic nerve sheath hemorrhage, juxtapapillary intrascleral hemorrhage, hemorrhage within orbital fat

EYELID

Anatomy-Histology

Layers

Skin (epidermis and dermis)

Subcutaneous tissue

Orbicularis muscle (elliptical sheet of concentrically arranged fibers)

Pretarsal plane (vessels and nerves)

Tarsal plate (flat semilunar plates of dense collagenous tissue- provide rigidity)

Palpebral conjunctiva

Upper versus lower lid

Upper lid- longer, rectangular configuration, tarsus much longer, more meibomian glands

Lower lid- shorter, triangular configuration, fewer meibomian glands

The gray line (anatomic landmark for lid surgery)

Between lash line and orifices of meibomian glands

Corresponds histologically to most superficial portion of the orbicularis muscle, (muscle of Riolan).

Eyelid glands

Sebaceous (holocrine)

Meibomian glands- tarsal plate

Zeis glands (empty in to lash follicles)

Sweat glands
Eccrine sweat glands
Three segments: secretory portion, intradermal duct, intraepithelial duct (eccrine sweat pore)
Apocrine sweat gland (glands of Moll)- decapitation secretion, apical snouts, empty into lash follicles
Accessory lacrimal glands
Glands of Wolfring (Ciaccio)- superior margin of tarsal plate; 2-5 upper, 2 lower
Glands of Krause- conjunctival cul-de-sac, 42 glands in upper, 6-8 in lower)
Glands of Popoff (caruncle)- give rise to oncocytomas

Skin Pathology Terminology

Acanthosis-thickening of squamous epithelium due to proliferation of "prickle cells"
Hyperkeratosis-excess production of surface keratin layer, epidermal granular layer present
Parakeratosis-retained parallel pyknotic nuclei in keratin layer. Epidermis lacks granular cell layer

A characteristically feature of…

Actinic Keratosis

Sun-exposed skin; fair-skinned, middle-aged individuals
Scaly, keratotic flat-topped lesions; early erythematous nodules
Epithelial dysplasia (partial-thickness replacement by atypical cells)
Parakeratosis with focal loss of granular cell layer, dyskeratosis
Irregular buds of atypical keratinocytes extend into papillary dermis
Openings of pilosebaceous units spared, underlying dermis shows elastotic degeneration (similar to that seen in pinguecula and pterygium)
Progression to squamous cell carcinoma uncertain- 12-13% incidence reported in past. Recent large series found much lower incidence (0.1%), spontaneous regression common.
Squamous cell carcinoma arising from actinic keratosis thought to have excellent prognosis compared to SCC *de novo* (incidence of metastasis only 0.5%)

Acantholysis-prickle cells separated by spaces. Results from rupture of intercellular bridges

A characteristically feature of…

***Inverted Follicular Keratosis - (IFK)**

"Irritated seborrheic keratosis"
Acantholysis, squamous eddies, inflammation
Can recur rapidly if incompletely excised

Dyskeratosis-aberrant intraepithelial keratinization of single cells (e.g. HBID)
Dysplasia-disorderly cellular maturation. The normal maturational sequence of cells is disturbed. Partial thickness replacement of epithelium by atypical cells.
Mild dysplasia-less than 50% replacement
Severe dysplasia-more than 50% replacement
Note: the differentiation between severe dysplasia and carcinoma in situ is subjective and may not be clear cut
Carcinoma in situ-full thickness replacement of epithelium by malignant cells without invasion through basement membrane.
Invasive Squamous Cell Carcinoma-malignant cells have broken through epithelial basement membrane and have invaded dermis or substantia propria

Anaplasia-frank cytologic malignancy (pleomorphism, anisocytosis, abnormal nuclei and mitotic figures)

Congenital and Developmental Lesions

Cryptophthalmos, microblepharon, coloboma, ankyloblepharon, ankyloblepharon filiforme adnatum, blepharophimosis, epicanthus, euryblepharon, epiblepharon
Distichiasis -accessory row of lashes arises from meibomian glands
Ptosis

Aging changes

Dermatochalasis, senile entropion, senile ectropion

Inflammatory Lesions

***Hordeolum (stye)**

Acute infection of lash follicle (external) or Meibomian gland (internal)

***Chalazion**

Chronic lipogranulomatous inflammatory reaction to sebum in tissues. (endogenous "foreign body" reaction)
Epithelioid cells and giant cells surround empty lipid vacuoles (fat dissolved out by tissue solvents)
Submit recurrent chalazia to rule-out sebaceous carcinoma
Atypical chalazion-like lesions in some xanthogranulomatous disorders

Fungal Infections

Blastomycosis, Coccidioidomycosis, Cryptococcosis, Sporotrichosis

Parasitic Infestations

Phthiriasis palpebrarum

Pubic lice, often sexually transmitted, 30% of patients may have another sexually transmitted disease, lice droppings can cause follicular conjunctivitis. Be sure to examine lashes!!!

Demodicosis - (*Demodex folliculorum* and *brevis*)

D. folliculorum mites live in hair follicle, feed secluded in follicle during day, prowl on skin surface at night. Extremely common, suspect in chronic blepharitis, pathogenic?- corneal manifestations have been reported
D. brevis are smaller, live within sebaceous glands

Myiasis- fly larvae, esp. *Dermatobia hominis*, intraocular involvement rare
Subcutaneous dirofilariasis- zoonose, D. tenuis (raccoon) in USA
Leishmaniasis-
Cysticercosis- larval form of t. Solium

Cysts

***Epidermal Inclusion Cysts** (Follicular cyst, infundibular type)

Round or oval, single lumen (unilocular)
Lined by keratinized stratified squamous epithelium
Filled with foul-smelling, cheesy keratin debris
Epithelial lining of cyst may connect with epidermis via pore

***Dermoid Cyst** (cystic dermoid- anterior orbit)

Lining epithelium has **epidermal appendages**, hair shafts mixed with keratin in lumen, sebaceous and sweat glands. Nasal dermoids may have conjunctival epithelial lining

***Sweat Ductal Cysts** (sudoriferous cysts, hydrocystomas)

Multilocular, branching lumen appears empty or contains serous fluid. Lined by dual layer of epithelium resembling sweat duct.
Most are **eccrine hydrocystomas**

Apocrine hydrocytomas: lined by apocrine cells with eosinophilic cytoplasm and “apical snouts” of decapitation secretion. Fluid in lumen often pigmented, contains lipofuscin; may simulate melanocytic lesions.

Vascular lesions

***Capillary Hemangioma**

"Strawberry" hemangioma- perinatal onset; express placental antigens
Grows rapidly, then involutes
Cosmetic blemish, danger of amblyopia
Nonencapsulated; early lesions composed of sheets of endothelial cells, mitoses may be numerous; later, capillary spaces appear as lesion loses cellularity
RX: observation, beta-blockers (propranolol), steroid injections in past, cryo, sclerosing solutions, interferon alfa 2a, surgery
In Dermatology literature, acquired lesions are called pyogenic granulomas

***Cavernous Hemangioma**

Large blood-filled spaces lined with endothelium, fibrous septa

Lymphangioma

Many present at birth, slowly progressive, do not involute,
Poorly circumscribed lesion, anastomosing lymphatics lined by single layer of endothelium, hemorrhage into lesion common-"chocolate cyst", D2-40 immuno stain stains lymphatic endothelium; part of spectrum of low flow vascular malformation that includes varices

Glomus tumor, cutaneous angiosarcoma, Kaposi sarcoma

Epidermal lesions: basics for histopathological evaluation

Basal cell lesions are **BLUE**, **Squamous cell** lesions are **PINK**
Benign lesions rest anterior to plane of epidermis **(benign-"above")**
Malignant lesions invade deep to the plane of the epidermis **(malignant-"below")**

Benign Epithelial Tumors

Squamous papilloma**-keratinized epidermal fronds with fibrovascular cores. (**note**: papilloma is a ***growth pattern)

***Seborrheic keratosis**-benign papillomatous proliferation of basal cells, ("blue-above") lesion of elderly, sits like a button on surface of skin, greasy keratin crust, may be pigmented, pseudo-horn cysts, hyperkeratosis, adenoid variant with interweaving bands of bland epithelial cells.

Umbilicated or Cup-shaped Lid Lesions

Keratoacanthoma (? benign)
Molluscum Contagiosum
Basal cell carcinoma

Keratoacanthoma (? benign)

Squamous lesion with central keratin-filled crater, elderly patients
Rapid onset (weeks), spontaneous involution, "pushing margins", overhanging buttress of normal skin at margin
Configuration on low magnification suggests diagnosis; It is Impossible to differentiate from squamous cell carcinoma in small biopsy.

Note: Classically thought to be a benign variant of pseudoepitheliomatous hyperplasia; However, ***many authorities now consider keratoacanthoma to be a variant of squamous cell carcinoma***. Deeply invasive and metastatic lesions have been reported

Recommended therapy for eyelid keratoacanthoma: **total excision (preferably with frozen sections)**

Viral Lesions

****Molluscum Contagiosum**

Lobular acanthosis with large basophilic inclusions of pox virus (Henderson-Patterson corpuscles), dome or crater configuration, cause of follicular conjunctivitis, massive eyelid involvement in HIV/AIDS

Verruca Vulgaris

Papilloma with spire-like fronds, apical parakeratosis, viral inclusions, coarse keratohyaline granules, HPV 2 (DNA papovavirus)

Herpes simplex (vesicles, intranuclear inclusions, multinuclear giant cells)

Herpes zoster

Common Eyelid Malignancies

****Basal Cell Carcinoma**

Most common eyelid malignancy in Caucasians (18-39 times more common than squamous cell carcinoma)- rare in African Americans, rare in India

Location: Lower lid> medial canthus > upper lid> outer canthus

"Blue" and "below"

Variants: nodular, nodulo-ulcerative, multicentric, cystic, diffuse (morpheaform), pigmented variant can be confused with melanoma

Histology: tongues and islands of basaloid cells connected to overlying dermis (If no connection, "adnexal carcinoma"), **peripheral palisading, retraction artifact, stromal desmoplasia,**

Malignant **morpheaform** variant- slender infiltrating tendrils of "Indian file" cells, margins indistinct

Metastases extremely rare, lethal tumors directly invade cranial cavity with secondary meningitis

"Rodent ulcers"-hideous, neglected cases

Dysregulated or aberrant Hedgehog (Hh) signaling has been implicated in the pathogenesis of BCC. ***Smoothened*** inhibitors such as vismodegib for advanced, unresectable or metastatic disease (drug very expensive)

Nevoid basal cell carcinoma syndrome (Gorlin-Goltz Syndrome)

Mutations in patched1 gene (PTCH1) -9q22.32, vismodegib therapy

Found in 0.7% of patients with BCC, Autosomal dominant

Multiple BCC in young patients (10-30), odontogenic jaw cysts, skeletal anomalies (bifid ribs), palmar and plantar pits, neurologic anomalies, endocrine disorders

Skin lesions occur around puberty, tumor may contain osteoid or bone.

Clinically may be confused with Brooke's tumor.

Sebaceous Carcinoma (or Sebaceous Gland Carcinoma)

More common than ocular adnexal squamous cell carcinoma in Caucasians

Most common eyelid malignancy in India

Elderly (rare before 40), more common in females, Asians

Predilection for eyelids, **2/3's arise from upper lid**, extremely rare elsewhere in body (General pathologists often unfamiliar; may misdiagnose)

Can arise from meibomian glands, Zeis glands (sebaceous glands of lash follicles), or sebaceous glands in caruncle

Broad clinical spectrum - **may mimic chalazion** or **chronic blepharoconjunctivitis (masquerade syndrome)- misdiagnosis common**

Histology-

Lobules of cells with foamy, lipid laden cytoplasm, (Oil red O fat stain can establish diagnosis in less differentiated cases- must be done on frozen sectioned tissue --**Save wet tissue if you suspect!!!!);**
New **Adipophilin** Immuno stain works on routine paraffin sections
Islands of central necrosis (comedocarcinoma pattern)
Intraepithelial "Pagetoid" or "bowenoid" invasion and/or replacement of overlying epithelia – 47%

Mortality-15% in old AFIP series; better recently
Spreads by direct extension, node and distant metastases (lung, liver, brain, skull) possible
Factors associated with Poor Prognosis (Rao et al, AFIP)-
Upper lid origin, size>10mm, Meibomian gland origin, Sx > 6 mo., infiltrative growth pattern, poor sebaceous differentiation, pagetoid invasion, lymphatic, vascular and orbital invasion.
RX: early diagnosis, wide local excision with frozen section control of margins, radiation for palliation of advanced cases only!!!

Benign sebaceous lesions

Senile sebaceous gland hyperplasia- mature sebaceous lobules, central duct
Umbilicated lesions often misdiagnoses as basal cell carcinoma

Sebaceous adenoma

Muir Torre Syndrome- multiple sebaceous gland neoplasms and visceral cancer, esp. carcinoma of colon; germline mutations in MSH2, MSH6 & MLH1 DNA mismatch repair (MMR) genes (2p) cause microsatellite instability; Carriers are heterozygous, tumors lack nuclear staining; MMR defects rare in typical sebaceous carcinoma, suspect in adenomas and low-grade carcinomas

Squamous cell carcinoma

Elderly fair-skinned individual, lower lid margin most common
More common than basal cell in upper lid and outer canthus!!!
Only 5% of lid epithelial tumors (12-39 BCC / 1 SCC),
Potential for regional or distant metastasis
Early skin lesions rarely metastasize (especially if arise from actinic keratosis), wide local excision usually curative
Polygonal cells with pink eosinophilic cytoplasm, nuclear atypia, infiltrating cords into dermis, dyskeratotic cells, keratin pearls

Melanocytic tumors-

Arise from nevus cells, epidermal melanocytes, dermal melanocytes.
Neural crest origin, nevus cells arranged in nests, lack dendritic processes

Benign melanocytic tumors

*__NEVI__ (nevocellular origin) 3 types

Junctional - flat, pigmented; nests of nevus cells at ***epidermal-dermal JUNCTION***. Thought to have malignant potential
Compound-usually slightly elevated or papillomatous, pigmented. Nevoid nests at JUNCTION and in DERMIS, junctional component gives malignant potential
Intradermal (dermal) -**most common** type; papillomatous, dome-shaped or pedunculated, many slightly pigmented or amelanotic, hair shafts indicate intradermal variety, malignant change extremely rare. Amelanotic lesions frequently misdiagnosed clinically as papillomas
Nevoid nests separated from epidermis by collagenous GRENZ ZONE, may "infiltrate" orbicularis muscle.
Nevus Polarity-
Type A nevus cells in upper dermis larger;

Type B in mid-dermis smaller, lymphoid;
Type C in lower dermis fibroblastic, spindled nuclei, little or no melanin.

Other types of nevi

Blue nevi and cellular blue nevi (dermal melanocytes-spindled or dendritiform)
Nevus of Ota (oculodermal melanocytosis)
Balloon cell nevi
Spitz nevus (spindle or epithelioid cell nevus ("juvenile melanoma")
Congenital intradermal nevi (large (> 2cm) nevi are melanoma precursors 4-6%)

Benign pigmented lesion arising from dermal melanocytes

Blue nevi and cellular blue nevi
Nevus of Ota (oculodermal melanocytosis)

Benign pigmented lesions arising from epidermal melanocytes

Freckle (ephelis)-hyperpigmentation of basal cells, melanocytes not increased.
Lentigo simplex- evolving junctional nevus; increased number of basal melanocytes, elongated rete ridges
Lentigo senilis- 90% of elderly whites, evolves into adenoid seborrheic keratosis

Malignant Melanocytic Tumors

***Malignant melanoma- rare (**1% of eyelid malignancies in U.S.)

Lentigo maligna (Hutchinson's malignant freckle)
Elderly, sun-exposed skin, flat pigmented macule with irregular borders
Diffuse hyperplasia of atypical pleomorphic melanocytes at basal cell layer, involves pilosebaceous units. Malignant transformation in 25-30%

Lentigo maligna melanoma- (vertical growth phase) - fascicles of spindle-shaped cells. 10% metastasize. 5 year survival -90%

Superficial spreading melanoma (Pagetoid melanoma)
Patients younger, nonexposed skin (upper back, legs); spreading faintly palpable macule with irregular outlines, variable pigmentation. Pagetoid nests in all levels of epidermis, Invasive phase marked by papules and nodules, varicolored appearance, white areas of spontaneous regression, 5 year survival- 69%

Nodular melanoma
Age 40-50, 2 men/1 woman, always palpable, rapid growth 5 year survival-44%

Acral lentiginous melanoma- palms and soles, subungual regions

Skin melanomas and nevi
20% of nodular and 50% of superficial spreading arise from nevi
Clinical signs of **malignant transformation**:
Change in color (red, white and blue, sudden darkening)
Change in size
Crusting, bleeding, ulceration
Softening or friability
Pain, itching, or tenderness
Change in shape (e.g., rapid elevation of flat lesion)
Change in surrounding skin (e.g., redness, swelling, satellites)

Prognostic factors in dermal malignant melanoma

Clark classification	**5 year survival**
LEVEL I - epidermis only, basement membrane intact	100% LMM
LEVEL II - early invasion of papillary dermis	100% LMM
LEVEL III - fills entire papillary dermis	80% SSM
LEVEL IV - reaches reticular dermis	65% NM
LEVEL V -invades subcutaneous tissues	15% NM

Tumor thickness (Breslow)
<0.76 MM- 100% five year survival
>01.5 MM- <50% five year survival
Histologic type- LMM best, SSM intermediate, nodular worse
Other factors associated with poor prognosis: male sex, lesions of trunk and mucous membranes, lymph node involvement, ? amelanotic lesions, mitotic index, absence of lymphocytic infiltrate at base of lesion.
BRAF and C-KIT activating mutations- therapeutic targets
"vemurafenib" for **V**600**E** B**RAF** mutation.

Familial atypical mole melanoma (FAM-M) syndrome (dysplastic nevus syndrome, B-K mole syndrome)
Autosomal dominant; multiple large atypical nevi in childhood,
Patients at high risk for cutaneous melanoma, intraocular tumors reported

Other eyelid lesions

***Xanthelasma**
Soft flat or slightly elevated yellowish plaques- inner canthi
May have normal lipids, half have lipid disorders
Aggregates of foamy, lipid-laden histiocytes around vessels in dermis.
(Note: atypical xanthelasma-like lesions may herald xanthogranulomatous disorders: Erdheim-Chester Disease, necrobiotic xanthogranuloma with paraproteinemia, orbital xanthogranuloma with adult-onset asthma

Fibrous histiocytoma
Juvenile xanthogranuloma (JXG) macronodular type
Langerhans' cell histiocytosis
Lipoid proteinosis (Urbach-Wiethe) *1q21 extracellular matrix protein gene 1*
Autosomal recessive, multiple waxy nodules along lid margins (moniliform blepharosis), hoarseness due to laryngeal involvement, intracranial calcification
Deposits of hyaline material in dermis, submucosa

Sweat Gland Tumors

Syringoma
Multiple facial nodules, young women
Tadpole-shaped ductules with dual epithelial lining in desmoplastic stroma

Eccrine acrospiroma (clear cell hidradenoma)
Syringocystadenoma papilliferum
Hidradenoma papilliferum
Pleomorphic adenoma (benign mixed tumor of skin)
Endocrine mucin-producing sweat gland carcinoma- IHC + for neuroendocrine markers, ER; precurser of mucinous carcinoma
Mucinous sweat gland adenocarcinoma (can metastasize)
Must R/O met from colloidal breast carcinoma; IHC identical
Eccrine sweat gland adenocarcinoma (signet ring carcinoma)
Adenoma and apocrine adenocarcinoma of gland of Moll

Tumors of hair follicle origin

Pilomatrixoma (pilomatricoma, calcifying epithelioma of Malherbe)
Reddish mass on upper lid or brow, basophilic hair matrix cells and necrotic shadow cells, calcification develops in necrotic areas of shadow cells, foreign body giant cells common

Trichoepithelioma (Brooke tumor)
Multiple tumors may be inherited as autosomal dominant; CYLD gene, 16q12.1)
Multiple horny cysts with fully keratinized center surrounded by islands of proliferating basaloid cells

Trichofolliculoma
Most differentiated pilar tumor, hamartoma
Slightly elevated umbilicated nodule, small white hairs in pore highly suggestive
Central dilated hair follicle filled with keratin surrounded by branching immature hair follicles

Trichilemmoma
Benign, arises from glycogen-rich clear cells of outer hair sheath
Solitary papules or nodules with irregular rough surface
Lobular acanthosis of PAS+, diastase-sensitive clear cells
Central hyalinization, usually several hair follicles
Peripheral palisading, distinct basement membrane

Cowden disease: multiple hamartomas, especially facial trichilemmomas; marker for breast or thyroid cancer *(AD, 10q23, PTEN tumor suppressor gene)*

Eyelid involvement in systemic disease

Sarcoidosis
Ocular involvement in 38%, skin involvement in 23%
Slightly elevated and umbilicated papules, may be partially depigmented in blacks; noncaseating epithelioid tubercles

Primary systemic amyloidosis
Multiple confluent yellowish or waxy papules, hemorrhage (purpura) spontaneously, or with minor trauma

Leprosy
Ocular involvement most common in lepromatous leprosy
Madarosis (loss of brows and lashes) starts laterally

Mycosis fungoides
Cutaneous t-cell lymphoma, Lutzner cells, Pautrier abscesses

Lymphomatoid papulosis: CD30 positive, may resemble keratoacanthoma

Miscellaneous Eyelid Lesions - rare!!

Merkel cell tumor (cutaneous apudoma, trabecular carcinoma)
Dermal neuroendocrine tumor with neurosecretory granules
Painless violaceous or reddish-blue cutaneous nodule, carcinoid-like histology
20% fatal, wide local resection with frozen section control, focal CK20 staining
Merkel cell polyoma virus

Phakomatous choristoma (Zimmerman tumor)

Pseudorheumatoid nodule (granuloma annulare)
1st decade, lateral canthus and lateral upper lid
Zonal granuloma surrounding central necrobiotic collagen
No associated systemic disease

Nodular fasciitis: benign reactive proliferation of myofibroblasts

Juvenile fibromatosis (also orbit, pediatric tumor, distinguish from fibrosarcoma)

Granular cell tumor (granular cell myoblastoma)
Benign lid margin nodule composed of cells with abundant acidophilic granular cytoplasm, PAS + granules, basement membrane, s-100 +, ? Modified Schwann cells

Eyelid metastases
Common primaries: breast, lung, cutaneous malignant melanoma, may mimic atypical chalazion clinically
Breast metastases may have "histiocytoid" histology

Erdheim-Chester disease- xanthogranulomatous infiltrate, atypical xanthelasma

Necrobiotic xanthogranuloma – “atypical xanthelasma”, necrosis, mult myeloma

Carney complex (autosomal dominant syndrome- PRKAR1A- 17q**)**
Myxomas, spotty mucocutaneous pigmentation, and endocrine abnormalities
Myxomas- skin, breast, **heart** (cardiac myxomas: multiple,venticular, early onset)
Pigmented spots on face, conjunctiva, **plica semilunaris**
Rare testicular tumors in males (large cell calcifying sertoli tumors), endocrine abnormalities
Eye findings can herald potentially fatal cardiac myxoma

Intravascular papillary endothelial hyperplasia
Most within distended vein, confusion with angiosarcoma, also orbit

Silica granuloma of the eyelid
Foreign body granuloma, may mimic sarcoidosis

CONJUNCTIVA

Histology
Nonkeratinized squamous epithelium with goblet cells
Substantia propria: loose connective tissue stroma
Palpebral conjunctiva firmly adherent to tarsus
Substantia propria of bulbar conjunctiva is areolar, permits chemosis

Pseudoglands of Henle
Gland-like invaginations formed by proliferating tarsal conjunctival epithelium and goblet cells, lymphocytes and plasma cells in stroma

Acute conjunctivitis
Hyperemia, chemosis and exudation
Bacterial conjunctivitis-
Conjunctival smear: polys, bacteria
Remember: **gonococcus will be blue on Giemsa stain**
Viral conjunctivitis
Conjunctival smear: lymphocytes

Chronic conjunctivitis

Follicular conjunctivitis
Follicles: gray-white round to oval elevations, avascular center, vessels at periphery
Well-circumscribed focus of **lymphoid hypertrophy**: reactive hyperplasia of conjunctiva's resident population of lymphocytes
Overlying epithelium usually thinned.

Differential diagnosis of follicular conjunctivitis

Infectious -*acute*
Adenoviruses- (Type 3-PCF [pharyngoconjunctival fever], Type 8-EKC); Herpes simplex virus; Newcastle virus (swimming pool conjunctivitis); Enterovirus 70 (acute hemorrhagic conjunctivitis); Inclusion conjunctivitis of adults (paratrachoma); Blood-borne (measles, German measles)

Infectious- *chronic*
Trachoma, Psittacosis, Moraxella, Infectious mononucleosis

Non-infectious
Pseudotrachoma, Topical medications (IDU, Eserine, Atropine), Cosmetics, Antigenic material (e.g. molluscum contagiosum, "crab" droppings, allergy (exogenous agents), physiological folliculosis of childhood

Papillary hypertrophy (conjunctival papillae)

Nonspecific change, tarsal conjunctiva, **central vascular tuft**, pale avascular valleys, epithelial proliferation, stromal hyperplasia. Deep infoldings of epithelium, rich vascular stroma with chronic inflammatory cells, granulation tissue

Vernal conjunctivitis

Bilateral, recurrent, adolescents with atopic history
Itching, worse in spring, thick ropy discharge with eosinophils (Maxwell-Lyon sign)
Giant "cobblestone" papillae- upper tarsus, limbal papillae, Horner-Trantas dots
Path- **chronic papillary hypertrophy**
Epithelial hypertrophy, then atrophy
Fibrovascular papillary core contains perivascular and diffuse infiltration of lymphocytes and plasma cells, numerous eosinophils
Trantas dot: intra- and subepithelial collection of eosinophils, cellular debris
Limbal vernal: more common in blacks

Giant papillary conjunctivitis

Similar to vernal, soft and hard CL's, ocular prostheses
Fewer eosinophils than vernal, basophils

Parinaud oculoglandular syndrome

Granulomatous conjunctivitis with regional lymphadenopathy (preauricular node)
Differential diagnosis: Bacterial conjunctivitis, **cat scratch fever** (silver stain for bacteria- *Bartonella henselae*), Tularemia, Tuberculosis, Actinomycosis, Leptothrix, syphilis, Rickettsia, Chlamydia (Lymphogranuloma venereum), Viruses (especially Ebstein-Barr [infectious mono]), Sarcoidosis

Chlamydial conjunctivitis

TRIC agent (**tr**achoma, **i**nclusion, **c**onjunctivitis) small obligate intracellular parasites sensitive to antibiotics, elementary body, initial body, inclusions

Trachoma

One of the most significant causes of blindness in the world
Spread by direct contact, secretions, insects, poor hygiene
Bilateral keratoconjunctivitis, may be asymmetrical
Initial epithelial infection followed by subepithelial inflammation with follicles in substantia propria
Conjunctival smear: polys and lymphocytes
Epithelial cells contain initial bodies, **basophilic intracytoplasmic inclusions of Halberstaedter and Prowaczek**
Immunohistochemical stains available
WHO Diagnostic Criteria (must have 2)
1. Lymph follicles on the upper tarsus
2. Conjunctival scarring (Arlt's line)
3. Vascular pannus (Inflammatory pannus destroys Bowman membrane)
4. Limbal follicles or remnants of limbal follicles in late stages (Herbert's pits)

MacCallan classification

STAGE I: Initial conjunctival follicle formation, diffuse punctate keratitis, early pannus
STAGE IIA: Florid follicular conjunctivitis with follicular necrosis
STAGE IIB: Papillary conjunctivitis
STAGE III: Cicatricial stage with secondary sequelae
STAGE IV: Arrest of the disease

Inclusion conjunctivitis (paratrachoma)

Inclusion blenorrhea in infants, major cause of acute purulent conjunctivitis in newborn

Inclusion conjunctivitis in adults - venereal disease. Follicles in lower fornix

Conjunctival Membranes

True membrane

Inflammatory exudate **firmly adherent to epithelium**, **bleeding** occurs when peeled, e.g.-diphtheria, gonococcus, beta-hemolytic strep, Stevens-Johnson syndrome

Pseudomembrane

Less adherent, **peels without bleeding**. e.g., -viral (HSV, adenovirus 8 [EKC], adenovirus 3 [PCF]); bacterial (staph, pneumococcus, meningococcus, pseudomonas, coliforms); chemical burns, ocular pemphigoid, foreign body, ligneous conjunctivitis

Ligneous conjunctivitis (AR mutations in plasminogen gene, 6q26)

Bilateral, chronic pseudomembranous conjunctivitis, begins in childhood, may recur

Massive, woody accumulation of **fibrin** (not MPS), granulation tissue

An autosomal recessive systemic disease- similar lesions in vagina, other mucosae; obstructive hydrocelphalus has been reported

Mycotic, parasitic conjunctivitis, etc.

Rhinosporidiosis

Large round fungus causes infectious strawberry-like papilloma studded with white microabscesses, pathognomonic histology with sporanga, large round trophozoites, rare in USA, most cases in India

Ophthalmia nodosa

Caterpillar hairs (setae), may invade anterior chamber

Synthetic fiber granuloma (“teddy bear granuloma”)

Epibulbar foreign body granulomatous response to synthetic fabric "fuzz balls", can mimic ophthalmia nodosa, fabric fibers contain delustering agent,

Allergic conjunctival granuloma (Ashton)

Presumed parasitic granulomas; Splendore-Hoeppli phenomenon (eosinophilic deposits of antigen-antibody complexes)

Filaria- Loa loa “eye worm”

Allergic conjunctivitis

Contact hypersensitivity (acute allergic conjunctivitis)

Hay fever, animal dander, topical drugs

Chemosis, itching, dermatitis

Eosinophils in smear

Acute anaphylactic reaction due to mast cell degranulation

? cell-mediated hypersensitivity reaction

Phlyctenular conjunctivitis

Hypersensitivity to bacterial proteins

2-3 mm whitish inflammatory nodules on bulbar conjunctiva surrounded by zone of dilated vessels, epithelial ulceration

Degenerations

***Pinguecula**

Raised yellowish-white mound of degenerated subepithelial connective tissue near limbus in interpalpebral space (actinic elastosis)

Probably related to environmental exposure, light damage

Histology: solar elastosis, acellular homogeneous deposit, basophilia, thickened vermiform collagen fibers, late hyaline deposits. Elastotic material stains

positively with Verhoeff-van Gieson elastic stain, but is not sensitive to elastase digestion.
Similar findings in some cases of pterygium
Material may stimulate granulomatous response in advanced cases ("actinic granuloma")

Amyloidosis
Yellow, avascular deposits, bulbar or palpebral conjunctiva
"Starch-like" acellular eosinophilic material, Congo Red, Crystal Violet, Thioflavin-T positive, apple-green birefringence, dichroism with polarization microscopy. Often light chain amyloid, but typically unassociated with systemic disease

Conjunctival Cysts and Tumors

Congenital Cysts

Inclusion Cysts
Lined by conjunctival epithelium; lumen empty or filled with mucous; traumatic or surgical implantation

Ductal Cyst
Analogue of sudoriferous cysts in skin, arise from accessory lacrimal glands
Dual layer of epithelium, clear lumen

***Solid Epibulbar Dermoid**
Choristomatous mound of interweaving, coarsely-thickened collagen fibers covered by skin-like epithelium, often with epidermal appendages (hair, sebaceous and sweat glands).
An isolated finding, or in association with **Goldenhar syndrome**:
(epibulbar solid dermoids, preauricular appendages, aural fistulas)

Complex Choristoma: also contains cartilage, fat and/or lacrimal gland elements

Dermolipoma (dermolipoma)
Choristoma of fat and connective tissue,
Can extend deep within orbit, avoid surgery or excise carefully!

Epibulbar Osseous Choristoma - mature bone, superotemporal quadrant

***Pyogenic Granuloma**
Fleshy red mass of exuberant granulation tissue ("proud flesh")
Abberrant inflammatory repair response.
May form after surgery, e.g, chalazion I&D, strabismus, etc (see inflammation)

Conjunctival Neoplasms- 3 basic categories:
Squamous - proliferation of conjunctival squamous epithelium
Lymphoid- proliferation of normal resident population of lymphocytes
Melanocytic

Squamous lesions (OSSN - Ocular Surface Squamous Neoplasia)

***Squamous Papilloma**
Benign proliferation of conjunctival epithelium as multiple fronds with central fibrovascular cores
Vascular "hair-pin" loops clinically
Bulbar or palpebral conjunctiva
Can be multiple and recurrent, especially in children
Many are viral lesions (HPV, human papilloma virus), DNA hybridization
NOTE: conjunctival dysplasia or squamous carcinoma can have papillomatous configuration.

Inverted Papilloma

Hereditary Benign Intraepithelial Dyskeratosis-

Inherited disorder of triracial "Haliwa-Saponi Indians" in North Carolina. 4q35
Nonmalignant leukoplakic squamous lesions of conjunctiva and other mucous membranes marked by dyskeratosis (single cell keratinization)

*** Actinic keratosis**

Focal, leukoplakic; epidermoid cells, parakeratosis, actinic elastosis
Rarely recur

Conjunctival Intraepithelial Neoplasia (**CIN**, **OSSN: Ocular Surface Squamous Neoplasia**, Dysplasia)

A disease spectrum characterized by a replacement of the conjunctival epithelium by atypical squamous cells. Basal germinative layer involved first. Characteristically abrupt transition between normal and acanthotic dysplastic epithelium. Interpalpebral limbal location, keratinization (leukoplakia) clinical marker for squamous lesion, often diffuse, some lesions gelatinous, frequently recur; characteristic vascular loops

Mild dysplasia: < 50% of epithelium replaced
Severe dysplasia: >50% of epithelium replaced

Some cases are caused by viral infection with human papillomavirus (HPV)
In situ DNA hybridization has demonstrated **HPV 16/18**
Tumor immunoreactive for CK17, p53, cycling cells (Ki-67), negative for CK,
Normal conjunctiva CK7+/CK17= and p53 negative, very low cycling index

Carcinoma in situ:

Total replacement of epithelium by frankly malignant cells.
Epithelial basement membrane is intact, no invasion into substantia propria
Spindle and epidermoid variants.

Invasive squamous cell carcinoma:

Malignant cells have broken through epithelial basement membrane invading substantia propria
Squamous cell carcinoma may have papillary growth pattern
Rarely can invade interior of globe, eyelid, orbit
More common in Middle East, Africa (association with HIV/AIDS in Africa)
Rarely metastasizes, excise locally

Mucoepidermoid carcinoma

Rare variant of squamous cell with mucin production
Behaves more aggressively with early invasion and recurrence

Spindle Cell Carcinoma- (sarcomatoid squamous cell carcinoma) aggressive, poorly-differentiated variety of squamous cell carcinoma, may be cytokeratin (-)

Lymphoid tumors (See further discussion in orbit section)

Arise from conjunctiva's resident population of lymphocytes
"Salmon-patch" or fish-flesh appearance clinically
Reactive lymphoid hyperplasias, atypical lymphoid hyperplasia or malignant lymphomas. Most are stage IE well-differentiated lymphocytic lymphomas, i.e., **Extranodular Marginal Zone Lymphomas (EMZL) of mucosa associated lymphoid tissue** - (WHO classification) or **MALT lymphomas**
CD20+, CD5-, CD10-, CD23-)
Systemic malignant lymphoma rarely presents as a conjunctival lesion.
Associated systemic disease in 20% (prior, concurrent or subsequent -Jakobiec) 31% in Shields clinical series; esp with forniceal or midepibulbar involvement
Follicular appearance suggests benign process clinically

Benign lesions have following histopathological features:

Germinal centers (N.B. small residual follicles may be present in EMZL)
Abundant capillaries with plump endothelial cells

Polymorphous infiltrate containing mixture of cells, i.e., mature lymphocytes, plasma cells, eosinophils.

?? Polyclonal infiltrate with immunohistochemical markers

Flow cytometric assessment of lymphoid markers Is opitimal, but the amount of tissue in conjunctival lesions isoften insufficient. In such cases immuno can be done on paraffin sections.

Signs of malignancy: monomorphic infiltrate, cytologic atypia, monoclonality

Management: noninvasive systemic workup, low dose radiotherapy, ? rituximab

Questionable association of conjunctival MALT lymphoma with with *Helicobacter pylori* or *C. psitacci* infection is controversial; ? role of antibiotics

Melanocytic tumors

Racial (constitutional or complexion-related) melanosis

Pigment in squamous cells- no atypical melanocytic hyperplasia; usually most intense in basal cells, caps of melainin cover more superficial nuclei

Note: squamous tumors in darkly pigmented individuals may be pigmented due to secondary acquired melanosis – contain bland dendritic melanocytes

Freckles (ephelis)

Congenital, increased melanin in basal epithelium, normal number of melanocytes; indistinguishable from PAM without atypia

***Nevi**

Most are derived from dendritic melanocytes within epithelium
(blue nevi and Neuvs of Ota are exceptions)

Nests of benign nevus cells along epithelial base (junctional activity) and/or substantia propria, may be amelanotic

A congenital lesion- typically enlarge or become more pigmented at puberty or during pregnancy, cosmesis often an indication for excision

3 variants:

Junctional: nevus cells confined to epithelial-subepithelial junction (anterior to the epithelial basement membrane)

Junctional nevi of the conjunctiva occur in children and are extremely rare!!! (They are nearly impossible to distinguish from primary acquired melanosis in a small biopsy without an adequate clinical history...

The junctional component diminishes with age- A junctional nevus of the conjunctiva in an adult is PAM until proven otherwise!!!)

Subepithelial: nevoid nests confined to substantia propria- found in older patients whose nevi have lost junctional component

Compound:(Many conjunctival nevi are compound!!)

Nevus cells in both locations. **Cystic or solid epithelial rests** are very common in compound conjunctival nevi, They suggest a nevus clinically, but do not rule-out melanoma because malignant transformation of nevi is possible; size of cysts increases with age

Subepithelial nests of nevus cells typically do not stain for HMB45 and have scant cellular cyclinig with KI-67 proliferation marker.

Melanomas typically are HB45 positive with more cycling. Both stain with Melan A.

Blue nevi- Slender pigmented spindle cells and dendritiform cells in substantia propria. Blue nevi appear dark brown in conjunctiva.

Cellular blue nevi

Combined nevus- combination of nevocellular and blue nevus

***Nevus of Ota**

(Congenital Oculodermal Melanocytosis)

Slate gray pigmentation due to dendritiform nevus cells deep in substantia propria and episclera, associated blue nevus of periocular skin

Heterochromia iridum reflects diffuse nevus of uvea.

Predisposition to uveal, orbital, & meningeal melanoma; ***not*** conjunctival MM

***Primary acquired melanosis** (PAM**,** Reese's Cancerous Melanosis. C-MIN, IMP)

Unilateral pigmentation in middle-aged or elderly whites

Insidious onset, waxes and wanes, malignant potential

32% incidence of progression to melanoma in older series **(much too high!!).**

Shields' recent series- 13% progression to melanoma – (PAM with severe atypia)

Extent in clock hours an important prognostic factor

PAM without atypia - epithelial hyperpigmention with or without benign melanocytic hyperplasia restricted to basilar region of epithelium. Melanocytes show no nuclear hyperchromaticity or prominent nucleoli. Very low risk for conjunctival melanoma (0%- Shields)

PAM with atypia: Atypical melanocytic hyperplasia or **malignant melanoma *in situ* involving conjunctival epithelium**

High risk for developing conjunctival melanoma!!!

75% if PAM contains **epithelioid cells**

90% if **Intraepithelioid pagetoid spread** is present

(Only 20% if atypical melanocytes confined to basilar part of the epithelium)

Atypical cells confined to epithelium constitute **radial growth phase**

Vertical growth phase-invasive malignant melanoma

PAM can be amelanotic (**primary acquired melanosis *sine pigmento***) and can occur in blacks (rare)

UV (Wood's light) may highlight subtle pigmentation

Management: Observe carefully with photographic documentation. Biopsy thickened areas (presumptive melanomas), excision, cryotherapy, ? mitomycin C

Controversy about terminology:

(**C-MIN**: conjuctival intraepilthelial neoplasia (Damato- Coupland) vs **IMP**: intraepithelial melanocytic proliferation (Jakobiec)

Important questions for pathologist when assessing pigmented conjunctival lesions:

- *Is melanocytic hyperplasia present, or is pigment within epithelial cells?*
- *If melanocytic hyperplasia is present are the melanocytes atypical*
- *Where are the melanocytes located? (at base or all levels of epithelium)*
- *What is the pattern of atypical melanocytic hyperplasia?? (at base of eoithelium –'lentigious', nests, pagetoid involvement, melanoma in situ)*

***NB; Immunohistochemical stains greatly facilitates evaluation* of pigmented lesions** (melanocytic hyperplasia can be inapparent in routine H&E sections)

- Melan A and SOX10 are excellent markers for melanocytes
- HMB45 more likely positive in malignancies (but not 100%)
- Ki-67 to assess cellular cycling index (mitoses rare)
- (The use of red chromagen in recommended in pigmented lesion)

Old Zimmerman Classification of PAM

Stage I-Benign Acquired Melanosis

A. with minimal melanocytic hyperplasia (increased melanin within epithelium)

B. with atypical melanocytic hyperplasia
1. mild to moderately severe
2. severe ("in situ" malignant melanoma)

Stage II-Malignant Acquired Melanosis
A. with superficially invasive melanoma (tumor thickness < 1.5mm)
B. with more deeply invasive melanoma (tumor thickness > 1.5mm)

Malignant melanoma of the conjunctiva

Relatively rare: uveal/conjunctiva MM ratio 10/1 (AFIP)
26% mortality, unpredictable behavior
(Note: Callender classification is not applicable to conjunctival melanomas!!)

Can arise from:
Primary acquired melanosis *(majority of cases)*
Preexisting nevus
De novo (nodular melanoma)

Primary acquired melanosis found in 75%, Nevi 25%
Conjunctival melanomas behave like skin melanomas, not uveal melanomas
Have BRAF mutations like skin melanomas (not found in uveal melanomas)
Lymphatic spread common (preauricular and intraparotid nodes)-poor prognosis.
Within lymph nodes melanoma cells gain access to blood vessels via anastomoses between lymphatics and blood vessels.
Sentinel node biopsy has its advocates
Factors associated with poor prognosis: extralimbal tumor location, nasal location, caruncular involvement, involvement of surgical margins, de novo melanoma without PAM, inadequate initial surgical management

Differential Diagnosis of Pigmented Epibulbar Lesions

	Congenital Melanosis	Acquired Melanosis	Nevus	Malignant Melanoma
Location	episcleral subepithelial	intraepithelial	intraepithelial subepithelial	intraepithelial subepithelial
Course	stationary	waxes & wanes	stationary	progressive
Special Features	heterochromia iridis		epith cysts	
Pigmentation	slate gray	variable	variable	variable
Inflammation	(-)	(+)	(+)	(++)

Other pigmented lesions of the conjunctiva

Argyrosis (silver containing eye drops, Argyrol)
Senile scleral plaque (of Cogan) calcification
Ochronosis (alkaptonuria; homogentisic acid oxidase deficiency)
Drug deposits (epinephrine; phenothiazine; tetracycline)
Cosmetics (mascara, kohl)

CORNEA

Congenital Lesions

Microcornea <11mm
Megalocornea >13mm
X-linked inheritance, deep anterior chamber, no dm ruptures
Cornea Plana
Bilateral, familial (autosomal dominant or recessive)
Corneal flattening with peripheral opacification
Sclerocornea
Cornea diffusely scarred and vascularized resembling sclera
No hereditary pattern
Epithelium thickened, Bowman membrane absent, anterior third of stroma scarred and vascularized, Descemet membrane very thin.
Solid epibulbar dermoids and complex choristomas (see conjunctiva)
Goldenhar syndrome (hemifacial microsomia with epibulbar dermoids)
Axenfeld/Rieger syndrome
(dysembryogenesis of the angle, "mesodermal dysgenesis", angle cleavage syndromes) AD, several genes- (PITX3, PITX2, FOXC1, RIEG2)
A **clinical spectrum** that includes:
Posterior embryotoxon of Axenfeld
Prominent, anteriorly displaced Schwalbe's ring
Axenfeld Anomaly
Posterior embryotoxon plus iris processes to ring
50% have glaucoma
Rieger Syndrome

Axenfeld anomaly plus iris stromal defects such as hypoplasia, slit pupils, polycoria, pseudocoria;
Skeletal and dental anomalies, umbilical hernia;
Autosomal dominant, 50% have glaucoma

Peters Anomaly
Bilateral central corneal opacities, iridocorneal and keratolenticular adhesions
Descemet and Bowman membrane absent centrally, anterior polar cataract
Mutations in PAX6, PITX2, CYP1B1 or FOXC1, fetal-alcohol syndrome, Accutane®

Posterior Ulcer of von Hippel
Congenital corneal opacities
Resembles Peters but no lens involvement
Endothelium and Descemet membrane absent centrally

Posterior Keratoconus
Posterior umbilication of central corneal stroma
Descemet membrane present, but thin

Congenital Corneal Staphyloma
Markedly atrophic iris adheres to back of markedly thickened, scarred, and vascularized cornea

Inflammatory Conditions

Acute keratitis and corneal ulcerations

Bacterial
Polys collect between lamellae, basophilic necrosis, stromal loss, ulceration

Fungal
Fungal hyphae permeate stroma, often located deep- may be missed in superficial scraping, readily perforate Descemet membrane & invade anterior chamber
In USA, 80% caused by Aspergillus, Candida, or Fusarium

Mycobacterial
M. tuberculosis, atypical mycobacterial infections, leprosy

Descemetocele: herniation of Descemet membrane through floor of deep corneal ulcer

Infectious Pseudocrystalline keratopathy
Large interlamellar bacterial colonies with vaguely crystalline configuration
Adjoining stroma relatively non-inflammed
Avirulent strains of *Streptococci* sequestered by glycocalyx
Typically occurs in corneal grafts on chronic steroid therapy

Viral Keratitis

Chronic keratitis
Lymphocytes, plasma cells, vascularization

Herpes simplex disciform keratitis

***Herpes Simplex Keratitis**
Most common infectious keratitis leading to visual loss in USA and Europe; HSV type I; frequent recurrence due to latent virus in Gasserian ganglion

Dendritic keratitis
Primary epithelial infection, Cowdry type A intranuclear inclusion bodies, cultures positive in 75%

Geographic epithelial keratitis

Disciform keratitis (deep stromal keratitis without ulceration)

Cultures negative, but TEM has shown virus in stroma
May be primarily an immune reaction to persistent viral antigen rather than infection (recent controversy)
Scarring, lymphocytes and plasma cells
Granulomatous reaction to Descemet membrane (suggestive of Herpes but also seen in other entities

Deep keratitis with ulceration (metaherpetic keratitis)
Stromal thinning, perforation, Descemetocele

Granulomatous reaction to Descemet membrane
(classically associated with chronic herpetic keratitis, but not pathognomonic)

Parasitic keratitis- ***Onchocerca volvulus*** (onchocerciasis)
"River blindness"- major cause of blindness worldwide
Vector (black simulian fly) breeds in swift-running mountain streams
Adult worms breed in dermal nodules releasing microfilaria
Secondary closed angle glaucoma due to keratitis; chorioretinal degeneration

Protozoal keratitis-

*__Acanthamoeba keratitis__ (*A. castellani, polyphaga*)
Soft contact wearers, contaminated solutions, homemade saline, swimming or bathing in hot tubs while wearing lenses
PK may be necessary, patients typically have severe pain (? neurotropism)
Annular infiltrate (ring ulcer) - a late finding
Amoebic cysts, trophozoites, moderate necrosis in stroma, loss of epithelium and keratocytes. Cysts are readily seen in routine H&E stains; previously touted Calcofluor white fluorescent stain no longer available in many areas

Microsporidial keratitis- may mimic Herpes. microsporidia may be birefringent

Chronic keratitis
Lymphocytes, plasma cells, vascularization

Interstitial (stromal) keratitis

Herpes simplex disciform keratitis (see above)

Luetic (syphilis)- Old luetic IK
In patients with congenital syphilis; first or second decade;
Rarely seen in acquired syphilis, unilateral, sectoral.
Acute "salmon patch", severe photophobia, edema, lymphocytic infiltrate
Late findings: faint nebulous corneal opacity, deep ghost vessels
Bowman membrane lost; deep vessels (posterior 1/3 of stroma);
thickening of Descemet membrane, occasionally massive with formation of hyalinized bridges and strands

Tuberculosis, leprosy, Cogan Syndrome (non-luetic IK with deafness)
Protozoal (see above), onchocerciasis (see above), systemic disease (sarcoidosis, Hodgkin disease, mycosis fungoides), foreign bodies (insect hairs [ophthalmia nodosa]), plant material, drugs (systemic gold, arsenic), trachoma (see conjunctiva)

Inflammatory pannus
Peripheral ingrowth of fibrovascular membrane beneath epithelium
Bowman membrane is destroyed (classically seen in Trachoma)

Degenerative pannus
Common finding in chronically edematous corneas
Bowman membrane intact
Fibrous tissue interposed between base of epithelium and Bowman membrane

Peripheral ulcerations

Marginal ulcers

Staphylococcal toxins

Collagen vascular diseases: Lupus, periarteritis nodosa, Wegener granulomatosis, rheumatoid arthritis

Ring ulcers

Mooren ulcer

In USA, unilateral disease of elderly

In Africa, severe bilateral disease in young

Central overhanging margin of ulcer

Immune disorder? ischemic necrosis? limbal collagenase? assoc with hepatitis C

Terrien ulcer

Bilateral, slowly progressive, males

Trough-like stromal thinning begins superiorly

Epithelium intact, Bowman and superficial stroma lost

Vascularization, occasional lymphocytes and plasma cells

Corneal degenerations

***Pterygium** (*pter:* "wing" - lesion resembles insect wing)

Interpalpebral fissure, most common nasally

Caused by environmental factors: light, dust, wind?? limbal stem cell loss??

Resembles conjunctiva histologically, but invades cornea

Increased stromal vessels, often has elastotic degeneration of collagen

Bowman membrane lost; overlying epithelial dysplasia possible

***Calcific band keratopathy**

Interpalpebral cornea, begins at limbus, clear zone, holes

Calcification of Bowman membrane and anterior stroma secondary to ocular inflammation (Still disease, sarcoidosis), or systemic disease (hypercalcemia, vitamin D intoxication, Fanconi syndrome, gout, myotonic dystrophy, hypophosphatemia, "milk-alkali" syndrome, silicon oil, chronic RD)

Basophilic granules (“basophilic stippling”) in Bowman membrane

Non-calcific variant is form of chronic actinic keratopathy

***Chronic actinic keratopathy** (elastotic degeneration)

(Many synonyms: climatic droplet keratopathy, spheroidal degeneration, Labrador keratopathy, Bietti hyaline degeneration, etc.)

Common etiologic factor is **light damage**

Round, droplike deposits of amorphous, hyaline, mildly basophilic material

Stains + with Verhoeff-van Gieson elastic stain, autofluorescent to UV light

Yellow olive oil-droplet appearance clinically

May coexist with calcific band keratopathy

Salzmann's Nodular Degeneration

Whitish focal mounds of subepithelial hyaline connective tissue; Bowman membrane destroyed (massive focal degenerative pannus, ? cause)

Lipid keratopathy

Secondary deposition in heavily vascularized stroma

Corneal keloid

Massive scarring and thickening of stroma; epidermalization common

Corneal staphyloma

Atrophic iris adheres to posterior surface of massively thickened cornea

In underdeveloped regions frequently follows **measles keratitis**

Keratoconjunctivitis sicca

Deficient tear or mucous production
Corneal drying, SPK, filamentary keratitis (detached strands of epithelium and mucous)
Sjøgren syndrome (triad)
Keratoconjunctivitis sicca, xerostomia, rheumatoid arthritis
Lacrimal gland infiltrated with lymphocytes with persistent myoepithelial islands (lymphoepithelial lesion of Godwin); lymphoma develops in 10%

Xerophthalmia (avitaminosis A)
Corneal epithelial keratinization, epidermalization; night blindness, keratomalacia and perforation. Increased infant mortality. Malnourished children in underdeveloped countries, alcoholics in USA

Bitot spot

Exposure keratopathy

Dellen (Fuchs)
Focal stromal thinning central to elevated limbal lesion, surface ulceration.

Neurotrophic keratopathy (neuroparalytic keratopathy); bland melts

White limbal girdle of Vogt

White ring of Coats: ring opacity at level of Bowman, inferior half of cornea, iron-calcium protein complex

Secondary amyloidosis

Keratoconus
Bilateral, onset around puberty, heredity questionable
Association with: Down syndrome, atopic dermatitis, Ehlers-Danlos, Marfan syndrome, Leber congenital amaurosis, floppy mitral valve syndrome, hard contacts, floppy eyelid syndrome, eye rubbing
Central stromal ectasia, abnormal consistency of cornea, "***wiggly dehiscences"*** **in Bowman membrane,** DM thin, endothelium often healthy
Munson sign, Vogt striae, stromal folds, Rizutti sign
Ruptures in Descemet lead to **acute hydrops** (especially in Down syndrome)
Fleischer ring surrounds cone (iron in epithelium)
Cause uncertain,? abnormality in extracellular matrix?, ? defect in tissue metalloproteinase inhibitors?
DALK – pneumatic artifact in stroma from air injection

Pellucid degeneration
Resembles keratoconus histopathologically, hydrops possible

CORNEAL RINGS

Corneal iron lines - ferritin particles within epithelium	
Fleischer ring:	keratoconus, surrounds base of cone
Hudson-Stähli:	horizontal, line of lid closure, physiological aging
Stocker:	advancing head of pterygium
Ferry line:	in front of filtering bleb (Ferry = filter)

Arcus Senilis
Deposition of lipid in stroma, similar clinically inapparent deposit in sclera

Arcus Juvenilis
Arcus at an early age (< age 40 in males may be significant for ASCVD)
May occur in Type II and III hyperlipoproteinemia

Corneal lipid deposition also occurs in hypolipidemia syndromes :LCAT deficiency, fish eye disease, Tangier disease

Kayser-Fleischer Ring (Wilson hepatolenticular degeneration)

Copper in Descemet membrane (corneal copper also in chalcosis, primary biliary cirrosis, rare cases of myeloma or lung tumors that make copper transport proteins)

Corneal dystrophies

Definition: In classic ophthalmic usage, dystrophy usually denotes an inherited, relatively symmetric bilateral disease unassociated with vascularization or inflammation in its early stages. Commonly applied to hereditary diseases of the cornea and macula.

Dystrophy: modern concepts

Inherited genetic disorder (defective enzyme or structural protein)
Not evident at birth (becomes clinically evident later)
Pathology localized to an ocular tissue (systemic effects absent or inapparent)
Specific genetic defects recently have been elucidated in many dystrophies:

***NOTE:** Granular, lattice, Avellino and Reis-Bückler dystrophies have been shown to be associated with different mutations of the **TGFBI gene (formerly BIGH3)** on the long arm of chromosome 5. The corneal epithelium is rich in **TGFBI** protein. (also called **keratoepithelin)** Different patterns of aggregation or precipitation of the mutant forms of **TGFBI** protein presumably are responsible for the various clinical manifestations of the several dystrophies. (see table of mutations below)

Meesman dystrophy is caused by mutations in corneal epithelium-specific keratins K3 and K1

The **2015 Revision of the IC3D Classification of Corneal Dystrophies** now classfies corneal dystrophies as 1. epithelial and sub-epithelial dystrophies, 2. epithelial-stromal dystrophies caused by mutations in TGFBI, 3. stromal dystrophies, and 4, endothelial dystrophies. Category 2 includes the five corneal dystrophies caused by mutations in the TGFBI gene including Reis-Bücklers and Thiel-Behnke dystrophies that previously were classified as Bowman layer dystrophies. The revised classification also placed dystrophies into evidence-based categories. The claasification is available free on line.

Modified Classification of Corneal Dystrophies (Revised IC3D Classification- 2015)

1. Epithelial and sub-epithelial dystrophies,

Meesman Corneal dystrophy (Stocker-Holt)

Autosomal dominant, early onset, recurrent erosions, good vision
Myriad small punctate intraepithelial vacuoles, may pool fluorescein at corneal surface. Abnormal epithelial cells contain cytoskeletal "**peculiar substance**"
Thickened epithelial basement membrane. Increased epithelial fragility caused by mutations in corneal epithelial specific cytokeratins K3 and K12 (12q12-q13)

Epithelial Basement Membrane Dystrophy (Map, dot and fingerprint dystrophy, Cogan microcystic dystrophy)

A clinical spectrum that results from poor epithelial adhesion to its basement membrane

***Most cases are not inherited*, not considered a dystrophy**
(rare autosomal dominant cases have been reported)
Identical histopathological changes found in 56% of eyes with chronic bullous keratopathy, recurrent erosions) --
Pathogenesis: poor epithelial adhesion or bulla formation permits epithelial reduplication and/or folding with excess sub- or intraepithelial production of basement membrane material and collagen. Normal epithelial maturation modified by anatomical constraints
Clinical subtypes (often coexist)
Microcystic: white putty-like contents reflect degenerated epithelial cells trapped within disorderly epithelium
Fingerprint: parallel relucent lines of basement membrane separating tongues of reduplicated epithelium
Map (geographic): subepithelial connective tissue resembling degenerative pannus

Lisch Epithelial Corneal Dystrophy (band-shaped and whorled microcystic dystrophy)
Foci of epithelial cells contain intracytoplasmic vacuoles- Xp22.3

Gelatinous droplike corneal dystrophy (Familial Subepithelial Amyloidosis)
Massive subepithelial amyloid deposits, recurs rapidly after PK
Caused by mutations in **TACSTD2** gene (1p32.1),
Amyloid contains lactoferrin, but lactoferrin gene normal, many cases in Japan

2. Epithelial-stromal dystrophies caused by mutations in TGFBI

Reis-Bücklers Corneal Dystrophy
Autosomal dominant, begins in first decade with recurrent erosions
Subepithelial scarring, ring-shaped opacities
A superficial variant of granular dystrophy, may be confused with lattice dyst.
Irregular "saw-toothed" epithelium, subepithelial connective tissue, destruction of Bowman layer. Laminated pannus contains intensely eosinophilic crystalloids that stain like material in granular dystrophy (red with Masson trichrome)
TGFBI mutation- mutant kerato-epithelin, 5Q31.1

Thiel-Behnke Corneal dystrophy
Very similar to Reis-Bücklers clinically and pathologically, but storage material is composed by "curly filaments" shown by TEM; TGFBI mutation (also 10q24).1
Cases of Thiel-Behnke were reported as Reis-Bückler's in American literature

Lattice Corneal Dystrophy, type I (LCDI, Biber-Haab-Dimmer, Bückler Type III)
Localized corneal amyloidosis (Klintworth),
Autosomal Dominant, bilateral, onset first decade
PK usually necessary in 4th or 5th decade
Delicate branching relucent lines in stroma (Not degenerating corneal nerves)
Recurrent erosions; superficial scarring can mimic Reis-Bückler
Intrastromal and subepithelial deposits of **amyloid**
Amyloid stains **Congo red**, crystal violet, thioflavin T Positive
Apple green birefringence and **dichroism** with polarization microscopy
Material also PAS (+), argyrophilic (Wilder's reticulum)
Can recur in graft
TGFBI gene mutation - mutant protein forms amyloid, 5q31.1
(Other variants: III, IIIA, I/III, IV)

Note: Meretoja syndrome or familial amyloidosis, Finnish type, previously was called Lattice Corneal Dystrophy, Type II
Lattice dystrophy in patients with autosomal dominant systemic amyloidosis.

Midperipheral deposits, less visual loss. (actually may represent amyloid degeneration of corneal nerves)
Cranial nerve palsies, dry lax itchy skin, typical mask-like "hound dog" facies with protruding lips, pendulous ears, systemic amyloid deposits
Amyloid deposits composed of mutant **gelsolin,** an enzyme involved in actin metabolism. **GSN gene** 9q34

Granular Corneal Dystrophy, Type 1 (GCD1, Groenow Type I, Bückler Type I)
Autosomal dominant, most benign clinically, visual loss late
Bilateral, central superficial ring or crumb-like opacities
Hyaline "rock-candy" stromal deposits stain intensely **red with Masson Trichrome** (acid fuchsinophilia) , more eosinophilic than normal stroma, PAS (-), MPS (-), Luxol fast blue (+++), less birefringent than normal stromal lamellae.
TEM: electron-dense granules with periodicity
Can recur in graft, material may be produced by epithelium
TGFBI gene mutation- mutant TGFBI protein forms granules, 5q31.1

Granular Corneal Dystrophy, type 2 (GCD2, formerly Avellino Dystrophy)
Combines features of granular and lattice type I, TGFBI mutation
Rapid recurrence after trauma; avoid LASIK

Polymorphic Amyloid Dystrophy (Klintworth)- Lattice variant, “ice chips” TGFBI

Representative TGFBI Mutations in TGFBI Corneal Dystrophies

Corneal Dystrophy	Mutation
Lattice type I	Arg124Cys
Granular type ii	Arg124His
Granular type I	Arg555Trp
Reis-Bückler	Arg555Gln
Lattice type IIIA	Pro501Thr

Stromal Dystrophies

Macular Corneal Dystrophy (16q22 CHST6 sulfotransferase gene)
Localized corneal mucopolysaccharidosis:
Autosomal Recessive!!, Most severe, visually disabling
Superficial opacities with indistinct borders begin axially.
Diffuse stromal haze between opacities, may need PK in third decade
The corneal manifestation of an otherwise benign systemic disorder
Heterogenous- Type I patients lack circulating keratan sulfate in serum, cartilage
Defective sulfonation of keratan sulfate molecules (proposed Type I enzyme defect)
Insoluble non-sulfated keratan "sulfate" accumulates in keratocytes, endothelium, and between stromal lamellae; abnormal stromal hydration
Unlike systemic mucopolysaccharidoses the **corneal stroma is not thickened.**
Colloidal iron stain or Alcian blue stain for MPS (+)

Schnyder Corneal Dystrophy (SCD, formerly Schnyder central stromal crystalline dystrophy (SCD)
Autosomal dominant, **UBIAD1 gene, (1p34.1-p36).**
Needle shaped polychromatic **cholesterol** crystals in anterior stroma, prominent bilateral arcus; ***No longer called crystalline*** because ***only 50% have crystals***!!
Diffuse stromal clouding in some may necessitate PK (age 40-50)

? association with systemic lipid disorder in some cases (xanthelasma, elevated serum lipids)

Fleck Corneal Dystrophy (François-Neetens Fleck Dystrophy dystrophie mouchetée)

Vision normal, flecks in stroma found incidentally
Autosomal dominant, occasionally unilateral, PIP5K gene (2q35).
Swollen keratocytes contain GAGs, lipid

Others

Congenital Stromal Corneal Dystrophy- Decorin gene
Posterior Amorphous Corneal Dystrophy
Central Cloudy Dystrophy of Francois
Pre-Descemet corneal dystrophy

Note: corneal ***stromal dystrophies*** classically included: Granular, Lattice and Macular Dystrohies, Granular and Lattice are caused by mutation in the TGFBI gene and are included in that category.

Mnemonics for three classic stromal dystrophies:
Mickey Mouse Goes Home to L.A.
Marilyn Monroe Got Hers in L.A.
(Macular, Mucopolysaccharide; Granular, Hyaline; Lattice, Amyloid)

Endothelial dystrophies

Fuchs Endothelial Corneal Dystrophy (FECD, cornea guttata)

Primary endothelial dystrophy (Adult onset); 5% over age 40 in the USA
Very common (major indication for DSEK, DMEK)
Anvil-shaped guttate excrescences of abnormal basement membrane material secreted on Descemet membrane; DM thickened, often multilaminar, guttae may be "buried" by retrocorneal membrane; pigment phagocytized by endothelium.
Secondary stromal edema, bullous keratopathy (Fuchs described epithelial changes), endothelial cells often contain iris pigment epithelial melanin
Complex inherited disorder, FH often negative, many genes, rare COL8A2 mutations

Congenital Hereditary Endothelial Dystrophy (CHED)

Recessive- **SLC4A11 gene**
Thickened edematous stroma, massively thickened Descemet, atrophic or nonfunctioning endothelium
Auto dominant CHED now considered to be posterior polymorphous dystrophy

Posterior Polymorphous Corneal Dystrophy (**PPCD**) (Schlichting)

Irregular blebs or vacuoles at level of Descemet membrane surrounded by gray opacification. Heterogenous disease spectrum also includes congenital corneal opacification, gutters or troughs, changes resembling ICE syndrome or Axenfeld-Rieger syndrome
Most autosomal dominant, some recessive; several genes implicated(? TCF8)
Endothelial cells have epithelial characteristics: (multilayered, tonofilaments, multiple microvilli, surface keratin differentiation)

X-linked endothelial Corneal Dystrophy- moon crater-like endothelial changes

Iridocorneal Endothelial (ICE) Syndrome- (unilateral, not a dystrophy)

Corneal Involvement in Systemic Diseases

Systemic mucopolysaccharidoses
Severe, early opacification in MPS-IH (Hurler), I-S (Scheie), VI (Maroteaux-Lamy) – corneal disease in Hurler's not ameliorated by bone marrow transplant
Mucolipidoses
Fabry disease (alpha galactosidase deficiency)
Cornea verticillata in 90% of affected males
Wilson disease: Kayser-Fleischer ring, Copper in Descemet membrane
Ochronosis (alkaptonuria): brown granules in sclera, peripheral Bowman
Refsum disease
LCAT deficiency, fish eye disease, Tangier disease
Gout
Cystinosis
Multiple myeloma, protein dyscrasias

Corneal crystals
Cystinosis, tyrosinemia,
Immunoglobulin (multiple myeloma)
Uric acid (gout)
Bietti crystalline dystrophy
Cholesterol (Schnyder' crystalline dystrophy)
Plant sap injury (Dieffenbachia)
Clofazimine (antibiotic for leprosy, reversible if treatment stopped)

Enlarged Corneal Nerves
MEN Type IIb (ganglioneuromas?) – medullary thyroid CA, elevated calcitonin
Hereditary Icthyosis
Hansen Disease (leprosy)
Keratoconus
Refsum Disease
Fuchs corneal dystrophy
Primary amyloidosis
Failed PKP
Congenital glaucoma
Acanthamoeba keratitis
Neurofibromatosis type I

Sclera

Blue sclera- osteogenesis imperfecta tarda, autosomal dominant; sclera thin, type I collagen fibers are immature, 50% reduced diameter
Congenital ectasias and staphylomas
Scleral icterus
Ochronosis (alkaptonuria)- homogentisic acid oxidase deficiency, autosomal recessive, 70% have worm-shaped pigment deposits anterior to rectus muscles
Cogan senile scleral plaque: deposition of calcium salts (calcium phosphate) anterior to rectus tendon insertions, gray translucent appearance clinically.
Episcleral osseous choristoma - upper temporal quadrant

Inflammation
Simple episcleritis
Spontaneous, recurrent; average age in 50's; sexes equal
Pain, injection; may last several weeks despite steroids
Histology: nongranulomatous, vascular dilation, perivascular lymphocytic infiltration
Nodular episcleritis

Pathology similar to rheumatoid scleritis, but limited to episclera
Palisade of epithelioid cells bordering central fibrinoid necrosis

Primary scleritis

More severe than episcleritis, visual loss possible
More prevalent in women, later onset, >50
10-33% have co-existing **rheumatoid arthritis**; rheumatoid arthritis patients who have scleritis have poorer prognosis.
Systemic manifestations (cardiac, pulmonary, etc) may prove fatal:
Scleromalacia perforans: 21% 8-year-mortality

Other connective tissue diseases associated with scleritis: Wegener's granulomatosis, SLE, polyarteritis nodosa, relapsing polychondritis, IBD, (also gout, ochronosis)

Infectious scleritis- Gram negative bacteria (Pseudomonas), fungi, Tb, lues

Anterior scleritis

Symptoms: Redness, photophobia, severe pain, 50% bilateral
Conjunctival and episcleral injection may mask scleral inflammation
Scleral perforation with uveal prolapse (scleromalacia perforans) uncommon (15-20%)

Posterior Scleritis

Usually unilateral limitation of motility, proptosis, retrobulbar pain, field loss, retinal detachment, uveal effusion, disk edema, optic neuritis, may mimic uveal tumor

Histology: Nodular Scleritis

Zonal necrotizing granuloma surrounding sequestrum of scleral collagen, fibrinoid necrosis, chronic inflammation, fusiform thickening, immune complex deposition with complement activation. When collagen has been destroyed, inflammation and swelling recede, uvea herniates into defect

Histology: Diffuse (Brawny) Scleritis

Sclera markedly thickened by diffuse involvement of large areas of scleral collagen by granulomatous inflammation

N.B.: Zonal pattern of chronic granulomatous inflammation surrounding a central nidus of necrotic sclera = systemic disease, e.g. rheumatoid arthritis, etc.

Presence of microabscesses and necrosis suggests infectious scleritis

LENS

Congenital Anomalies

Posterior umbilication - fixation artifact in young eyes

Lenticonus

Capsular thinning or defects allows cortex to bulge
Anterior lenticonus: bilateral, males, X-linked Alport's syndrome of hereditary hemorrhagic nephritis, deafness, abnormal type 4 collagen (rare association with posterior polymorphous dystrophy)
Posterior lenticonus: unilateral, sporadic

Lens coloboma

Secondary to absence of zonules in ciliary body coloboma; rarely due to ciliary body tumor (e.g., embryonal medulloepithelioma)

Congenital cataract: *rule of thirds*

1/3 hereditary, 1/3 idiopathic, 1/3 associated with systemic disease

Zonular cataract: zone of opacified fibers, e.g. Neonatal tetany
Anterior pyramidal cataract (congenital anterior subcapsular cataract)
Posterior variants result from abnormal hyaloid resorption
Rubella cataract: dense pearly nuclear cataract, retained nuclei in embryonic nucleus
Lowe syndrome: discoid lens, capsular increscences
Down syndrome

Cataract

Opacification or optical dysfunction of crystalline lens
"End-stage" or final common pathway of lens pathology - many causes
4 basic types of cataract recognized histopathologically
(Lens has limited vocabulary of histopathologic expression)
Anterior subcapsular cataract
Fibrous plaque beneath folded anterior capsule secreted by irritated metaplastic anterior epithelial cells
Cells in plaque surrounded by basement membrane capsules
Rare clinically, common in eye pathology lab; often hidden clinically by posterior synechias and pupillary membranes
*****Similar mechanism of epithelial proliferation and fibrosis operative in posterior capsular opacification and wrinkling (capsular fibrosis)***
Posterior subcapsular cataract
Posterior migration of lens epithelium (normal termination at lens equator); **bladder or Wedl cell** formation (eosinophilic globular cells that have nuclei!!)
Clinically interferes with near vision early, causes glare symptoms
Elschnig pearls- Wedl cells formed by proliferation of residual lens epithelial cells post-ECCE
Cortical Degeneration
Lens fibers fragment, ooze degenerated protein, liquefaction
Vacuoles, water clefts, total liquefaction (Morgagnian cataract)
Morgagnian globules (round, eosinophilic, **no nuclei**!!!)
Liquefied cortex exerts osmotic effect (intumescent cataract)
Lens substance can leak through intact capsule
Loss of substance leads to shrunken hypermature cataract with prune-like wrinkled capsule; can incite bland macrophagic response, **phacolytic glaucoma**
Cholesterol crystals (Christmas tree cataract)
Calcification can occur in severely degenerated cortex
Nuclear Sclerosis
Inevitable in growth and development of lens
Old, inwardly sequestered lens fibers degenerate (analogous to desquamating keratin in skin)
Increased eosinophilia, loss of artifactitious clefts
Urochrome photo-oxidation pigment: blue-yellow color defects
Lenticular myopia due to increased index of refraction
Cataracta brunescens, cataracta nigra
Calcium oxalate crystals may occur in sclerotic nucleus

Complicated cataracts

Fuchs heterochromic cyclitis
Low grade asymptomatic uveitis, no rx required; fine stellate or filiform kp's
Involved eye lighter in 90%; iris darker in inverse or paradoxical heterochromia due to severe stromal atrophy
Patients tolerate cataract surgery well

Fine vessels in angle without synechia formation, filiform hyphema; secondary open angle glaucoma in 10-50%; possible association with rubella infection

Chronic uveitis

Sarcoidosis, juvenile rheumatoid arthritis (RF seronegative ANA+, pauciarticular)
Retinitis pigmentosa (posterior subcapsular)

Tumors- ciliary body tumors compress lens, cause posterior migration of lens cells

Glaukomflecken- focal areas of lens epithelial necrosis with associated cortical damage post acute attack,? toxins in stagnant aqueous

Aldose reductase and **osmotic cataracts (Sugar Cataracts)**

Diabetes mellitus: normal glycolytic pathway overwhelmed by elevated glucose level. Insoluble sugar alcohol **sorbitol** is synthesized by alternate aldose reductase pathway. Osmotic cataract formation. (*causes diabetic retinal microangiopathy too!*)

Galactosemia: recessive hereditary defect in galactose 1-P uridyl transferase; mental retardation, oil droplet cataract; sugar alcohol dulcitol or galactitol formed by similar mechanism; dietary therapy

Galactokinase deficiency: rare cause of presenile cataract in adults

Ectopia lentis (spontaneous dislocation of the lens)

Lens dislocation in connective tissue disorders is caused by heritable mutations in elastic microfibrillar protein fibrillin (Marfan, Weil-Marchesani), or by mutations that affect fibrillin structure secondarily (homocystinuria, sulfite oxidase deficiency).

Marfan syndrome (arachnodactyly) 15q21, fibrillin 1 gene

Lens dislocates **up** and out (80%)
Tall stature, spidery digits, cardiac disease, dissecting aneurysm
Autosomal dominant defect in elastic microfibrillar glycoprotein **fibrillin-1,** major constituent of zonules (and framework for elastic tissue deposition)
Severe axial myopia, retinal detachment

Homocystinuria

Autosomal recessive, **cystathionine beta-synthase deficiency** (21q21.3)
Zonules deficient in cysteine, reduced sulfhydryl cross-linking weakens fibrillin
Blonde, marfanoid habitus, increased urinary excretion of homocystine (diagnose with serum homocystine levels)
Zonules absent; lens dislocates **down** and in, or into anterior chamber
PAS (+) layer of abnormal zonules on ciliary body; peripheral RPE degeneration
Platelet abnormality, hypercoagulability, tendency to **thromboembolic complications, especially** under general anesthesia, 75% die by age 30, MR

Weill-Marchesani Syndrome (bradydactyly)- autosomal recessive or dominant

Dominant form linked to fibrillin-1 gene; recessive 19p13
Short stature and digits, hearing defects, inflexible joints
Microspherophakia, secondary pupillary block glaucoma worsened by miotics
Lens dislocates axially
Other ocular anomalies: high lenticular myopia (15-20 D), cataract, microcornea

Dominant Spherophakia, McGavic Type

Sulfite oxidase deficiency-autosomal recessive

Infants with seizures, mental retardation, Lens dislocation in 50%
Most have molybdenum cofactor deficiency

Hyperlysinemia ?- association with ectopic lentis has been doubted

Ehlers-Danlos Syndrome - only a single reported case

Anterior megaloglobus, ectopia lentis et pupillae, aniridia, buphthalmos
Trauma Tertiary syphilis
Traboulsi Syndrome (facial dysmorphism, lens dislocation, anterior segment abnormalities, spontaneous filtering blebs)

Lens Capsular Abnormalities
True Exfoliation of lens capsule (capsular delamination)
Split in capsule forms scrolls clinically, classically secondary to occupational exposure to infrared radiation (glass blowers, steel puddlers), also an aging change; no association with glaucoma
Pseudoexfoliation of lens capsule (Exfoliation Syndrome, PXE)
Abnormal extracellular matrix material (of complex composition); produced by lens epithelial cells, extruded through lens capsule
Found on anterior lens capsule, posterior iris, ciliary body, zonules, vitreous face.
On lens: central disk, clear interval, peripheral zone
Flakes at pupillary margin suggest diagnosis in undilated patient
Associated with **secondary open angle glaucoma** (glaucoma capsulare) 50%
Abnormal iris- pigment epithelial "sawtoothing", poor dilation
Pigment dispersion-Sampaolesi line
Ocular manifestation of **systemic elastosis** (also found in conj, skin, lung, liver)
Immunoreactive with zonular elastic microfibrillar proteins
Abnormal zonules- high incidence of **IOL and capsular dislocation**
LOXL-1 gene (Lysyl oxidase-like 1), 15q24.1
Polychromasia capsulare- iridescence of lens capsule, very rare, autosomal dominant

Traumatic Cataract
Perforating injuries, ruptured lens
Vossius ring: iris pigment on lens capsule
Contusion cataract (petalliform cataract or contusion rosette)
Sign of old contusion injury, look for angle recession
Soemmerring ring cataract: donut of residual equatorial cortex
Siderosis lentis: iron deposited in epithelium
Chalcosis lentis: copper deposited in basement membrane
Mercurialentis- mercury deposition in lens capsule (occupational)
Electrical cataract
Argon laser cataract
Blue light absorbed by yellow sclerotic nucleus; avoid with krypton red
Phacoanaphylactic endophthalmitis (phacoantigenic uveitis)
Localized endophthalmitis (*Propionibacterium acnes, Candida parapsilosis),*
Large bacterial (or fungal) colonies grow within capsular bag post ECCE, white plaques, delayed chronic granulomatous response

Toxic cataracts
Corticosteroids: posterior subcapsular, dose uncertain
Occurs in approximately 1/3 (12-60%) with chronic daily dose of 10mg
Incidence 20% if patient receives >15mg prednisolone for 2-8 years-
Anticholinesterases: anterior subcapsular vacuoles (84%)
Naphthalene, DNP, triparanol, mercury, phenothiazine

Cataract Associated with Systemic Diseases

Myotonic Dystrophy- chromosome 19, accumulation of CTG trinucleotide repeats
Myotonia, testicular atrophy, frontal baldness, cataract,
Presenile cataract with polychromatic anterior and posterior subcapsular cortical crystals. (EM: spirally birefringent concentrically multilaminated "rice grains")

Wilson Disease (Hepatolenticular degeneration)
Sunflower cataract, Kayser-Fleischer ring
Deposition of copper in lens capsule, Descemet membrane
Similar findings occur in chalcosis; Copper deposition also has been reported in primary biliary cirrhosis, familial cholestatic cirrhosis, monoclonal gammopathies associated with multiple myeloma and pulmonary carcinoma.

Diabetes mellitus

Galactosemia

Fabry disease
X-linked deficiency of alpha-galactosidase A; Xq22.1
Sphingolipidosis, storage of ceramide trihexoside
Cornea verticillata (Fleischer-Gruber) 90% of affected males
Posterior spoke-like opacities

Hereditary hyperferritinemia-crystals of L-ferritin

Cataract Associated With Skin Diseases
Atopic dermatitis (Andogsky Syndrome),
Ectodermal dysplasias (Rothmund, Werner)
Acrodermatitis enteropathica

Retina

A peripheral colony of brain cells

Anatomy:
3 neuron system,10 layers

Retinal hemorrhages

Flame or splinter (superficial retinal hemorrhages)
Blood tracks along axons of **nerve fiber layer**

Blot and dot
Deep retinal layers, blood "corralled" by axons oriented perpendicular to Bruch's membrane

Scaphoid or boat-shaped (two types)
1. **Sub-ILM**: hemorrhagic detachment of internal limiting membrane (common in abusive head trauma) punctate Gunn's dots may be visible on inner surface
2. **Sub-hyaloid:** blood between ILM and posterior hyaloid
True subhyaloid hemorrhages do occur in patients with proliferative diabetic retinopathy

Sub-RPE hemorrhages
Dark-colored, can be confused with choroidal melanoma

Roth spot
White centered hemorrhage, central abscess in SBE,
Also leukemic cells, central nidus of fibrin

Blood retinal barrier – analogous to blood-brain barrier

Inner- retinal capillary endothelial cell tight junctions

Outer- RPE tight junctions (fenestrated choriocapillaries leak)

Retinal exudates

Hard, yellow waxy exudates
Pools of eosinophilic lipoproteinaceous material in outer plexiform layer:
"watershed zone" between retinal and choroidal circulations.

Fluid derived from leaky retinal capillaries, competent capillaries absorb water, leaving protein and lipid behind
May be phagocytized by macrophages (Gitter cells)
Note: *Lipidized histiocytes in the subretinal space or outer retina may also appear as hard exudates*.

Circinate retinopathy
Ring of hard exudate surrounding focus of leakage

Macular star
Stellate pattern of perifoveal hard exudates reflects **radial** orientation of **Henle fibers**

Cotton wool spots (soft exudates)
Microinfarctions of nerve fiber layer due to occlusion of precapillary arteriole
Blockage of axoplasmic flow in nerve fiber axons traversing ischemic focus produces **Cytoid bodies** or end bulbs of Cajal: swollen axons with eosinophilic nucleoid composed of dammed organelles.
Clinical marker for retinal ischemia, e.g. preproliferative diabetic retinopathy
Isolated finding in collagen vascular disease, HIV/AIDS
Confined to territory of radial peripapillary capillaries

Angioid streaks

Breaks in calcified Bruch's membrane
Pseudoxanthoma elasticum (peau d'orange fundus)- major association
Paget's disease of bone, sickle cell (Hb SS) Idiopathic, Ehlers-Danlos
Subretinal neovascularization and disciform degeneration a complication

Central retinal artery occlusion

Ischemic infarction of retina
Clinical findings: sudden visual loss, milky-white loss of retinal transparency (regains in several days), slight retinal thickening
Early stages: coagulative necrosis, pyknosis, edema of inner retinal layers
Macular **cherry red spot** :"window" of thin, transparent foveolar retina surrounded by opacified infarcted tissue
Late stages: **"inner ischemic retinal atrophy"** (atrophy of all layers supplied by central retinal artery) In contrast to glaucomatous atrophy, also **involves inner nuclear layer**
Inner layers have hyalinized appearance, gliosis absent (glial cells killed)

Causes of CRAO:
*Atherosclerosis of CRA at or posterior to lamina cribrosa
(Atherosclerosis does not involve retinal arterioles)
*Emboli:
cholesterol (73%) or platelet fibrin (15%) from carotid plaques
calcific (11%) from heart
tumor (atrial myxomas in young patients)
*Vasculitis , e.g., **giant cell arteritis**, collagen vascular disease
Stat sed rate in elderly with CRAO!!

PAMM: Paracentral acute middle maculopathy; capillary ischemia affecting middle layers of macula, Discovered using OCT

Cherry red spot in sphingolipidoses (e.g. **Tay-Sachs Disease**) results from storage of GM2 ganglioside in retinal ganglion cells. <u>There are NO ganglion cells in foveola</u>
Tay-Sachs Disease- GM2 Gangliosidosis type I
TEM: multimembranous inclusions ("Zebra bodies")
Cherry red spot also seen in Sandhoff's, Niemann Pick, others..

Ophthalmic Artery Occlusion

Resembles CRAO, but no cherry red spot due to simultaneous choroidal infarction
Severe visual loss, A wave of ERG absent

Retinal Venous Occlusions

85% branch, 70% superotemporal
Associations: AS, hypertension, DM, >age 50, male, high body mass index
Local causes: glaucoma, papilledema, subdural, large optic disk drusen
Most related to arterial disease
Sclerotic artery compresses vein within common adventitial sheath; turbulence, endothelial damage, thrombosis of CRV within lamina
Hemorrhagic infarction of the retina
Early stages:
Edema, numerous deep and superficial hemorrhages, full-thickness and preretinal hemorrhages, hemorrhagic detachment, focal necrosis, cotton wool exudates, CME, shallow RD, disk edema
Late stages:
Disruption of retinal architecture, marked gliosis, hemosiderosis, hemosiderin-laden macrophages, thick walled vessels, neovascularization
CRV: recanalization, endothelial proliferation, phlebitis
Neovascular glaucoma ("90 Day glaucoma") -20% incidence in ischemic occlusions, NVD and NVE much less common
Ischemic CRVO occlusion characterized by: severe visual loss, cotton wool spots, capillary nonperfusion

Retinal arteriolarsclerosis

Chronic hypertension induces fibrosis in arteriolar wall
Healthy vessel walls transparent, only blood column in vessel seen
Widening of vascular light reflex, copper and silver wiring results from gradual obscuration of blood column by increasing fibrosis in wall.
AV crossing defects ("nicking") result from thickened arteriole hiding underlying venule

Hypertensive Retinopathy

Severe hypertension produces marked vasospasm, then muscular and endothelial necrosis and vascular incompetence and/or occlusion.
Edema, hard and soft exudates, exudative retinal detachment
Fibrinoid necrosis of vessels, optic disk edema
Choroidal vascular involvement: Elschnig's spots, Seegrist streaks

Retinal Arteriolar Macroaneurysms

Arterioles posterior to equator, elderly patients with vascular disease:
BP, ASCVD, 75% female. 67% hypertension
Edema, exudation, hemorrhage, (subretinal "H" can mimic MM)
Histology: greatly distended retinal arteriole, surrounding fibroglial proliferation, dilated capillaries, hemosiderin, exudates, hemorrhages.

Toxic Maculopathies and Retinopathies

Gentamicin - inadvertent intraocular injection causes retinal infarction
Chloroquine, hydroxychloroquine (plaquenil)- (bull's-eye maculopathy)
Dose related, primary effect on RPE? - drug stored in melanin granules
Thioridazine (Mellaril) -high doses
Methoxyflurane (anesthetic)
Crystalline retinopathy, oxalate crystals

Chloramphenicol (chronic use in cystic fibrosis)
Atrophy of maculopapillary bundle, cecocentral scotomas
Quinine
Tamoxifen: nonsteroidal antiestrogen- breast cancer therapy, flecklike retinopathy
Nicotinic acid (Gass)- atypical nonleaking CME
Canthaxanthine (crystalline retinopathy)- tanning agent
Chemotherapeutic agents

THE MACULA,
Definitions:
Macula: macula lutea-"yellow spot", nonspecific clinical term.
Darker on IVFA: xanthophyll, more lipofuscin and melanin in taller RPE cells
Fovea: "pit"- depression in retina, 1 DD in size
Foveola: Floor of pit, greatest retinal thinning, avascular; anatomy: only photoreceptors, outer nuclear layer, some Henle fibers,
Age Related Maculopathy (Age-related macular degeneration, senile macular degeneration, SMD, ARMD)
Major public health problem, leading cause of irreversible blindness in people over age 50 in developed world
More common in blue-eyed patients, rare in blacks: suggest pathogenic role of chronic light exposure
Chronic inflammation may play a role in pathogenesis. Inflammatory mediators and complement components found in drusen and damaged RPE cells. Strongly associated with a common variant of complement factor H (CFH) gene- Tyr402His polymorphism 5-7x increased risk of AMD in homozygotes
"DRY" ARMD
RPE degeneration, pigment clumping, areolar loss of RPE with concomitant degeneration of outer retina and involution of choriocapillaris; AREDS
"WET"ARMD:
Choroidal neovascular membranes (CNV), exudation, focal serous detachment of retina, hemorrhagic RPE detachment, organization of hemorrhage, subretinal scar formation (disciform degeneration)
RPE cells contribute to collagen production in vascularized scar
A CLINICAL SPECTRUM: "wet" and "dry" variants can be found in same patient
Aging Changes in Bruch's Membrane:
Thickening, PAS positivity, focal calcification, drusen
Drusen- a clinical marker for "sick" RPE
Focal deposits of extracellular debris located between the basal lamina of the retinal pigment epithelium and the inner collagenous layer of Bruch's membrane.
Complex composition, confusing classification schemes
Probably made by "sick" or stressed RPE cells
Hard drusen (cuticular)
Globular excrescences of densely hyaline PAS (+) material
Association with dry or atrophic ARMD has been questioned (Green)
Soft Drusen- found only in macula, amorphous membranous debris
Diffuse drusen- very strong association with exudative ARMD (esp. basal laminar deposit)
Basal laminar deposit (very important variant of diffuse soft drusen)
May be quite extensive, but not evident clinically

Thick diffuse layer of abnormal 1000 Å banded basement membrane material ("curly collagen") located between plasma membrane and basement membrane of RPE.
Composition: laminin, type IV collagen, heparin sulfate proteoglycans
Appears as pink granular band between Bruch's membrane and RPE.
Very common pathologic finding in ARMD (84% "wet", 53% "dry", 19% control - Grossniklaus)
Predisposes to RPE detachment and tears, SRNVM, disciform degeneration
May interfere with biochemical modulation of choriocapillaries by RPE, barrier to diffusion, bind or sequester angiogenesis factors, displaces RPE from blood supply

Basal Linear Deposit
Second type of diffuse soft drusen composed of a layer of multivesicular phospholipid material localized within Bruch's membrane external to RPE basement membrane. It is impossible to distinguish from basal laminar deposit without electron microscopy

Subretinal Neovascular Membrane (CNV, choroidal neovascular membrane)
New vessels derived from choroid, extend through breaks in Bruch's membrane
Vessels leak, bleed with resultant hemorrhagic RPE and/or retinal detachment
Disciform scar caused by organization of hemorrhage by granulation tissue and collagenous connective tissue (disciform degeneration)
Propensity for foveal and parafoveal region
Excised membranes very difficult to orient histopathologically
Vascular Endothelial Growth Factor and VEGF inhibitors, OCT

Hemorrhagic Detachment of the RPE-can mimic choroidal melanoma

Diseases with SRNVM, disciform scar formation
ARMD
Focal choroiditis (e.g , presumed ocular histoplasmosis syndrome)
Angioid streaks
Myopic degeneration
Choroidal rupture
Central serous (rare)
Dominant drusen
Choroidal tumors
Juvenile disciform degeneration

Ocular Histoplasmosis Syndrome (POHS)
Triad:
Disciform degeneration of macula, peripapillary atrophy, peripheral punched-out spots
Focal chronic choroiditis, organisms rarely found

Macular Holes (Idiopathic)
Shrinkage of prefoveal cortical vitreous exerts lateral traction on retina causing localized foveal detachment, then hole (fibrocellular membranes rarely found)
Better VA after surgery reflects smaller size of sealed hole and resorption of SRF

Classification of macular holes (Gass)
Stage I- foveal detachment (impending hole or macular cyst) – about 50% progress
Stage II- early hole formation
Stage III- full thickness hole with vitreofoveal detachment
Stage IV- full-thickness hole with posterior vitreous detachment

Cystoid Macular Edema (CME)

Multiple cystoid spaces in macula with petalloid appearance on IVFA
Irvine-Gass Syndrome – CME after cataract surgery
In past very high incidence with iris supported IOL's
Secondary finding over choroidal tumors, especially hemangioma
Occurs with peripheral uveitis, peripheral tumors
OCT and anti-VEGF therapy (Lucentis, Avastin), intravitreal Kenalog®
Initial intracellular edema within Mueller cells? (Fine, Brucker)

SD-OCT (spectral domain optical coherence tomography)

Powerful technology to assess retinal disease; CME, SRF
Retinal layers on OCT do not correlate exactly with histopathology
4 outer lines: XLM, ellipsoid of inner segments; cone OS/contact cylinder region;RPE

Ophthalmic lasers (argon, krypton, dye, diode)

Thermal coagulation (light absorbed by pigment, converted to heat)
Blue argon wavelengths absorbed by yellow macular pigment, damage retina
Green argon wavelengths absorbed by blood, melanin
Red krypton wavelengths absorbed by melanin, not by blood or luteal pigment
YAG: short pulse mode does not rely on thermal coagulation; optical breakdown "explosion" physically disrupts tissues
TTT (transpupillary thermotherapy), diode laser, large spot size, slow delivery, thermal effect
Excimer- molecular disruption

Retinitis pigmentosa (primary pigmentary retinopathy)

An extremely large heterogeneous group of diseases sharing:
Progressive photoreceptor degeneration typically leading to blindness by middle age
Rods affected more severely than cones in early disease
Night blindness and peripheral field loss, tunnel vision, blindness
Attenuation of retinal vessels, waxy pallor of optic disc, bone spicule pigmentation in peripheral fundus
Posterior subcapsular cataract, macular edema, optic disk drusen

Genetics

Sporadic 39%, dominant 20%, recessive 37%, sex-linked 4%,
Consanguinity 30-40%
Severity: Autosomal dominant< autosomal recessive < X-linked
RP genes are located on chromosomes 1, 3, 4, 5, 6, 7, 8, 11, 14, 15, 16, 17, 19, and X (most identified by linkage studies)
Non-syndromic RP is caused by more than 3000 mutations in 57 different genes. Examples: RHO, PDE6A, PDE6B, CNGA1, SAG, RPE65, RLBP1, ABCA4, RGR, RDS, ROM1, PROML1, NRL, CRX, RP1, RP2, RPGR, CRB1, and TULP1.4
Some encode proteins involved in rod phototransduction cascade:
Rhodopsin (RHO)
15-20%% of patients with dominant RP- most single AA substitutions (missence mutations), most common His-23-Pro
subunits of rod c-GMP-phosphodiesterase
subunit of c-GMP-gated cation channel
arrestin guanylate cyclase activating protein
Others encode for proteins of unknown function
Peripherin/RDS

(Mutations also found in occasional patients with macular dystrophies such as Best's Vitelliform or Butterfly dystrophy)
(Null mutation cause photoreceptor degeneration in **RDS** mice)
ROM 1, Myosin 7A, RPGR- 13% of cases, NRL

Histopathology

Primary photoreceptor degeneration- atrophy involves outer retina
Loss of photoreceptors, ONL
Bone spicule pigmentation caused by intraretinal RPE migration
TEM: intraretinal formation of new perivascular "Bruch's membrane"
Macromelanosomes (PR atrophy may allows RPE to invade retina)
RPE usually fairly well preserved

Variants of Retinitis Pigmentosa

Leber Congenital Amaurosis (congenital blindness of early onset RP)- 18 variants recognized–
CEP290- most common gene – 20% of cases
RPE65 gene – taget of gene therapy in humans and Briard dogs
Sector retinitis pigmentosa
Usher Syndrome (association of RP and hearing loss- 3 types)
Retinitis pigmentosa with Coats'-like response
Retinitis punctata albescens

X-linked Juvenile Retinoschisis (Xp22.2) retinoschisin

Split in nerve fiber layer (in periphery)
Stellate maculopathy does not stain with fluorescein: OCT all layers
? abnormal vitreous-like material in retina (Brownstein)

Macular dystrophies (hereditary, bilateral)

Fundus flavimaculatus (Stargardt disease) 1p21-p13

Once thought to be a primary RPE disease, but causative **ABCA4 gene** is expressed only in photoreceptor outer segments. Defect in ABCR transport protein leads to accumulation of toxic vitamin A derivative A2-E in outer segments that poison RPE's phagolysosomal system, leading to accumulation of lipofuscin in RPE, with resultant “terminal constipation” of RPE cells.
Autosomal recessive, onset in teens
Yellow pisciform flecks in RPE, atrophic macular degeneration
RPE PAS+, cells contain massive amounts of abnormal lipofuscin
Posterior RPE cells massively enlarged
"Dark" choroid on IVFA, vermilion fundus due to **RPE lipofuscin**
Fundus flavimaculatus without macular lesion lacks abnormal pigment

Best disease (Vitelliform macular dystrophy)

Dominant, bestrophin gene (BEST1) on chromosome 11q (11q13)
Some cases of adult vitelliform caused by defects in peripherin/RDS gene
Egg yolk lesion "scrambles" with age, Abnormal EOG
RPE disease with increased amounts of abnormal lipofuscin

Sorsby Macular Degeneration

Dominant presenile macular degeneration; similar to ARMD clinically
Massive deposit of BLD-like material beneath RPE
Defect in gene (chromosome 22) encoding TIMP 3 (Tissue inhibitor of metalloproteinase 3)
Theory- mutant TIMP3 could inhibit MP that normally catabolize Bruch's membrane too well.

Kearns-Sayre Syndrome

Progressive external ophthalmoplegia, heart block, atypical pigmentary retinopathy; large deletion in **mitochondrial DNA**

"Salt and pepper" retinopathy, no bone spicules, involves posterior fundus,

Other mitochondrial cytopathies (MERRF, MELAS) occasionally affect retina

Oguchi Disease

Form of stationary night blindness- golden fundus reflex - Mizuo-Nakamura phenomenon- mutations in arrestin or rhodopsin kinase; some patients may develop late retinal degeneration

Gyrate atrophy (autosomal recessive ornithine-delta-aminotransferase deficiency)

Hyperornithinemia, ornithine aminotransferase deficiency

Ornithine may act as an RPE toxin

Choroideremia

X-linked degeneration of RPE, choroid and photoreceptors (primary site unknown)

Asymptomatic female carriers have patchy pigmentation and RPE and choroidal degeneration.

CHM gene which encodes for Rab escort protein-1 (REP1),

Mucopolysaccharidoses

Inherited deficiencies of catabolic lysosomal exoenzymes.

Fibrillogranular and multimembranous inclusions.

Outer retinal atrophy due to RPE degeneration; marked in Sanfilippo (MPS III); mimics primary retinitis pigmentosa

Sphingolipidoses

Syndromic RP: Bardet-Biedl, Senior Loken, Bassen-Kornzweig, Bietti corneoretinal crystalline dystrophy, cystinosis, neuronal ceroid lipofuscinosis, Refsum disease, autosomal dominant cerebellar ataxia type II, Joubert syndrome, Hallervorden Spatz, etc.

Diabetes mellitus

Diabetic retinopathy

Microangiopathy

Loss of capillary pericytes (Normal endo/pericyte = 1/1)

Role of sorbitol in pericyte loss

Thickening of capillary basement membranes

Capillary nonperfusion (capillaries are totally avascular)

Angiogenic factor (**VEGF-** vascular endothelial growth factor) produced by ischemic retina

Neovascularization of disk and retina

Microaneurysms

Seen in diabetes and other retinal diseases with ischemia

DM: mainly posterior pole, CRVO: throughout retina, others: periphery

50-100µ, most not ophthalmoscopically visible (One sees associated hemorrhage)

Increased number of endothelial cells (proliferation versus migration)

Wall initially thin and leaky, thickens, PAS (+), eventual occlusion

Background retinopathy

Hemorrhages, hard exudates, retinal edema

Preproliferative retinopathy

Many cotton wool spots are a marker for retinal ischemia

Intraretinal Microvascular Abnormalities (IRMA)

Proliferative retinopathy

Neovascularization of disk, retina, iris; angiogenic factor (VEGF)
New vessels proliferate on scaffold of partially detached vitreous
Progressive vitreous detachment rips vessels causing subhyaloid and vitreous hemorrhage
Scarring and organization of hemorrhage produces vitreoretinal
Traction, tractional retinal detachment

Diabetic iridopathy

Iris neovascularization (NVI, rubeosis iridis):
Higher incidence post-lensectomy
Lens acts as barrier to anterior diffusion of angiogenic factor

Diabetic lacy vacuolization of iris pigment epithelium
Glycogen-filled cysts in IPE, contents PAS (+), diastase-sensitive

Basement membrane thickening
Retinal capillaries
Nonpigmented ciliary epithelium (can be diagnostic)
Corneal epithelial basement membrane (epithelium can desquamate as sheet)

Diabetic cataract
Role of aldose reductase, sorbitol

Albinism (oculocutaneous and ocular albinism)
Foveal hypoplasia- occurs in varieties caused by different genes), iris transillumination
X-linked ocular albinism: macromelanosomes in RPE, skin

Sickle Cell Retinopathy
Proliferative retinopathy **most severe** in **Hb SC** disease
Blockage of retinal vessels by sickled cells leads to nonperfusion of temporal peripheral retina, peripheral shunts
Neovascular fronds (**sea fans**) develop at junction between perfused posterior and nonperfused peripheral retina
Late stages: hemorrhage, secondary retinal detachment
Black sunburst sign: chorioretinal scar with RPE proliferation secondary to old hemorrhage

Peripheral Retinal Degenerations

Peripheral microcystoid degeneration (typical)
Very common, found in all adults > 20 years
Blessig-Iwanoff cysts in outer plexiform layer
Filled with hyaluronidase-sensitive acid mucopolysaccharide
Coalescence of cysts leads to typical degenerative retinoschisis

Reticular cystoid degeneration
18% of adults, bilateral in 41%
Posterior to, and contiguous with typical microcystoid
Finely stippled, inferior temporal quadrant
Cysts in nerve fiber layer
Can lead to reticular degenerative retinoschisis

Typical degenerative retinoschisis
1% of adults, inferotemporal retina
Split in outer plexiform layer, large holes in outer layer
Vessels in inner layer; irregular outer layer has beaten-metal appearance, turns white on scleral depression

Peripheral Chorioretinal Degeneration
(Paving stone or Cobblestone degeneration, CRA)

Incidence 27% over age 20
Probably caused by choroidal vascular insufficiency
Pattern of outer ischemic atrophy: loss of choriocapillaris, RPE, outer retina
Chorioretinal scar: outer retina fused to bare Bruch's membrane

Lattice Degeneration (vitreoretinal degenerative process)
6-11% of population
Sharply demarcated, circumferentially-oriented areas of retinal thinning, anterior to equator, vertical meridians
Secondary RPE proliferation, Only 12% of lesions have white lines
Histology:
Discontinuity in ILM
Retinal thinning with loss of inner layers
Overlying pocket of liquefied vitreous
Vitreous condensation and gliosis at margins of pocket
Sclerosis of major vessels in lesion, capillary occlusion
RPE hypertrophy, hyperplasia and migration
Lattice predisposes to retinal breaks (firm adherence of vitreous to margin of lesions)
Posterior margin breaks, lattice in operculum (30%)

Pars Plana Cysts
Split between pigmented and nonpigmented layers of ciliary epithelium
Aging – cysts contain hyaluronic acid
Multiple myeloma- cysts filled with myeloma proteins are white after fixation

Retinal detachment
Fluid collects in potential space between inner and outer layer of optic cup; retinal separation a better term.
Artifactitious versus real RD in tissue sections (Almost all unopened eyes fixed by immersion in formaldehyde have an artifactitious retinal detachment.)
True retinal detachment
Photoreceptor degeneration, eosinophilic proteinaceous fluid in subretinal space, RPE budding or papillary proliferation with chronicity
Artifactitious retinal detachment:
No fluid in subretinal space, photoreceptors healthy, RPE granules adhere to outer segments
Rhegmatogenous retinal detachment
Secondary to **retinal holes and breaks**
Most holes due to vitreous traction in eyes with posterior vitreous detachment, vitreous degeneration, lattice degeneration
Horseshoe tears- “the horse always walks toward the optic disk”
Incidence of retinal holes: 4.8-10% (path), 5.8-13.7% (clinical)
Important prognostic criteria: **Symptoms**, subclinical detach, aphakia
Exudative retinal detachment (serous)
Tumors (most melanomas, hemangiomas, metastases)
Uveal effusion, Harada's, toxemia of pregnancy, oxygen toxicity
Tractional retinal detachment
Proliferative diabetic retinopathy
Chronic retinal detachment
Funnel or morning glory configuration, photoreceptor degeneration, gliosis, macrocystic degeneration; may have secondary pigmentary retinopathy

Proliferative vitreoretinopathy,

Vitreous

Posterior vitreous detachment
63% incidence in 8th decade, rare before age 55
7.5% have associated vitreous hemorrhage, 15% have retinal breaks
Flashes, floaters, Weiss ring (peripapillary condensation)
Important role in retinal detachment

Vitreous opacities
Hyaloid remnants (muscae volitantes, or mouches volantes-"flying flies")

Vitreous hemorrhage
Blood breakdown products in chronic hemorrhages ("**ochre membrane**")
erythrocyte ghost cells, hemoglobin spherules, hemosiderin-laden macrophages: Hemolytic, ghost cell glaucoma,
Complications: organization leading to tractional RD, hemosiderosis (repeated hemorrhage)

Causes: trauma, retinal tears, PVD, diabetic retinopathy, sickle cell, Eales', disciform degeneration of the macula, tumors, Terson's syndrome (subarachnoid hemorrhage)

Asteroid hyalosis (Benson disease, Scintillatio nivea)
2% incidence, unilateral (80%), increases with age
Generally does not interfere with vision
Spherules of calcium hydroxyapatite attached to vitreous framework (Not **calcium soap** as previously stated)
Gray spheres with Maltese cross birefringence on polarization

Synchisis Scintillans (cholesterolosis bulbi)
Rare, bilateral, blind eyes, young patients
Cholesterol crystals derived from old hemorrhage
Not fixed to vitreous framework, crystals sink to bottom of globe

Primary Amyloidosis Of The Vitreous
Vitreous involvement in Familial Amyloidotic Polyneuropathies (FAP's); 18q12.1
Amyloid comprised of mutant transport protein **transthyretin** (prealbumin)
Several missence (AA substitutions) mutations (e.g. common Met 30 variant
Often presents in elderly patients with no family history)
Associations include cardiac disease, amyloid neuropathy, carpal tunnel syndrome
Amyloid probably enters via retinal vessels

Intravitreal Tumor Cells

Retinoblastoma
Vitreous seeding common in advanced cases, important cause of treatment failure, poor prognostic sign

Primary Lymphoma of CNS and Retina (NHL-CNS)
("ocular reticulum cell sarcoma"- old, incorrect, outdated term)
Bilateral vitritis, CNS lymphoma, dementia
Poor prognosis (mean survival 22 months)
Most cases have large B cell lymphocytic lymphoma
Primary CNS lymphoma spares uvea, but sub-RPE deposits are common
No systemic involvement outside CNS
Diagnostic vitrectomy reveals:

Atypical lymphocytes with prominent nucleoli, mitoses, abundant cellular necrosis

NOTE: Systemic lymphomas can involve vitreous secondarily in rare cases, but; uveal infiltration is more typical in such cases

Whipple Disease- rarely mimics primary CNS lymphoma with bilateral vitritis, dementia, Cells PAS (+), contain causative bacteria ***Tropheryma whipplei***

Metastatic Skin melanoma- predilection for retinal and vitreous metastasis

Vitreous Membranes (proliferative vitreoretinopathy, PVR)

RPE, glial cells, myofibroblasts

Vitreous detachment allows cells to proliferate on inner and outer surface of retina, along scaffold of detached vitreous

Membranes cause fixed folds, inoperable RD

Proliferation on posterior face of detached vitreous responsible for funnel shape of chronic RD

Anterior variant of PVR- organization of vitreous on pars plana inaccessible to vitrectomy; anterior loop retinal detachment, posterior traction on iris

Surface Wrinkling Retinopathy (Cellophane retinopathy)

Epiretinal glial proliferation; contraction of membrane folds ILM

Intraocular Tumors

Uveal Malignant Melanoma

Most common primary intraocular tumor in white adults

Risk Factors

Race

Uveal malignant melanoma is predominantly a tumor of blue-eyed Europeans (2/3's of cases occur in patients of European descent who comprise 13% of world's population)- Retinoblastoma is most common primary malignant IOT

Incidence in U.S. whites is 8.5 times greater that blacks

Incidence in USA is 21 times greater than in Taiwan (6 vs. 0.28/million)

Tumors in blacks are larger, more pigmented, more necrotic and have same survival as tumors in whites.

Age

Incidence increases with age, median age at diagnosis- 53 (AFIP), 59 (COMS)

Larger tumors, poorer survival with increasing age**:**

Size	**Median age**	**10 year survival***
small [<10 mm]	53 yr.	80%
medium [10-15 mm]	56 yr.	60%
large [>15 mm]	61 yr.	35%
with metastases	65 yr.	----

* Survival after enucleation [Non tumor deaths excluded]

Male = female in COMS study

Predisposing Lesions

Genetic mutations

GNAQ/GNA11

GNAQ mutations present in 50% of uveal melanomas

Also found in Nevus of Ota, blue nevis, ocular melanocytosis
An early or initiating event- present at all stages of malignant progression
G-protein-coupled receptor (RAF/MEK/ERK pathway)

BAP1- (very important prognostic marker)

84% incidence of inactivating mutations in in class II uveal melanomas
association with monosomy 3
loss of chromosome 3 appears to uncover recessive mutations in chromosome 3
BAP1 Syndrome- autosomal dominantly inherited familial cancer syndrome
icaused by mutations in BAP1. uveal melanomas, mesotheliomas and benign biphasic nevus–like skin lesions (MBAITS)
Congenital ocular or oculodermal melanocytosis [**Nevus of Ota**]
1/400 lifetime risk of MM in Caucasians; twice greater risk for metastases
Dysplastic nevus syndrome (familial atypical mole melanoma syndrome)
Uveal nevi- estimated rate of malignant transformation- 1/9000 (Singh)
Neurofibromatosis
Ultraviolet light- more common in blue eyes, inferior iris
Chemical carcinogens?? Pregnancy
BDUMP Syndrome- (Bilateral diffuse uveal melanocytic proliferation associated with systemic malignancy).
Remote effect of disseminated malignancy
Bilateral diffuse thickening of uvea with pigmented nodules. "giraffe skin" fundus
Melanomas may arise from generalized low-grade spindle cell proliferation

Clinical Presentation of Uveal Melanoma

Incidental finding on routine examination
Visual Loss
Retinal Detachment [solid and/or serous, rarely hemorrhagic], foveal overhang, CME (peripheral tumors), cataract formation [CB tumors], vitreous hemorrhage [rare, usually requires retinal perforation]
Extrascleral extension [anterior or orbital mass with proptosis]
Glaucoma
Iris heterochromia
Inflammatory signs mimicking endophthalmitis or orbital cellulitis- necrotic tumors
Unsuspected tumor diagnosed in pathology lab in blind painful eye

Gross Pathology

Choroidal Tumors- most common location
Pathologic classification by size: (LTD- largest tumor diameter)
Small- LTD ≤ 10 mm- most are discoid tumors confined to choroid
Medium- LTD 11- 15 mm
Most break through Bruch's membrane and grow in subretinal space
Typical mushroom or collar button configuration (63%)
Dilated vessels in head of mushroom caused by cinch-like effect of Bruch's membrane on waist of tumor.
Large- LTD > 15 mm
Tumor invades and destroys ocular tissues, may fill globe
Extrascleral extension more common
May be **diffuse** infiltrating type
Uncommon, grows laterally with little choroidal thickening
Extrascleral extension more common
Ciliary body melanomas
Less common that choroidal tumors – poorer prognosis

Diagnostic delay- may be asymptomatic, no RD
Tend to have a more spherical shape
Can invade anterior chamber anterior ("tip of the iceberg")
Diffuse type of malignant melanoma may cause ring configuration around circumference of angle and ciliary body. Prone to anterior extrascleral extension
Can cause cataract; sentinel vessels, CME

Cytology and Histopathology

Callender Classification [modified by McLean et al, 1978]
Association between mortality and cytology or **cell type** of melanoma

Spindle cells
Bipolar cells with spindle-shaped cytoplasm- arranged in parallel fascicles
Grow as syncytium- cellular margins indistinct by LM

Spindle A- slender cigar-shaped nucleus with finely dispersed chromatin and indistinct nucleolus. Nuclei often have chromatin stripe or streak caused by fold in nuclear membrane (most benign)
Spindle B- plumper, oval nucleus with coarser chromatin and a more prominent nucleolus
Intermediate cells- nuclear characteristics intermediate between spindle B and epithelioid
Epithelioid melanoma cells- most malignant
Polyhedral cells with abundant glassy cytoplasm
Large and pleomorphic, bizarre giant cells occasionally seen
Poorly cohesive with distinct cytoplasmic borders
Large round to oval nucleus with peripheral margination of coarse chromatin (chromatin clumped along interior of nuclear membrane)
Prominent eosinophilic or purple nucleolus
"Epithelioid cells look back at you!"

Four subcategories of tumors based on cytology cellular constituents

Spindle cell nevus- composed entirely of benign spindle A cells
Spindle cell melanoma
Composed of malignant spindle A, spindle A and B or Spindle B cells
A. 72% 15 year-survival
Mixed cell melanoma- very common
Mixture of spindle and epithelioid cells –
86% of medium and large posterior tumors in COMS study
Epithelioid cell melanoma- rare, poorest prognosis
Composed predominantly of epithelioid cells

Other pathologic features

RPE and outer retinal degeneration at tumor apex
Retinal invasion common, retinal perforation rare; epiretinal seeding
Most cases have secondary exudative retinal detachment
13% incidence of extrascleral extension (tumors extend extraocularly along scleral emissarial canals, vortex veins)
Optic nerve invasion rare (usually in cases with diffuse growth pattern)
Orange pigment- macrophages laden with lipofuscin; indicates actively growing lesion, but is not pathognomonic for melanoma

Prognostic Features

Clinical Risk Factors (AJCC)

- **Size** (Prognostic classes based on basal diameter and height)
- **Ciliary body involvement**
- **Extraocular extension**

Histopathologic Risk Factors

Cell type (modified Callender classification)

Patients with spindle cells tumors have better prognosis than patients whose tumors contain epithelioid cells (survival of 4728 patients at AFIP):

Cell type	5-yr-survival	10-yr-survival	15-yr-survival
Spindle cell nevus	100%	100%	100%
Spindle melanoma	90%	79%	72%
Mixed cell, Epithelioid cell, and Necrotic	58%	44%	37%

Tumor size- as important as cell type

1. Tumors can be difficult to accurately measure
2. **Largest tumor diameter (LTD) is best prognostic indicator:**

Size	Dimensions	5-yr-survival	10-yr-survival	15-yr-survival
Small	< 11 mm	86%	76%	70%
Medium	11-15 mm	66%	51%	43%
Large	> 15 mm	56%	41%	35%

Cell type and tumor size are most important factors that can be assessed histopathologically

Other Prognostic Factors Assessable During Routine Pathologic Exam

Extraocular extension

Mitotic activity- more mitoses- worse prognosis

Lymphocytic infiltration- associated with worse prognosis

Vascular mimicry patterns (formerly called extracellular matrix patterns (EMP) or vascular loops and networks (Folberg)

Necrosis- more necrotic tumors have worse prognosis- may present with inflammatory signs such as orbital cellulitis

Pigmentation- not very important- more pigmented tumor- worse prognosis

Melanophagic infiltration- poorer prognosis

Prognostic Factors Assessed By Special Testing

Chromosomal Abnormalities – monosomy 3, trisomy 8q

Monosomy 3- *50% die within 3 years*

Gene expression Profile (Harbour)

Proprietary commercial test- expensive

Class IA melanomas - low-grade, do not metastasize.

Class IB melanomas – New category- late metastasis

Class 2 melanomas - high risk for early metastases, primitive neural/ectodermal stem cell-like phenotype, contain epithelioid cells, vacular mimicry patterns

BAP1 gene inactivation- *strongly associated with metastasis*

Size and variability in nucleolar size (ISDNA, MTLN)- research techniques

Loss of HLA-1 expression- Better Survival

Hypothesis: NK-cell mediated surveillance in blood during hematogenous metastasis

Metastasis (At least 30% die from metastatic disease)

Hematogenous spread-

Uveal melanoma has a predilection for hepatic metastasis

Liver mets in more than 90% of cases, detected first in 80%

More than 50% of patients with metastatic uveal melanoma are dead within 1 year.

Currently, no good therapy for metastatic uveal melanoma

Late metastases occur in some patients.

Diagnosis

Indirect Ophthalmoscopy

Observation for growth

Ultrasonography- acoustically hollow, low internal reflectivity, choroidal excavation

IVFA (No pattern pathognomonic for MM)

FNAB- limited application, reserve for tumors in which diagnostic uncertainty persists after routine tests (e.g. woman with history of breast cancer who has solitary choroidal mass that could be amelanotic melanoma)

P^{32} test- not specific for melanoma, largely abandoned, indications rare

Therapy

Observation for growth ? (some large nevi indistinguishable from melanomas by all clinical criteria except growth) Enucleation is not a medical emergency! -

Enucleation- still treatment of choice for large tumors

Zimmerman's hypothesis- "Enucleation may disseminate tumor cells and increase tumor deaths" (**NOT TRUE**)

Radiation:

Plaques (plaque brachyradiotherapy) radiation source (Iodine125 in USA) placed on sclera over tumor for calculated period of time, now outpatient

Charged particle beams (Proton beam, Helium Ion)

Mortality post-plaque similar to enucleation (COMS)

TTT (transpupillary thermotherapy – form of laser therapy- thin tumors

Plaque plus hyperthermia (experimental)

Photocoagulation- only effective for very small tumors.

Cryotherapy

Local resection- iridectomy, iridocyclectomy, partial lamellar sclerouvectomy

Collaborative Ocular Melanoma Study (COMS- prospective NEI study)

Very small tumors- observation

Small to medium sized tumors

Randomized to I125 plaque versus enucleation

Survival after enucleation and plaque are similar, confirming prior nonprospective data

Large tumors- randomized enucleation versus enucleation versus preop EBRT

Preop EBRT does not improve survival

The Futility of Local Therapy?

It is thought that most uveal melanomas already have metastasized (clinically inapparent micrometastases) when the patient presents to the ophthalmologist. Local treatment has no effect on survival. Metastatic melanoma responds poorly to therapy. It is hoped that early chemo might improve survival if high-risk patients could be identified (FNAB for gene expression classes, monosomy 3 studies, immuno markers)

Metastatic melanoma - ***current therapy is largely ineffective; poor survival***

Iris melanoma

Iris affected least often- inferior iris most common location
Best prognosis- 4% overall mortality (actually may be higher)
Visible to patient, small size at detection
Most pigmented tumors of the iris are benign nevi- only 6.5% grow when observed for 5 years.
Treat by local resection [iridectomy or iridocyclectomy if CB extension present]
Reserve enucleation for tumors with epithelioid cells or intractable glaucoma
Diffuse iris melanomas that cause **heterochromia** and **secondary glaucoma** usually (89%) contain epithelioid cellls

Differential Diagnosis of Posterior Uveal Melanoma)

Nevus
Malignant transformation rare- photos and observe
Suspicious nevi: larger, overlying drusen, even serous detachment

Melanocytoma (magnocellular nevus)
Maximally pigmented magnocellular nevus; more common in blacks
Classically an optic nerve tumor, but can occur anywhere in uvea
Can enlarge, but malignant transformation extremely rare
Bleached sections required to disclose bland cellular details during diagnosis

Choroidal hemangioma
Benign cavernous hemangioma; thin walled vessels, scant stroma
Sporadic tumors: localized, orange mass
Sturge-Weber: diffuse tumors- “tomato catsup” fundus
Cystoid retinal edema, exudative retinal detachment
Distinguish with IVFA, US;
Treatment with PDT or radiation to preserve eye

Uveal metastases – 50% breast, 20% lung
Most common intraocular malignancy (autopsy series- many cases not seen clinically)
Often multiple, amelanotic nummular lesions, posterior pole (greatest blood flow)
One third of patients have no history of cancer/some primaries remain occult
Women-breast carcinoma, prior history of mastectomy (50% of mets are breast)
Men-occult lung primary (20% of mets are lung)
Treatment-irradiate to conserve vision
Role of FNAB (Fine Needle Aspiration Biopsy)- confirm diagnosis when standared tests are equivocal, e.g. met vs amelanotic mm in woman

Congenital Hypertrophy of the RPE (Halo nevus)
Flat black circular or oval lesion with depigmented lacunae, surrounding halo
RPE cells hypertrophic with macromelanosomes
Localized scotoma
POFL’s (pigmented ocular fundus lesions(in **Gardner's syndrome** (Familial adenomatous polyposis with extracolonic manifestations and colon carcinoma) are bilateral, multiple and do not resemble solitary sporadic CHRPE or typical bear tracks.
CHRPE occasionally enlarge, rarely evolve into solid tumors

Congenital grouped pigmentation of the RPE (Bear tracks)
A variant of RPE hypertrophy- cells contain more melanin, larger granules.

Tumors of the Retinal Pigment Epithelium

- Reactive proliferation of RPE is very common
- True RPE neoplasms are extremely rare
- Benign adenomas and cytologically malignant adenocarcinomas
- Bands of tumor cells on septa; very atypical cells, low proliferative index
- Cells often coexpress cytokeratin (CK7) and Melan A
- Malignant RPE tumors locally infiltrate, but do not metastasize
- Some are deeply pigmented, abrupt margins, retinal invasion, exudation

Combined Hamartoma of the RPE and Retina

Tumors of the Ciliary Epithelium

- Very rare (except Fuchs or coronal adenoma)
- Adenomas and adenocarcinomas, from pigmented or nonpigmented epithelium
- Arise from epithelium on inner surface of ciliary body, not from stroma
- Bands of tumor cells on septa; pools of MPS

Leiomyoma

- Most cases found in young woman
- Amelanotic tumors usually located in supraciliary space, may show increased transillumination
- Mesectodermal type resembles neural tumor by LM but shows smooth muscle differentiation immunohistochemistry (smooth muscle actin+) or TEM

Peripheral Nerve Sheath Tumors- rare (choroidal Schwannoma)

Retinal vasoproliferative tumor- probably reactive proliferation of glial cells, vessels, primary and secondary types

Choroidal Osteoma (osseous choristoma)

- Young women (67%), may be bilateral (20%)
- Yellow-orange, scalloped margins, can decalcifiy and involute, CNV
- Plaque of bone in choroid, w/u with CT, US
- Bone within choroidal stroma, not its surface like osseous metaplasia of RPE

Other Lesions That Can Simulate Posterior Uveal Melanoma

- **Hemorrhagic Vascular Lesions**
  - Age related macular degeneration (disciform degeneration)
  - Age-related extramacular degeneration (peripheral disciform degeneration)
  - Hemorrhagic detachment of the RPE or retina
- **Inflammatory Lesions**
  - **Posterior scleritis (nodular)**
    - More common in women, inflammatory signs, cloudy subretinal fluid
    - Same color as surrounding fundus, concentric choroidal folds
    - Ultrasound: retrobulbar edema, thickened sclera and choroid, high internal reflectivity
  - **Chorioretinal granuloma** (sarcoidosis, tuberculosis, syphilis, etc.)
- **Cystic Lesions**
  - Degenerative retinoschisis
  - Iridociliary cysts
- **Choroidal detachment**
- **Uveal Effusion Syndrome**
- **Rhegmatogenous retinal detachment**
- **Others**
  - **Vitreous hemorrhage**
  - **Subluxed lens**
  - **Compression of globe from external mass**

RETINOBLASTOMA

Most common intraocular tumor in children (1/15-20,000 births)
World-wide: most common primary intraocular tumor
Decreasing incidence with age. Majority diagnosed by age 4.
Observed in premature babies and rarely in adults.
No sex preference, 33% bilaterality.

Clinical Presentations

Leukocoria (white pupil) the "amaurotic cat's eye reflex"

90% of patients with retinoblastoma in North America and Europe present with leukocoria.

Other common causes of leukocoria include toxocariasis, persistent hyperplastic primary vitreous (PHPV), and Coats disease.

Strabismus- present in 35%

Children with strabismus should have fundus exam to rule-out a small foveal retinoblastoma or other foveal pathology

Fixed dilated pupil, hyphema, NVG and heterochromia iridis (rare)

Pseudoinflammatory presentation

Pseudohypopyon (tumor seeds in AC, endophytic or diffuse infiltrative tumors)

Aseptic orbital cellulitis due to extensive necrosis of tumor and intraocular structures in eyes with severe glaucoma.

Orbital tumor due to massive extrascleral extension (third world)

Congenital retinoblastoma (very rare!!!)

Clinical Work-up

EUA, Computed tomographic scanning, magnetic resonance imaging, ultrasound, and fluorescein angiography may provide useful clinical information. Avoid needle biopsy

Gross Pathology

White, encephaloid appearance with calcific flecks (mini- "brain tumor")

Growth Patterns

Endophytic growth pattern: arises from inner retina, seeds vitreous, may mimic inflammation

Exophytic growth pattern: arises from outer retinal layers, causes solid retinal detachment; retinal vessels course over mass

Most tumors have **mixed** growth pattern

Diffuse infiltrative: least common (1.4%), no obvious mass, diffuse growth within retina; late presentation (mean age 6 years) with pseudoinflammatory signs- pseudohypopyon – always unilateral

Histopathology

Poorly differentiated neuroblastic cells with basophilic nuclei, scant cytoplasm; apoptotic cells, many mitoses

Tumor arises from and destroys retina

Blue, pink and purple areas under low magnification

BLUE- viable tumor cells with **basophilic nuclei and scanty cytoplasm**.

Viable cells form **90-110µ cuffs** around vessels giving rise to lobular pattern

PINK- eosinophilic zones of tumor **necrosis**

(tumor has striking tendency to outgrow blood supply)

PURPLE- foci of dystrophic **calcification** within necrosis

DNA deposition-basophilic DNA released by tumor necrosis preferentially deposits around vessels, lens capsule, in trabecular meshwork, ILM
Iris neovascularization, often with PAS, found in 50%
Tumor seeds - form when viable tumor cells are shed into vitreous or subretinal fluid. Outermost cells are viable; innermost cells are necrotic.

Characteristic Signs of Differentiation

Flexner-Wintersteiner Rosettes

Early **photoreceptor differentiation**
Central lumen corresponds to subretinal space, filled with hyaluronidase-resistant acid mucopolysaccharide similar to inter-photoreceptor matrix material
Cellular apices joined by XLM-like *zonulae adherentes*
Cilia (9+0) project into lumen
(Despite what the Academy manual says F-W rosettes are *not* pathognomonic for RB, they are also found in medulloepithelioma, pineal tumors!)
Numerous rosettes are found in tumors from very young children.
Retinoblastomas in older children are usually poorly differentiated.

Homer Wright Rosettes (after James Homer Wright)

Neuroblastic differentiation
No true lumen, tangle of neural filaments fills central space
Often observed in neuroblastoma, medulloblastoma, less frequently in retinoblastoma (mnemonic**: Homer** Simpson likes jelly donuts- no hole)

Fleurettes

Advanced photoreceptor differentiation
Small bouquet-like aggregate of benign-appearing tumor cells
Cells are aligned along segment of "XLM"
"Flowers" comprising bouquet are bulbous, eosinophilic inner segments
Photoreceptor outer segment disks occasionally are found (by EM)
Found in area of tumor that appears less cellular, more eosinophilic
Cells show low nuclear-cytoplasmic ratio, low mitotic activity, absent necrosis, greater resistance to radiation

Retinoma, retinocytoma

Benign variant of retinoblastoma with prominent areas of photoreceptor differentiation (fleurettes); some consider precursor of retinoblastoma
Bland nuclei, eosinophilic fibrillar cytoplasm, calcification within viable tumor
Resistant to radiation (like most benign tumors)
Previously thought clinically to be spontaneously-regressed retinoblastomas
Fish flesh appearance with cottage cheese calcification, surrounding annulus of atrophic RPE
Both copies of Rb1 gene are abnormal in retinoma/retinocytoma; additional mutations necessary for progression to retinoblastoma
May be a precursor to retinoblastoma

Complete Spontaneous Necrosis (regression)

True spontaneous regression
Associated with severe inflammation and phthisis bulbi, (? secondary to NVG)
Typical foci of calcification persist in fibrous matrix

Biological behavior and spread:

Most retinoblastomas exhibit relentless progression. If left untreated, the tumor fills the eye and completely destroys the internal architecture of the globe. Regardless of the pattern of growth, there is a striking tendency to invade the optic disc and optic nerve. The tumor may spread along the nerve to the chiasm and the contralateral

optic nerve or may spread through the pia to the subarachnoid space with seeding along the neuraxis.

Metastasis/Extension:

1. Direct Infiltration - along optic nerve to brain - into orbit - into cranium through foramina or bone
2. Dispersion of tumor cells through subarachnoid space to brain and spinal cord
3. Hematogenous dissemination to **lungs, bones, and brain**. Unlike uveal melanoma this is an uncommon event unless there is extraocular extension.
4. Lymphatic spread after invasion of the conjunctiva. There may be massive pre-auricular and cervical lymphadenopathy.
5. **Metastases typically occur within 2 years of treatment**.
6. Recurrence is due to retained tumor cells in orbit or beyond the point of optic nerve transection

Prognostic features:

Optic nerve invasion-

Retinoblastoma tends to invade optic nerve (unlike melanoma)

Survival correlates with depth of invasion:

No invasion-8%, prelaminar 15%, retrolaminar 44%, line of resection 64%
(Retrolaminar invasion usually indication for adjuvant chemotherapy)

Tumor can directly extend to brain, gain access to CSF

Choroidal invasion (role controversial) massive choroidal invasion- defined as greater than 3mm, full thickness

Orbital invasion (AFIP- more important than choroidal invasion)

Iris, anterior chamber and trabecular meshwork invasion- magnitude of effect unclear

Absence of rosettes, fleurettes

Lymphadenopathy with anterior perforation, conjunctival invasion

? Diffuse growth pattern (delay in diagnosis)

Pseudoinflammatory presentation (delay in diagnosis)

Prospective Study sponsored by Children's Oncology Group (ARET0332) currently investigating chemotherapy in patients with high risk histologic features

High Risk Histopathologic Features that are Indications for Adjuvant Chemo:

Retrolaminar optic nerve invasion,

Massive uveal invasion (massive >3mm)

any degree of concurrent optic nerve and uveal invasion

Risk factors associated with mortality	Odds Ratio
Invasion of ocular coats	
Choroid	1.8
Sclera	3.9
Orbit	21.6
Invasion of optic nerve	
Resected	3.8
Unresected	8.7
Bilaterality	2.9
Incorrect diagnosis	2.5

Treatment (See Oncololgy Notes – in evolution):

Small lesions are treated with chemotherapy, TTT, Radioactive plaques, photocoagulation, cryotherapy, (recent trend to avoid EBRT to prevent secondary tumors)
Large tumors - usually enucleated when unilateral
if bilateral, more severely involved eye is often enucleated with vision sparing therapy applied to the less involved eye.
Chemotherapy (Chemoreduction) now used as initial management of many cases with bilateral tumors, or after enucleation if high-risk histopathologic features present
Intraarterial chemotherapy- delivers chemo directly to eye via ophthalmic artery; use increasing; currently available in a few centers;
Ischemic atrophy of outer retina and choroid can occur; theoretical risk for metastases
Intravitreal Chemotherapy- appears to be effective for vitreous seeds;
Advanced tumors - Radiotherapy, chemotherapy, and orbital exenteration may be employed

Genetic variants of Retinoblastoma

VARIANTS	Frequency	Avg Age	Bilateral *	?Transmission?
Sporadic (somatic mutation)	64%	24 mos.	NO	NO
Sporadic (germinal mutation)	21%		YES	YES
Familial*	5-10%	12 mos.	YES	YES
Chromosome deletion (13Q-)	<5%			

(*Approximately 70% have bilateral tumors, can have multifocal tumors, secondary tumors)

The Retinoblastoma Gene: The Paradigmatic Recessive Oncogene
Located on **long arm of chromosome 13** (13 Q 1-4 band)
RB gene sequence contains 180,388 base pairs
The RB gene protein product (928 amino acids) is found in the nucleus
RB protein involved in control of the cell cycle (necessary for terminal differentiation)
During G1 resting phase RB protein forms complex with E2F transcription factor
Phosphorylation of RB protein causes separation from E2F.
Uncomplexed E2F activates a variety of other genes necessary for DNA synthesis.
Absence of RB protein causes continual cell division and lack of terminal differentiation (i.e. cancer).
Tumor virus proteins (adenovirus E1A and SV40 large T) cause tumors by binding to and inactivating RB protein.
Familial cases appear to be **autosomal dominant** (50% of offspring inherit)
The retinoblastoma (RB) gene actually is **recessive at the molecular level**;
Normal individuals have two functional copies of the RB gene (RB, RB)
Familial cases are heterozygous for retinoblastoma gene (RB, rb)
Tumors develops when both normal genes in a single retinal cell are lost or inactivated. (rb, rb)
Familial cases and **sporadic germinal** cases are genotypically heterozygous for the Rb gene (RB, rb). (Sporadic germinal cases are new familial cases.)
The genotype of a heterozygous carrier of retinoblastoma includes one functional and one inactivated gene. A single functional gene prevents malignant transformation. The spontaneous mutation rate of RB gene is $<10^{-7}$ or greater.
Development of each retina requires 10^8 cellular divisions. Therefore, strictly by

chance, at least one cell in both retinas of a genotypically heterozygous individual will lose both normal suppressor genes permitting malignant transformation. Tumors in cases of familial retinoblastoma are frequently (2/3's) bilaterally and can be multifocal. Bilateral involvement indicates that the patient is a carrier of familial retinoblastoma. Unfortunately, the opposite is not true. One-third of familial cases have unilateral tumors.

Sporadic somatic retinoblastomas result from the sequential inactivation of both genes in a single retinal cell in a patient whose genotype is normal (RB,RB). Sporadic somatic tumors are unilateral because the probability of this occurrence in more than one retinal cell is exceedingly small. **Most retinoblastomas are sporadic somatic**.

Autosomal dominant inheritance In familial cases is mimicked by the inheritance of heterozygosity with subsequent gene inactivation:

carrier normal

RB rb X RBRB = 50% RB rb + 50% RB RB

Chromosomal deletion (**13Q-**) retinoblastomas resemble familial cases. In this variant the gene deletion is karyotypically obvious. Patients with $13Q^-$ syndrome have other systemic abnormalities including mental retardation, imperforate anus, genital malformations and facial anomalies including low-set ears, a broad nasal bridge, and a thin upper lip

Rb1+/+ Retinoblastoma

No mutations in Rb1 gene; RB+/+ tumor caused by amplification of NMYC gene. Early onset, aggressive, poorly differentiated, large nuclei with nucleoli, no FW rosettes, No tumor risk for fellow eye or siblings (somewhat controversial)

Additional facts:

*Familial cases develop earlier (12 months) because only one gene has to be inactivated (ony 1 "hit" necessary –Knudson's 2 hit hypothesis)

*Sporadic somatic cases develop later because two genes have to be inactivated (2 "hits" required)

*Retinoblastoma is a disease of early childhood (average age 18 mo.) because gene inactivation usually occurs during cellular division. Most cellular division in retina ceases before birth.

*If a patient has bilateral retinoblastoma, you must assume that the disease can be transmitted to his offspring. **(bilateral =hereditary)**

(Unfortunately, the opposite is not true! Due to incomplete penetrance of gene, 1/3 of hereditary cases have unilateral tumors. 10-15% of unilateral sporadic tumors are heritable germinal mutations).

ASSOCIATED MALIGNANCIES:

Patients who are carriers of familial retinoblastoma are predisposed to develop other malignant tumors. Second Tumors are most common cause of death in Rb patients in the USA

Survivor of bilateral retinoblastoma has a 20-50% chance of developing a second tumor within 20 years. (AFIP series - 26% within 30 years)

These non-ocular tumors include **osteogenic sarcoma** (most common), chondrosarcoma, other soft tissue sarcomas, carcinomas of the upper respiratory passages, malignant melanomas, and carcinomas of the skin.

The majority of second tumors are **post-irradiation**, occurring within the field of irradiation (reason for trend away from EBRT.

Osteosarcoma of the lower extremities is the most common tumor outside of radiation therapy fields. Patients have a 500X increased incidence of osteogenic sarcoma of the femur.

Trilateral Retinoblastoma: ectopic retinoblastoma of the pineal gland or parasellar region. Occurs in bilateral or familial retinoblastoma. Fleurettes and Flexner-Wintersteiner rosettes may be observed in the intracranial tumor. decreased incidence after chemoreduction

The retinoblastomas gene has also been implicated in other systemic malignancies including breast and lung cancer

Some oncoviruses (SV40, HPV. adenovirus) are thought to produce cancer by making proteins that complexes and inactivates the suppressor protein product of the RB gene.

Genetic counseling: risk that subsequent child will have retinoblastoma:

Unilateral retinoblastoma

Affected parent with no affected children-	3%
Normal parents, one affected child	3%
One affected parent, one affected child	30%

Bilateral retinoblastoma

One affected parent, no affected child	40%
Normal parents, one affected child	10%
One affected parent, one affected child	50%

The Differential Diagnosis of Retinoblastoma

Three most common simulating lesions: **toxocariasis, PHPV and Coats' disease**

Ocular Toxocariasis (Nematode Endophthalmitis)

Ocular manifestation of visceral larva migrans- *Toxocara canis*

Unilateral, end of first decade, exposure to puppies

Diffuse nematode endophthalmitis, vitreous abscess with retinal fold, subfoveal granuloma

Larval fragment in eosinophilic abscess- serial sections usually necessary

Negative ELISA for Toxocara antigen excludes

PHPV / *PFV* (Persistent Hyperplastic Primary Vitreous or *Persistent Fetal Vaculature*)

Congenital (present at birth), unilateral

Eye usually **microphthalmic** at birth

Retrolental fibrovascular plaque, patent hyaloid vessel

Inwardly-drawn ciliary processes

Iris shunt vessels, other persistent fetal vessels

Lens may contain fat or even bone

Alternate term **- PFV: persistent fetal vasculature** (Goldberg)

Untreated eyes often develop secondary closed angle glaucoma

Coats disease

Exudative retinal detachment caused by congenital retinal vascular abnormalities

Unilateral, usually towards end of first decade, 2/3's in boys, macular lipid
Leaky retinal telangiectases, miliary aneurysms, adjacent capillary nonperfusion
Massive retinal thickening by hard exudates
Subretinal fluid rich in protein and lipid (foamy histiocytes, cholesterol clefts)
Bilateral Coats-like picture in f**acioscapularhumeral muscular dystrophy**

Retinopathy of Prematurity (retrolental fibroplasia)
Premature infants, supplemental oxygen therapy
Vitreoretinal neovascularization at posterior margin of peripheral nonperfused retina
Tractional retinal detachment- masses of detached retina can mimic retinoblastoma
Often bilateral and not present at birth (shared features with retinoblastoma)
Usually affects temporal retina, foveal dragging

Embryonal Medulloepithelioma (second most common primary pediatric IOT)
Symptomatic - age 4, diagnosed age 5, reare cases in adults
Arises from embryonic medullary epithelium, most ciliary body tumors, rare ON tumors
Cords and sheets of polarized neuroepithelial cells, pools of hyaluronic acid
Teratoid tumors (38%) contain heteroplastic elements: **cartilage, muscle, brain**
2/3's are malignant- contain undifferentiated retinoblastoma-like areas, sarcomatous stroma, rosettes, show invasive behavior
Fatalities after extrascleral extension, recur after local resection
Rare Association with **pleuropulomonary blastoma** – DICER1 germline mutations 14q31

Astrocytic Hamartomas and Astrocytomas
Tuberous sclerosis or NF- early lesions may be confused with retinoblastomas
Most patients with TSC have nonprogressive astrocytic hamartomas
Rare retinal giant cell astrocytomas- may grow

Norrie Disease
X-linked recessive
Bilateral masses of malformed detached retina (pseudogliomas)
Deafness, mental retardation
Norrin gene mutations in x-linked exudative vitreoretinopathy, predispose to severe ROP

Incontinentia pigmenti (Bloch Sulzburger)
X-linked dominant (lethal in males)
Peripheral vitreoretinal neovascular nonperfusion (congenital nonperfusion), RD
Post-natal vesiculo-bullous skin lesions rich in eosinophils, secondary marbleized pattern of skin pigmentation. Other CNS, dental and ocular anomalies
NEMO/IKK gamma gene on **Xq28-** activates eosinophil chemokine **eotaxin**

Retinal dysplasia
Most cases trisomy 13, rare isolated cases in normal patients
Dysplastic rosettes are larger, contain multiple retinal layer

Other...
Retinal Astrocytomas (Giant Drusen of ON, Tuberous Sclerosis)
Colobomas
Myelinated nerve fibers (papilla leporina)
Congenital cataract
Retinal detachment, vitreous hemorrhage, trauma

The Differential Diagnosis of Retinoblastoma and Simulating Lesions

Lesion	Unilateral	Bilateral	Age	Comments
Retinoblastoma	X	X	Mean 18 mo	Calcificaition on imaging; pseudoinflammatory presentations
Toxocariasis	X	-	6-11 yrs	Contact with puppies; eosinophilic abscess, serial sections to disclose worm fragment, negative ELISA excludes
PHPV / PFV	X	-	Present at birth	Microphthalmic eye with retrolental fibrovascular plaque, inwardly-drawn ciliary processes, iris shunts and other persistent fetal vessels
Coats Disease	X	Rare	18 mo to 18 yrs, peak end of 1st decade	2/3's male, abnormal leaky retinal vessels (Leber's miliary aneurysms), bullous RD with lipid-rich subretinal fluid, massive exudation; bilateral cases my have fascioscapulohumeral muscular dystrophy
Retinopathy of Prematurity	-	X	In early infancy, but not congenital	Premature infants, supplemental oxygen therapy
Incontinentia pigmenti (Bloch-Sulzberger)	-	X	Infancy	Perinatal bullous eruption with eosinophilia, whorled skin pigmentation develops, nonperfusion of periphery, X-linked dominent – lethal in males, NEMO gene, eotaxin
Norrie Disease	-	X	Congenital	Males, x-linked recessive, bilateral pseudogliomas caused by detachment of dysplastic retina, deafess, mental retardation, Norrin gene (plays role in other disorders)
Medullepithelioma	X	-	4 years (rare – adults)	"diktyoma", benign and malignant, teratoid and nontertoid, teratoid tumors contain cartilage, muscle brain
Retinal Dysplasia	X	-	Congenital	Microphthalmia, most have trisomy 13
Astrocytic Hamartoma of TSC		X	Early infancy	Tuberous sclerosis complex, family history, seizure disorder, retinal lesion easily confused with early RB Rare progressive giant cell astrocytomas
Other				Colobomas, congenital cataract, myelinated nerve fibers, retinal detachment, vitreous hemorrhage, trauma, endogenous endophthalmitis

ORBITAL DISEASE

Most orbital diseases cause ocular proptosis or exophthalmos
Direction of proptosis suggests location of lesion

Lymphoid Tumors and Orbital Inflammation

Orbital inflammatory disease and "pseudotumors' are more common than true neoplasms

Thyroid ophthalmopathy (Graves' disease, Graves' orbitopathy)

Most common cause of unilateral or bilateral exophthalmos
Proptosis due to enlargement of extraocular muscles, edema of orbital tissue
An immunological disease that affects both the EOM's and the thyroid
Orbitopathy can occur with high, normal or low thyroid function
Pathogenesis remains unclear- ? T-lymphocyte imbalance; B cells may produce anti-muscle antibodies; oribital fibroblasts may play important role as target cells
Enlarged muscles show foci of chronic nongranulomatous infiltration, secondary fibrosis.
Inflammation spares tendon, orbital fat (in contrast to pseudotumor)
Mast cells do not secrete excess MPS

Idiopathic orbital inflammation (idiopathic orbital pseudotumor)

Explosive onset, pain, muscle paresis, visual loss, proptosis
Can be acute, subacute or chronic, unilateral or bilateral; chronic cases rock-hard, can mimic carcinoma
Inflammatory signs, inflammation sharply delimited by orbital septum at rim; **"Pink" polymorphous lymphoid infiltrate**, lymphocytes, plasma cells, eosinophils, follicles, extensive **fibrosis** in ***sclerosing*** pseudotumor
Heavy infiltration of orbital fat, involves muscle tendon; late fibrosis
Following factors differentiate from lymphoid tumors:
Pink, not blue, hypocellular lesion with fibrosis, inflammatory signs
Exquisitely sensitive to corticosteroids

Variants (by structures involved)
Myositis-diplopia and pain on movement, involves tendon (unlike Grave's), Dacryoadenitis, Periscleritis, Perineuritis, Trochleitis

Pathology: light polymorphic infiltrate, fibrosis, late orbital cirrhosis, perivascular lymphocytic cuffing (diapedesis, not vasculitis), concentric fibrous lamellae surround vessels, orbital fat involved, can have granulomas, eosinophils, germinal centers

A diagnosis of exclusion!! r/o specific inflammatory diseases
Note: Some physicians (e.g. radiotherapists) persist in applying the term ***orbital inflammatory pseudotumor*** to reactive or atypical lymphoid hyperplasias of the orbit. Ophthalmic pathologic convention includes such lesions in the spectrum of orbital lymphoid tumors. The term ***idiopathic orbital inflammation*** or ***pseudotumor*** should be reserved for the lesion described below whose characteristic clinical and pathological findings usually serve to differentiate it from lymphoid neoplasms.

Tolosa Hunt Syndrome (painful external ophthalmoplegia)

IgG4-Related Disese- some cases of sclerosing pseudotumor; may have systemic sclerosing conditions; diagnostic criteria and importance not entirely clear. Follicular lymphoid hyperplasia, storiform fibrosis, obliterative fibrosis, >100 eos/HPE in lacrimal gland

Other orbital inflammations and infections

Sarcoidosis (dacryoadenitis, S-sign)
Orbital cellulitis: infection usually invades from sinus
Sub-**periosteal abscess**
Mucormycosis (phycomycosis, zygomycosis)
Large nonseptate hyphae with right angle branching - visible on H&E, vascular invasion with thrombosis and necrosis, acute and chronic granulomatous inflammation; fungus invades from sinuses, eschar a late sign
Acidotic patients (e.g, poorly controlled diabetics), deferroxamine therapy in renal dialysis patients;
Aspergillosis: resembles mucormycosis, but in healthy patients
Allergic Fungal Sinusitis- fungus grows in "allergic mucous", tissue not invaded
Vasculitides
Granulomatosis with polyangiitis (Wegener granulomatosis *or* **ANCA-associated granulomatous vasculitis)**
Necrotizing vasculitis of upper respiratory tract, lungs, and kidneys (necrotizing glomerulonephritis), cavities in lower lobes of lungs
Limited form - no renal involvement, **c-ANCA** helpful diagnostic test but may not be positive in early cases. 28.5% have ophthalmic manifestations: proptosis (40%), scleritis (25%), peripheral corneal ulceration. May present with eye findings
Path: granulomatous vasculitis with fibrinoid necrosis, stellate interstitial necrosis, Langhan's giant cells – orbit may lack classic histopathology
Polyarteritis Nodosa
Men 4:1, age 20-40, infarcts skin, CNS
Angiocentric inflammation with polys and lymphocytes
Immune complex disease, nongranulomatous
Orbital thrombophlebitis
Idiopathic midline destructive disease (NK cell lymphoma)
Angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma)
Kimura's disease (Asian males, eosinophilia, elevated IgE)- differs from above

Lymphoid Tumors
A histologic spectrum that includes polyclonal reactive lymphoid hyperplasias, cytologically indeterminate atypical lymphoid hyperplasias, and malignant lymphomas composed of cytologically atypical cells.
Clinical Characteristics
Average age 60 (later than other primary orbital tumors)
Rare in childhood- **rule out leukemia!** (myeloid sarcoma)
Insidious onset of painless, well-tolerated proptosis or conjunctival "salmon patch"; No inflammatory signs
90% of orbital lesions involve **superior orbit** behind septum,
> 40% arise in lacrimal gland, affect palpebral lobe (epithelial tumors involve orbital lobe)
CT Scan: Putty-like soft tissue molded by tissue planes, infiltrate may have straight-line angulations; diffuse "pregnant" pancake-like enlargement of lacrimal gland molds to globe, projects anterior to orbital septum.
Bone destruction rare, except in rare cases of multiple myeloma
EOM cases usually involve **one** muscle, **No** fibrosis, motility OK
Gross pathology: soft friable tissue lacks connective tissue stroma
Salmon color due to fine capillarity within lesion

Two thirds of ocular adnexal lymphoid tumors are monoclonal B cell malignant Non-Hodgkin's lymphomas. Most of these are low-grade. Many are MALT lymphomas 50-60% *(extranodal marginal zone lymphomas of mucosa associated lymphoid tissue)*

Reactive Follicular Lymphoid Hyperplasias

Polymorphic infiltrate with lymphocytes, plasma cells, eosinophils
Germinal centers with immunoblasts, tingible-body macrophages, polarity, mitoses confined to germinal center, BCL-2 negative
T-cell rich (≥ 60% T-cells, mainly T-helper; resembles systemic circulation) B cells polyclonal

Atypical Lymphoid Hyperplasias

(Cytologically indeterminate, borderline or "gray zone" lesions)

Monomorphic lesion with scant or no follicles, composed of well-differentiated lymphocytes.
Immunohistochemistry discloses that 70% of atypical lymphoid hyperplasia are monoclonal, i.e., they actually are low grade lymphocytic lymphomas (see below)

Malignant Lymphoma (monomorphic infiltrate)

Most ocular lymphomas are diffuse (16% follicular).
Essentially, all orbital lymphomas are **monoclonal B cell tumors** (typically composed of more than 60% CD20+ B lymphocytes).
Monoclonal B cells express only 1 type of light chain (kappa or lambda)
Lymphomas are best classifed by **Flow Cytometry**
Flow cytometry requires adequate quantity of **fresh, unfixed tissue**
Limited Immunophenotypic analysis can also be performed on paraffin embedded tissue, but stains for light chains (clonality) usually don't work
Gene rearrangement studies – questionable efficacy in the conjunctiva
The majority of ocular adnexal lymphomas are low-grade small lymphocytic lymphomas. 50-80% are classified as extranodal marginal zone lymphomas (EMZL) of mucosa-associated lymphoid tissue (MALT lymphomas, MALTomas)
Flow cytometry and immuno markers are used to distinguish other types of lymphoma in **WHO classification**, e.g. follicular lymphoma, mantle zone lymphomas, CLL, diffuse large B cell lymphoma.

Immunohistochemical staining of common adnexal lymphomas

Class of lymphoma`	**Lymphoma cells express**
MALT (EMZL)	**CD20+**, CD5-, CD10-, CD23-
FOLLICULAR	**CD20+**, CD5-, **CD10+**, **CD23+, bcl-2+**
MANTLE ZONE	**CD20+**, **CD5+**, CD10-, CD23-, **Cyclin D-1+ (bcl-1)**
CLL/SLL	**CD20+**, **CD5+**, CD10-, **CD23+**
Diffuse Large B cell	**CD20+**, CD5+/-, CD10+/-

CLL/SLL Small lymphocytic lyomphoma- tissue deposits of CLL

MALT- small lymphocytes, monocytoid lymphocytes, lymphoepithelial lesions, residual follicles- often contain plasma cells, indolent course, GI cases associated with **H pylori** infection; may be cured by antibiotics in gut, possibly conjunctiva

Follicular Lymphoma- 3 grades, higher grades contain more centroblasts, malignant follicles have ill-defined mantle zone, lack polarization and tingible body macrophages (CD20+, CD10+, follicles bcl-2 +)

Mantle Cell Lymphoma – small to medium lymphocytes with irregular nuclei, elderly men, widely disseminated at presentation; poor prognosis (CD20+, CD5+, bcl-1 +)

Systemic Involvement* in Ocular lymphoid Tumors

*Prior, concurrent or subsequent (Knowles, Jakobiec, et al, Human Pathol 21: 595, 1990)

Conjunctiva	20%
Orbit	35%
Eyelid	67%
All sites	33%
Bilateral lesions	38%
Polyclonal ocular lesion*	29%
Monoclonal ocular lesion	33%

Approximately one-third of patients with ocular lymphoid tumors have a history or, have, or will develop extraocular lymphoma!!!
The site of involvement and the cytologic type of lymphoma do correlate somewhat with systemic disease:

Patients who have conjunctival lesions are less likely to have extraocular lymphoma.
Patients with eyelid lesions (involving skin surface anterior to orbital septum) are more likely to have extraocular lymphoma.
Patients with low-grade ocular lymphomas are less likely to have extraocular lymphoma.
Patients with higher grades of ocular lymphoma are more likely to have extraocular lymphoma.

Most important prognostic factor - the **extent of the disease at the time of initial presentation disclosed by a thorough clinical staging.** *The vast majority of patients presenting with a clinical stage 1E ocular adnexal lymphoid proliferation,* regardless of histopathology or immunophenotypic analysis have a benign indolent clinical course" (Knowles et al, Coupland et al)

All patients with an ocular adnexal lymphoid tumor need a <u>thorough systemic evaluation</u> by a hematologist/oncologist.

This should include: a bone marrow biopsy and CT body scans, PE, CXR, CBC with differential, flow cytometric analysis with monoclonal antibodies, Coombs, serum protein electrophoresis

Long term follow-up with examinations every 6 months

Therapy

Stage IE, No systemic involvement- RADIOTHERAPY with eye shielding

Low grade lesions- 1500-2000 rads
High grade lesion- 2000-3000 rads

Extraocular (systemic) lymphoma present- CHEMOTHERAPY or immunotherapy

Supplement with adjunctive ocular radiotherapy if ocular regression subtotal

Other Lymphoid Tumors

Plasma cell tumors- myeloma, bone destruction
Lymphoplasmacytoid tumors- Waldenstrom's macroglobulinema, Dutcher bodies
Post-transplantation lymphoproliferative disorder (EBV, immunosuppression)
Hodgkin's disease
Burkitt's lymphoma (EBV infection)
Mycosis fungoides: T-cell cutaneous lymphoma, convoluted cerebriform nuclei, Pautrier abscesses
Reactive Lymphoid Hyperplasia of the Uvea- ***probably MALT lymphoma***
Multifocal choroiditis-like picture, biopsy epibulbar component
Myeloid or Granulocytic Sarcoma (leukemic infiltrate. "chloroma")
Suspect in children with “lymphoma”
Confirm granulocytic differentation with immuno or Leder esterase stains
May present when peripheral blood normal
A major cause of bilateral proptosis in children

ORBITAL TUMORS

A different spectrum of orbital tumors occurs in children and adults

Category	Children	Adults
Congenital	Dermoid cyst, teratoma	
Vascular	Capillary hemangioma Lymphangioma	Cavernous hemangioma Hemangiopericytoma
Neural	Plexiform neurofibroma Optic Nerve Glioma	Schwannoma Optic nerve meningioma
Mesenchymal	Rhabdomyosarcoma	Fibrous histiocytoma
Hematopoietic	Granulocytic sarcoma Histiocytoses	Lymphomas
Metastatic	Neuroblastoma, Ewing's Sarcoma, Wilms' Tumor	Carcinomas (lung, breast)
Other		Epithelial tumors of lacrimal gland

Well-circumscribed orbital tumors

Cavernous Hemangioma
Schwannoma
Hemangiopericytoma
Fibrous Histiocytoma / Solitary Fibrous Tumor
Epithelial Tumors of the Lacrimal Gland
Primary orbital melanoma

Vascular Tumors

Cavernous Hemangioma

Most common adult vascular tumor, middle aged females
Well tolerated, low grade proptosis, normal vision and motility

Discrete, round, encapsulated lesion; stagnant circulation -little opacification with CT contrast
Histology: large cavernous blood-filled, endothelial-lined spaces, fibrous interstitium with smooth muscle

"Hemangiopericytoma" (SFT)
Well-circumscribed, lights-up with contrast, "stag-horn" vessels, metastatic potential; **hemangiopericytomas have been reclassified as solitary fibrous tumors**; the latter often have "hemangiopericytomaous vascular pattern"

Lymphangioma (spectrum includes orbital varix, AVM's) – *see below*

Orbital Varix
Arteriovenous Malformations
Venous Angiomas
Glomus Tumor, glomangioma
Vascular Leiomyoma
Klippel-Trenaunay-Weber Syndrome
Blue Rubber Bleb Nevus Syndrome
Intravascular Papillary Endothelial Hyperplasia
Angiosarcoma (Malignant Hemangioendothelioma)
Kaposi's Sarcoma – homosexual men, HHV8

Mesenchymal Tumors

Fibrous Histiocytoma (fibroxanthoma)
In the past, said to be most common mesenchymal tumor of adults, mean age 43 (4-85) – **Fibrous histiocytomas have been reclassified as solitary fibrous tumors**
Orbit is site of predilection, superior (43%), nasal
Fibroblasts and histiocytes, storiform pattern
Benign, malignant and locally aggressive variants, **excise totally**!!

Solitary fibrous tumor (SFT) – pattern-less pattern, fibrous bands between cells, many cases have hemangiomatous vascular pattern. **Imuno: STAT6+**, CD34+, CD99", bcl-2+ (many cases diagnosed as hemangiopericytoma or fibrous histiocytoma in past)

Fibroblastic Tumors
Nodular Fasciitis (benign sarcomatoid proliferation of myofibroblasts)
Fibroma
Juvenile Fibromatosis or myofibromatosis
Fibrosarcoma (rare)
Myxoma

Tumors Of Adipose Tissue
Orbital fat inert - least likely to spawn tumors
Herniation Of Orbital Fat- Some cases have feautures seen in pleomorphic lipoma (floret cells and lochkern nuclei) - not a sign of malignancy
Very rare liposarcomas

Tumors of Smooth Muscle- very rare, most post radiation
Leiomyoma, Leiomyosarcoma

Fibro-osseous And Cartilaginous Tumors
Most arise from bones of orbit and sinuses
Ivory Osteoma- most common, dense, mature bone
Fibrous Osteoma
Fibrous Dysplasia

Trabeculae of woven bone without osteoblasts in fibrous stroma-
Juvenile Ossifying Fibroma (psammomatoid)
Osteosarcoma- sinus origin, with or without prior radiotherapy
Cartilaginous Tumors – very rare
Chondroma
Mesenchymal Chondrosarcoma

Neural tumors
Schwannoma (neurilemmoma)
Round, encapsulated, associated with peripheral nerve, may be painful
Antoni A: cellular area with palisading spindle cell nuclei, Verocay bodies
Antoni B: loose myxomatous area
Plexiform neurofibroma (NF 1)
Diffuse neurofibroma (NF 1)
Isolated neurofibroma (no NF by definition)

Lacrimal Gland Tumors
10-15% of orbital lesions biopsied (relatively rare tumors)
(In routine non-referral clinical practice, inflammatory and lymphoid lesions of the lacrimal gland are 5 times more common than epithelial tumors)
Limited spectrum of epithelial tumors: no Warthin's tumors, mucoepidermoid carcinoma rare, oncocytomas and acinic cell tumors very rare
LG is a *minor salivary gland*: greater incidence of malignancies than parotid
Important factors in clinical evaluation (Jakobiec)
Duration and types of symptoms:
Short duration (<6mo-1yr): inflammation, lymphoid or malignant epithelial malignancies
Pain: inflammation or epithelial malignancy
Presence or absence of bony destruction on x-ray
Bone changes and short duration: epithelial malignancy
Overall configuration of soft tissue lesion on axial and coronal CT
Rounded or globular- epithelial tumor
Long duration, well-tolerated- BMT
Short duration, significant symptoms: malignant tumor
Diffuse molded enlargement of lacrimal gland: lymphoid or inflammatory
Involvement of palpebral lobe: lymphoid or inflammatory (most epithelial tumors arise from deep orbital lobe, do not project beyond orbital rim)
"50-50" RULE (not true in clinical practice: most inflammatory or lymphoid!!)
50% of lacrimal gland lesions are **inflammatory**
50% are **epithelial**
50% of the epithelial tumors are **benign** (BMT)
50% are **malignant**
Adenoid Cystic Carcinoma
Malignant Mixed Tumor, rare types of adenocarcinoma

Epithelial Tumors of the Lacrimal Gland
Benign Mixed Tumor (Pleomorphic Adenoma)-50%
Usually arise from deep orbital lobe, rarely palpebral, accessory, skin
Painless, slowly progressive mass, well-tolerated Proptosis-"down and in"
60% in men, age 7-77 (mean age 39)

Tumor cells contain specific gene fusions involving PLAG1 and HMGA2 oncogenes; confirm diagnosis with immunostain for **PLAG1.**
CT: rounded or ovoid lesion, lacrimal fossa accentuated, regular well-corticated pressure indentation
Gross: encapsulated with "bosselations" (actually a pseudocapsule)
Cut surface may show mucinous and myxomatous areas
Histology:
***Mixture* of epithelial and mesenchymal elements**
Epithelial ductules composed of double layer of cells:
Inner cuboidal to columnar epithelium, outer flattened or spindled "myoepithelial" cells
Stromal cells derived from outer layer, undergo metaplasia (myxoid tissue, cartilage, rarely bone and fat), tyrosine crystals
TEM studies show origin from lacrimal gland duct cells (small secretory granules), outer cells not myoepithelial, actually basal germinal cells,
Management: complete excision within capsule (Lateral orbitotomy)
Do not biopsy suspected BMT!!! 1/3 will recur
Recurrences can invade orbital soft tissue, bone, brain
Widely separated non-encapsulated "tumorlets"
Malignant degeneration possible

Adenoid Cystic Carcinoma
Second most common epithelial tumor of lacrimal gland (25-30%)
Highly malignant, short duration of SX (6mo-1 year), dismal prognosis
58% in women, average age at presentation 40 years, can occur in children
Pain, numbness, ptosis, motility problems due to **perineural invasion**
CT: globular, rounded but with more serrated, irregular border. May have medial or posterior orbital extension
Destructive or sclerotic **bone changes** in 80%
Infiltrative malignancy, dissection may be difficult
Tumor invades nerves and bone early
Histology-five patterns
Cribriform ("Swiss cheese")
Not true ductules, hence "adenoid"
Basaloid (solid)
Sclerosing
Comedocarcinoma (lobules with central necrosis)
Tubular (true duct formation)
Cylindromatous pattern: tumor nests surrounded by thick basement membrane
Immuno stain for **MYB** specific, but not present in all cases
Prognosis: overall 10 year survival 20%
Basaloid component- 21% 5 yr. survival, 3 year median
No basaloid component- 71% 5 yr. survival, 8 year median
Death from perineural invasion through superior orbital fissure into middle cranial fossa, late (5-10 years) pulmonary metastases
Management (Controversial)
If Dx is suspected on clinical grounds, biopsy through lid; wait for permanent section diagnosis (***not frozen sections***); then exenteration, en bloc resection of tumor and contiguous bone, or radical orbitectomy including roof and lateral orbital wall. **? improved survival with neoadjuvant cytoreductive**

intraarterial chemotherapy followed by exenteration and intravenous chemotherapy (Tse)

Malignant Mixed Tumor- 13% (4-24%)

Malignant transformation of BMT, patients older than BMT

Adenoid cystic in BMT	age 43 (67% women)
Adenocarcinoma in BMT	age 52 (72% men)
Multiple recurrences of BMT	age 64

With multiple recurrences of BMT, 10% malignant in 20 years, 20% in 30yrs

Histology: clone of poorly-differentiated adenocarcinoma in most cases squamous, acinar or sebaceous differentiation,

Prognosis: death within 3 years of malignant degeneration, lymphatic spread via lacrimal gland lymphatics, lung metastases

Management: radical surgery with parotid and cervical lymph node dissection if no mets; if mets, debulk and localized radiotherapy

Mucoepidermoid Carcinoma

Rare, better prognosis than other epithelial malignancies

Exenteration, or wide local excision

"Paving stone" squamous elements and mucous-producing goblet cells.

Adenocarcinoma de novo

Poorly differentiated, older men (mean age 56)

Management, prognosis similar to MMT

Rarer types of lacrimal gland carcinoma

Acinic cell carcinoma, primary ductal adenocarcinoma, basal cell adenocarcinoma, lymphoepithelial carcinoma, epithelial-myoepithelial carcinoma, cystadenocarcinoma

Orbital Tumors In Children

Dermoid Cyst- (Cystic Dermoid) epidermal inclusion cyst with epidermal appendages associated with lining epithelium; result from entrapment of skin with its epidermal appendages in bony sutures within developing skull

Lesions in nasal orbit may have conjunctival epithelial differentiation

Congenital Orbital Teratoma

Vascular Tumors

Capillary Hemangioma

CT: poorly circumscribed, infiltrating, without capsule, placental antigens, **GLUT1** immunostain

Lymphangioma- recent controversy about terminology- Presence of lymphatic endothelium confirmed by D2-40 immuno stain

Vascular channels larger and more variable than those in cavernous hemangioma, contain lymphoid foci, may enlarge suddenly- lymphoid hyperplasia secondary to URI; intralesional hemorrhage- chocolate cyst formation; propranolol – first line of therapy

Rhabdomyosarcoma

Average age 7 years, boys more common

Fulminant and rapidly developing proptosis

Superior orbit most commonly involved

Rapid growth may mimic inflammatory disease

CT: deceptively well circumscribed, contrast enhances

60% erode lamina papyracea, may arise in sinus and invade orbit

Gross: flesh to yellow-colored, hemorrhage rare

Histology: not encapsulated, often infiltrates, occasional "pushing margins"

Variants:

Embryonal: most common, fascicles of tumor cells, loose myxomatous stroma, little collagen, spindle cells, strap cells, cells with eosinophilic cytoplasm (rhabdomyoblasts), cross-striations uncommon (<60%)
Botryoid: Submucosal (conj) presentation of embryonal rhabdomyosarcoma
Nicholson's cambium layer-denser beneath epithelium
Alveolar: second most common, inferior orbit, related to EOM
Cells enclosed by alveolar-like connective tissue trabeculae. Cells large, polygonal with abundant eosinophilic cytoplasm. Translocations t (92:13) and t (1:13); **FKHR gene at 13q14 is site of translocation.**
Tumors with the PAX3-FKHR translocation have a poorer prognosis.
Differentiated (pleomorphic)-rarest in orbit, older patients
Striated muscle differentiation obvious, cross-striations, strap cells with abundant eosinophilic cytoplasm, spider cells, glycogen; arises within preformed striated muscle

Most are embryonal, arise from pluripotential mesenchyme, not muscle
Confirm diagnosis with immunohistochemistry (myogenin, MyoD, muscle specific actin, desmin- transcription factors myogenic and MyoD are more accurate.) electron microscopy: thick 150 Å myosin filaments, sarcomeric units with Z bands, glycogen, basement membrane; admixture of fibrocytoid cells
If no evidence of striated muscle differentiation**:** embryonal sarcoma
Management: **expedient biopsy** to confirm diagnosis, radiotherapy (5-6000cGy) combined with two-drug chemotherapy using dactinomycin and vincristine (IRS III regimen 32). Exenteration rarely needed
Prognosis: 80% survival with radio- and chemotherapy, poorer with sinus involvement

Eosinophilic Granuloma (superior lateral orbit, bone destruction, localized form of Langerhan cell histiocytosis, CD-1a, Langerin (CD207), S-100 positive, Birbeck granules or racket bodies)

Granulocytic Sarcoma (chloroma, myeloid sarcoma)

Leukemic Infiltrate, orbital infiltration may antedate peripheral leukemia and bone marrow involvement
Confirm with immunohistochemical stains (e.g. MPO, stem cell markers CD34, CD117; older Leder esterase stain for granulocytic differentiation
Orbital "lymphoma" in a child is a leukemic infiltrate until proven otherwise!!

Burkitt's Lymphoma: Poorly differentiated B cell lymphoma, "starry sky", EBV

Sinus Histiocytosis With Massive Lymphadenopathy (Rosai-Dorfman)

Large S-100 positive histiocytes phagocytize lymphocytes (emperipolesis)

Metastases

Neuroblastoma

Late stages in children with known tumor, Periocular hemorrhages-"raccoon eyes"

Ewing's Sarcoma

Highly malignant (95% fatal) bone marrow tumor; related to PNET; CD99 +

Secondary Orbital Tumors

Metastases

Breast carcinoma- “Indian file” pattern, signet ring cells; sclerosing type may produce enophthalmos, many are lobular carcinomas

Direct infiltration from contiguous structures:

Eyelid tumors (basal cell, sebaceous gland carcinoma, squamous cell, melanoma)
Conjunctival tumors (mucoepidermoid and squamous cell carcinoma, malignant melanoma)
Intraocular tumors (uveal melanoma, retinoblastoma)
Carcinomas arising in paranasal sinuses
Mucocele-cystic invasion of ciliated respiratory epithelium in patients with paranasal sinus disease
Intracranial Meningioma

Optic Nerve

Optic Nerve Tumors

Optic Nerve Glioma (**Juvenile Pilocytic Astrocytoma**)
Most between age 2-6, 90% before age 20, slight female predominance.
Association with neurofibromatosis 10-50% (frequency may be underestimated because cafe au lait spots develop after therapy)
Unilateral visual loss and axial proptosis, disk pallor (with or without papilledema), strabismus, optic canal enlargement, afferent pupillary defect)
Fusiform swelling of nerve; tumor confined by intact dura, no invasion of orbital tissues, kinking or buckling of ON on CT
Proliferation of benign, spindle-shaped pilocytic astrocytes
Rosenthal fibers-eosinophilic clumps of filaments (□□□ crystalline,
In neurofibromatosis-tumor often invades pia and proliferates subdurally in subarachnoid space (central ON remnant on CT)
Mucinous degeneration can cause sudden increase in proptosis
RX: controversial: follow typical lesions, surgery or irradiation if threat of chiasmal involvement

Malignant Optic Nerve Gliomas In Adults
Most cases rapidly fatal

Optic Nerve Meningioma
Benign tumor arises from meningothelial cells of arachnoid of ON meninges
Severe visual loss, minimal proptosis, optociliary shunts, often optic atrophy
(Note: optociliary shunts actually are **retinal-choroidal venous collaterals!!**)
Primary- arise from optic nerve meninges
Secondary- invades from orbit
Ectopic- from ectopic rests of meningothelial cells
Tumor begins in meninges, may break through dura and invade orbital tissues
CT: diffuse swelling of ON with enlargement at orbital apex
May have calcification (psammoma bodies)
Meningothelial or transitional: paving stone clusters and whorls of cells, Intranuclear vacuoles of herniated cytoplasm, **psammoma bodies**
Optic nerve meningiomas may behave more aggressively in children

Melanocytoma
Medulloepithelioma
Hemangioblastomas (von Hippel)
Combined Hamartoma of Retina and RPE

Optic Nerve Aplasia
Optic Nerve Hypoplasia
Optic Nerve Pit

Usually unilateral, temporal disk margin
Probably related to anomalies in fetal fissure closure
Localized serous detachments and retinoschisis involving macula
Origin of fluid uncertain (No leakage on IVFA): vitreous probably source

Optic Nerve Coloboma

Incomplete closure of fetal fissure
Localized to disk or part of more widespread coloboma
Sporadic or autosomal dominant
2/3's bilateral

Microphthalmos With Cyst

Large cystic coloboma inferior to optic nerve
May produce superior displacement and proptosis of small globe

Morning Glory Disc Anomaly (MGDA)

Severe visual loss, funnel-shaped optic nerve with central connective tissue, surrounding elevated annulus of disturbed chorioretinal pigment, vessels emerge from disk edge – association with carotid stenosis, moyamoya disease in 50%

Colobomas With Choristomatous Malformation

Heterotopic fat, smooth muscle may be present. Usually found in congenitally blind eye

Optic Disk Edema (Papilledema)

ASSOCIATIONS: systemic hypertension, increased intracranial pressure, decreased intraocular pressure, increased intraocular pressure, increased intraorbital pressure, hypercapnia

Swelling results from <u>blockage of axoplasmic flow</u> at lamina cribrosa

Lamina cribrosa distorted by pressure gradient between intraocular and intracranial pressure. (Usually displaced anteriorly except in acute glaucoma)

Histopathology:

Nerve head swollen, narrowing of physiological cup
Lateral displacement of peripapillary retina, photoreceptors
Buckling (folds) of outer retina (Paton's folds)
Shallow peripapillary serous exudate
Late: gliosis, optic atrophy, cytoid bodies

Optic Disk Drusen

Not related to giant optic disk drusen or drusen of Bruch's membrane
Sporadic or familial, occurs in retinitis pigmentosa (0.3-2%)
Histology: anterior to lamina cribrosa within scleral ring, many nasal
Calcified, concentrically laminated globular aggregates
Pathogenesis: blockage of axoplasmic flow in eyes with narrow scleral canal?
Calcified mitochondria in prelaminar corpora amylacea may serve as nidus for further calcification (Tso)

Giant Drusen Of Optic Disk

Epipapillary astrocytic hamartoma with calcospherites (Tuberous Sclerosis)

Optic Neuritis

Ophthalmoscopic Classification

Retrobulbar Neuritis
Papillitis
Neuroretinitis

Topographic Classification

Perineuritis
Periaxial Neuritis

Axial Neuritis
Transverse Neuritis

Pathogenetic Classification
Secondary to intraocular inflammation
Secondary to orbital disease
Secondary to osseous and/or sinus disease
Secondary to intracranial disease
Secondary to vascular disease
Metastatic infections
Systemic demyelinating diseases
Nutritional and/or toxic
Hereditary

Leber's hereditary optic atrophy (LHON)
transmitted by mitochondrial DNA; NADH subunit 4 mutations; ND4 G11778A "Wallace mutation" is most common- poor prognosis for visual recovery, T14484C best prognosis

Optic Atrophy
Gross: shrinkage of parenchyma, redundant dura, widened subarachnoid space
Microscopic: Loss of axons and myelin sheaths, increase in glial cells (astrocytes), thickening of pial septa, widening and deepening of physiological cup.
Primary (descending): lesion in orbit or CNS
Secondary (ascending): primary lesion in retina or disk

Schnabel's Cavernous Optic Atrophy
Follows acute rise in IOP? Not all cases have glaucoma
Retrolaminar cavernous spaces contain hyaluronic acid (? from vitreous)
No gliosis or histiocytic reaction

Pseudo-Schnabel's- silicone oil; may migrate to CNS

GLAUCOMA

Definition 1. (Quigley): An optic neuropathy associated with a characteristic excavation of the optic disc and a progressive loss of visual field sensitivity

Definition 2. (Yanoff): A syndrome characterized by an elevation of intraocular pressure of sufficient degree or chronicity to produce tissue damage. Visual loss results from death of retinal ganglion cells and their axons.

Glaucoma kills retinal ganglion cells and ganglion cells axons that compose the optic nerve

Mechanisms Of Axonal Death

Vascular Theory

Mechanical Theory
Blockage of axoplasmic flow due to compression of axons in posteriorly-bowed lamina cribrosa. Laminar pore size correlates with clinical field defects (Quigley)- superior and inferior pores are more delicate, and hence, deformable
? Lack of neurotrophic factors causes apoptosis of ganglion cells

Intraocular Pressure: balance between production and outflow of aqueous.
Most glaucomas secondary to aqueous outflow obstruction

Outflow Pathways

Primary: Trabecular Meshwork

Secondary: posterior uveoscleral via vortex veins, ? iris vessels

Basic Angle Anatomy

To find scleral spur in sections, follow longitudinal ciliary muscle to its insertion.
Trabecular meshwork and Schlemm's canal are nestled in anterior crotch of scleral spur

Developmental Glaucoma

Primary Congenital Glaucoma

Most cases recessive, bilateral, males, 40% at birth, 86% first year
Rule of 2/3's- 2/3's male, 2/3's affected by age 1 yr., 2/3's autosomal recessive-
mutations in cytochrome P4501B1 gene (CYP1B1) on chromosome 2 (2p22-p21**)**
Theories: Barkan's Membrane, absence of Schlemm's canal,
"Fetal" angle configuration:

Anterior insertion of iris root and ciliary processes
Ciliary muscle fibers continuous with trabecular beams
Mesenchymal tissue in angle

Buphthalmos ("ox eye")

Corneal and anterior segment enlargement, limbal ectasia
Haab's striae (Descemet ruptures) circumferential or horizontal
(oblique in forceps injuries)

Syndromes with Congenital Glaucoma

Axenfeld/Rieger syndrome (50% have glaucoma)
Lowe's syndrome- congenital cataract and glaucoma
Aniridia
Sturge-Weber (if nevus flammeus involves upper lid, mechanisms:
dysembryogenesis, NVI, elevation of episcleral venous pressure
Neurofibromatosis (if plexiform neurofibroma involves upper lid)

Several mechanisms, may have "distinctive gonioscopic findings" due to hamartomatous infiltration of angle

Primary Open Angle Glaucoma (POAG, COAG)

Most common type, angle open gonioscopically, insidious elevation of IOP,
Heredity important, poorly understood, linked to 14 genes, myocillin (MYOC)
Theories:

Deposition of material in juxtacanalicular CT. e.g. Rohen's tendon and tendon sheath material, Mutant GLC1a gene product (myocilin), GAG's
Loss of trabecular endothelial cells leads to fusion of trabecular beams, decreased porosity, obliteration of trabecular cul de sacs abutting juxtacanalicular connective tissue (Alvarado)
Abnormalities of giant vacuoles in Schlemm's canal endothelium
Sclerosis in scleral spur blocking posterior uveoscleral outflow
Decreased CD44H and hyaluronan in JCT

Primary Closed Angle Glaucoma

Anatomic predisposition- small hyperopic eyes with crowded anterior segment
Rare before age 40
Shallow anterior chamber with narrow angle
Acute attacks: injection, pain, steamy cornea, fixed dilated pupil, GI sx, N&V
Most patients have asymptomatic course and do not suffer acute attacks.
Functional pupillary block or plateau iris mechanisms
Diminished loss of iris volume during papillary dilatation; expansion of choroidal volume (Quigley)
Peripheral anterior synechia formation
Papilledema (acute blockage of axoplasmic flow due to laminar distortion)

Clinical stigmata of prior acute attack:
Segmental iris atrophy (focal ischemic iris necrosis)
Dilated, irregular pupil (spincter and dilator necrosis)
Glaukomflecken (focal anterior lens epithelial necrosis)

Secondary Closed Angle Glaucoma

Angle closed by permanent **peripheral anterior synechias**

Causes Of Secondary Angle Closure Glaucoma:

Chronic Primary Angle Closure

Persistent Flat Chamber- wound leak, post-filtering surgery

Inflammation- (posterior synechias, iris bombe´)

Seclusion of pupil- 360^{o} posterior synechias
Occlusion of pupil- pupillary membrane

Other Causes Of Pupillary Block:

Phacomorphic (lens enlargement in elderly)
Absent or nonpatent iridotomy or iridectomy, iridovitreal synechias, Dislocated lens, microspherophakia, anterior displacement of lens-iris diaphragm posterior tumors, exudative RD, post-PRP
Cysts (anterior chamber or iris)

Malignant Glaucoma (ciliolenticular or ciliovitreal block)

Secondary Proliferative Glaucomas

Neovascular Glaucoma (NVI , rubeosis Iridis)

Angiogenic factor produced by ischemic retina, tumors, inflammation,
Abnormal vessels on normally avascular anterior surface of iris lack thick collagen coat of normal iris vessels
Clinically transparent fibrovascular membrane flattens anterior iris surface
Myofibroblasts provide motive force for angle closure, ectropion iridis

Many Causes of NVG:

Anterior Uveitis
Primary And Secondary Closed Angle Glaucoma
Post-Operative Anterior Segment Ischemia Or Necrosis
(after retinal or strabismus surgery)
Associated With Proliferative Retinopathy
Proliferative Diabetic Retinopathy
Ischemic Central Retinal Vein Occlusion- "90 day glaucoma"
Ischemic Oculopathy (Carotid Occlusion, Pulseless Disease)
Chronic Retinal Detachment, i.e., Coats' Disease
Ciliary Artery Occlusion With Retinal Infarct
Intraocular Inflammation
Various Pseudogliomas (Norrie's, ROP, late Coats' Disease)
Sickle Hemoglobinopathy
Post-traumatic Vitreous Hemorrhage
Retinoblastoma (50% Of Cases)

Epithelial Downgrowth

Contact inhibition by healthy endothelium may inhibit epithelium

Iridocorneal Endothelial (ICE) Syndrome (Proliferative Endotheliopathy with Iris Abnormalities)

Unilateral glaucoma in young to middle-aged women; synechias develop in open angle
Endothelial proliferation and secondary iris abnormalities
Cogan-Reese (Iris Nevus) Syndrome

Flattening and effacement of iris stroma, pigmented iris nodules

Chandler's Syndrome

Corneal edema at low IOP

Essential Iris Atrophy

Proliferating endothelium produces synechias in open angle; tractional iris holes, endothelial dystrophy

Fibrous Ingrowth (Stromal Overgrowth)

Secondary Open Angle Glaucoma (angle open gonioscopically)

Cellular proliferation before angle closure

Occlusion of open angle by cells, material or debris

Hyphema (blood, ghost cells, sickle cells)

The **"-lytic" Glaucomas:** classically **caused by macrophages** laden with:

Denatured lens material (phacolytic glaucoma),

Milky anterior chamber, crystals

Free high molecular weight lens protein alone? (Epstein)

Blood break-down products (hemolytic glaucoma)

Classically hemosiderin-laden macrophages, also ghost cells

Melanin from necrotic tumors (melanomalytic glaucoma)

Also caused by necrotic melanocytomas **(melanocytomalytic glaucoma)**

Glaucomatocyclitic Crisis (Posner-Schlossman)

Unilateral, age 20-50, inflammatory signs minimal,

Episodic, associated with POAG, ?trabeculitis

Pigmentary Glaucoma (pigment dispersion syndrome)

Young myopic males, iridodonesis, inverse pupillary block

Krukenburg spindle (melanin phagocytized by endothelium)

Iris transillumination: radial spokes correspond to zonular bundles

Heavy trabecular pigmentation; TM blocked by melanin

Campbell's Theory: zonular abrasion of pigment from posterior iris pigment epithelium; similar mechanism 2^{o} PC IOL'S

Pseudoexfoliation of the Lens Capsule (Exfoliation Syndrome, glaucoma capsulare)

EM evidence for synthesis of PXE within trabecular meshwork

Alpha-Chymotrypsin Induced Ocular Hypertension

Zonular fragments after ICCE with enzymatic zonulysis

Corticosteroid Glaucoma

Schwartz-Matsuo Syndrome

Open angle glaucoma in eye with chronic rhegmatogenous RD

TM blocked by photoreceptor outer segments

Tumor Cells

Anterior tumors: seeding or direct infiltration ("ring" melanomas)

Note: posterior tumors usually produce closed angle glaucoma due to forward displacement of lens-iris diaphragm or iris neovascularization

Damaged Outflow Pathways

Post-Contusion Angle Deformity

Trabecular Scarring in Uveitis, Siderosis

Corneoscleral and Extraocular Disease

Elevated episcleral venous pressure (carotid cavernous fistula, cavernous sinus thrombosis, mediastinal syndromes), pressure on globe (tumors, thyroid, retinal surgery)

Tissue Changes Secondary To Elevated Intraocular Pressure

Retina: Glaucomatous Retinal Atrophy

Atrophy of nerve fiber and ganglion cell layer, gliosis

Inner retinal atrophy secondary to ischemia (e.g., CRAO) also involves inner part of inner nuclear layer, hyalinized appearance

Optic Nerve: Glaucomatous Optic Atrophy

Cupping, posterior bowing of lamina cribrosa, loss of nerve tissue anterior to lamina, widened subarachnoid space, widened pial septa

Sclera: staphylomas (ectasias lined by uveal tissue) staph & uva = grape

Cornea: epithelial edema, bullous keratopathy, band keratopathy, degenerative pannus, secondary ABM changes

Other inflammatory diseases

Necrobiotic xanthogranuloma,
Touton giant cells, necrosis, association with myeloma
Erdheim-Chester disease
Bilateral, bone changes, retroperitoneal fibrosis
Orbital xanthogranuloma with adult onset asthma
Subacute sclerosing panencephalitis (SSPE, Dawson's encephalitis)
Fatal measles (paramyxovirus) slow virus infection of CNS
May present with macular retinitis
Eosinophilic nuclear inclusions in neuronal and glial cells
Behçet's disease
Pathological hallmark is vasculitis
Chronic nongranulomatous uveitis, hypopyon, aphthous ulcers
Perivasculitis and vasculitis leading to hemorrhagic retinal infarction, retinal detachment.
Herpes zoster
Perineuritis and perivasculitis affecting posterior ciliary arteries and nerves
Patchy necrosis and post-necrotic atrophy of anterior segment
Retinal perivasculitis, non-specific choroiditis, scleritis, keratitis

INFLAMMATORY SEQUELAE

Cornea

Scarring
Calcific band keratopathy: basophilic granules in Bowman membrane
Inflammatory pannus- subepithelial fibrovascular and inflammatory ingrowth with **destruction of Bowman membrane** (trachoma)
Degenerative pannus*:* fibrous tissue interposed between base of epithelium and intact Bowman membrane (seen in chronic corneal edema)

Anterior chamber

Organization of hypopyon or proteinaceous exudates
Retrocorneal fibrous membranes
Peripheral anterior synechias (PAS)
Posterior synechias- **seclusio pupillae** (360^{o} posterior synechias)
Occlusio pupillae- pupillary membrane

Iris:

PAS, posterior synechias, pupillary membranes, atrophy, neovascularization,

Lens

Anterior subcapsular cataract
Posterior subcapsular cataract

Ciliary body

Cyclitic membrane-retrolental collagenous membrane extending from ciliary body to ciliary body. Often results from organization and scarring of vitreous. Contraction leads to detachment of pars plana. Ciliary muscle remains adherent to scleral spur attachment. Ciliary body pivots on attachment.

Vitreous

Organization of inflammatory debris may lead to cyclitic membrane, fibrous vitreous bands. Tractional retinal detachment, posterior vitreous detachment.

Retina

Cystoid macular edema (CME)

Retinal vascular leakage vs. Mueller cell edema caused by inflammatory mediators

High incidence in iris-supported IOL's suggests production of prostaglandins, etc. by iris.

Reactive gliosis, may be massive

Intraretinal pigment migration (pseudoRP)

Chorioretinal scarring

Hypertrophy and hyperplasia of RPE

Drusen formation (abnormal basement membrane material)

Papillary proliferation of RPE follows loss of contact inhibition after retinal detachment

Fibrous and Osseous Metaplasia of the RPE

Large quantities of collagen and basement membrane material deposited on surface of Bruch's membrane.

Contains lacunae of RPE cells (pseudoadenomatous proliferation)

Bone results from dystrophic calcification, very common in "end stage" blind painful eyes.

Common sites: peripapillary or at ora **(Ringschwiele)**

Optic nerve

Papillitis

Papilledema

Entire globe

Wound healing

Skin wounds

Migration of epithelium beneath necrotic tissue and blood clot

Fibronectin binds epithelium to underlying dermis

Inflammatory cells and connective tissue proliferation in dermis

Superficial scab lost with maturation of epithelium

Central corneal wounds (full thickness)

Avascular tissue, absence of granulation tissue

Stromal lips swell, wound gapes anteriorly and posteriorly

Descemet membrane retracts and curves inwardly, fibrin plug

Anterior surface re-epithelialized, epithelial plug fills anterior wound gape

Fibroblasts enter, elaborate collagen

Endothelial migration and regeneration of Descemet membrane

Active phase of wound healing: 4-5 weeks, not totally complete at 6 months

Limbal wound (cataract incision)

Involves granulation tissue derived from episclera and conjunctival substantia propria

Superficial part of well-apposed wound sealed by epithelial migration, fibrin clot, and granulation tissue proliferation within superficial substantia propria within 24 hours

Posterior wound gapes, Descemet membrane curves inwardly

Granulation tissue enters external stromal wound at 8-10 days

At 2 weeks granulation tissue extends full length of wound, endothelial migration covers posterior aspect
Collagen production, maturation, reorientation

Iris

No healing of unsutured wounds, iridectomies remain patent unless closed by pigment epithelial migration

Lens

Small rents in capsule may be repaired by fibrous metaplasia of lens epithelium and capsular reformation.
Posterior synechias may close defect
Most lens wounds lead to cataract formation

Sclera

Sclera itself does not participate in healing of defects
Full-thickness wounds healed by ingrowth of granulation tissue from both episclera and superficial choroid

Surgical Complications

General Complications

"Surgical confusion"- misdiagnosis, faulty technique
Cataract surgery
Expulsive hemorrhage
Vitreous loss, vitreous incarceration, vitreous wick
Detachment of Descemet membrane
Endothelial decompensation- aphakic and pseudophakic bullous keratopathy
Flat chamber, wound leak
Choroidal detachment
Iris incarceration
Filtering bleb
Secondary glaucoma
Retained lens material
Capsular opacification
Dislocation of capsular bag (pseudoexfoliation)
Epithelial ingrowth, implantation cysts
Fibrous ingrowth (stroma overgrowth)
"Sputtering hyphema"-vascularization of posterior wound lip
Soemmerring ring cataract
Elschnig pearls, capsular fibrosis (after ECCE)
Cystoid macular edema (CME)
Uveitis
Endophthalmitis
Localized endophthalmitis "in the bag" (P. acnes, C. parapsilosis)
Retinal detachment
State of aphakia predisposes to RD post ICCE
Small horseshoe breaks at posterior vitreous base after ICCE, much lower incidence of RD after ECCE

Nonsurgical trauma

Corneal abrasion

Healing by sliding of wing cells, reconstitution of normal epithelial thickness by basal cell proliferation

Corneal facette – concave defect in Bowman , anterior stroma filled with epithelium

Corneal edema

Breaks in Descemet membrane (e.g. forceps injury)

Lens

Subluxation- partial disruption of zonules, lens remains in posterior chamber, but not in normal position

Dislocation- (luxation)- complete zonular disruption, lens in vitreous or anterior chamber

Vossius ring (imprint of iris pigment epithelium on anterior lens)

Contusion rosette (petalliform cataract, clinical marker for contusion)

Iris

Sphincter tear

Retina

Dialysis: Disinsertion of neurosensory retina from ora serrata due to sudden traction at vitreous base

Retinitis sclopetaria – distant effect of missile

Post-traumatic pigmentary retinopathy (pseudo-RP)

Commotio retinae (Berlin's "edema"- actually reflects photoreceptor damage; may lead to macular cyst or lamellar hole

Hemorrhages

Choroidal rupture

Avulsion of optic nerve

Rupture of the globe

Occurs most commonly at:

Limbus, opposite side

Beneath insertions of recti (sclera thinner)

Equator

Around optic nerve

Organization of blood and inflammatory debris

Cellular proliferation leading to formation of cyclitic membranes, preretinal membranes, retroretinal membranes, transvitreal membranes.

Membranes may form on pre-existing scaffolds (e.g. vitreous to wound)

Contraction of membranes leads to secondary changes:

Contraction of cyclitic membranes: ciliary body detachment and hypotony

Vitreal membranes: tractional retinal detachment

Pre- and retro-retinal membranes- fixed folds,

PVR-contraction of membranes due to myofibroblasts

Radiation

Premalignant Eyelid lesions

***Actinic Keratosis (Premalignant Lesion)**

Bowen's disease

Sharply demarcated red scaly plaques, fair complexion, avg. age 55

Intradermal squamous cell carcinoma with bizarre multinucleated cells (squamous cell carcinoma in situ)

Association with primary internal cancer has been questioned recently. Some cases are caused by arsenic exposure

Radiation dermatosis

Effect depends on total dose. Lid changes include loss of lashes, acute and chronic dermatitis with pigmentary changes, atrophy, telangiectases, involution of meibomian glands, post irradiation tumors

Xeroderma pigmentosa

Autosomal recessive defect in DNA repair (UV light specific endonuclease)
Freckles and scaling in early stage, develop variety of malignant tumors: BCC, SCC, MM, sarcomas-3% incidence of skin malignant melanoma

*

Pseudoepitheliomatous hyperplasia

Tumor-like proliferation of epithelium in response to inflammatory stimulus; acanthosis, inflammatory cells within epithelium

Conjunctiva

Congenital lesions

Cryptophthalmos, epitarsus, congenital ectropion, congenital lymphedema, hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber)

Immunological disorders with conjunctival findings

Ataxia telangiectasia (Louis-Bar)
Hereditary angioneurotic edema (C1 esterase inhibitor deficiency, autosomal dominant)
Toxic epidermal necrosis (Lyell's syndrome)
Wiskott-Aldrich syndrome

Vascular abnormalities

Hyperemia

Primary- Response to inflammation
Secondary- Passive (vascular congestion due to venous obstruction)
e.g.: space occupying orbital lesions, increased viscosity
Active- Increased filling of arterial system, e.g.: arterialization in carotid-cavernous fistula; external carotid
shunting in internal carotid occlusion.
Paroxysmal- associated with simultaneous lacrimation, rhinorrhea
Charlin's syndrome (migranous nasociliary neuritis)
Horton's cephalgia, Sluder's syndrome (neuralgia of the sphenopalatine ganglion)

Vascular sludging

Increased blood viscosity or decreased circulatory velocity

Chemosis

Edema due to increased permeability of conjunctival vessels

Subconjunctival hemorrhage

Differential diagnosis:
Idiopathic (spontaneous without sequelae),inflammation, including febrile illness, SBE, hypertension and arteriosclerosis, trauma, orbital stasis, vitamin C deficiency (scurvy), menstruation, trichinosis, hemorrhagic diathesis
Kaposi's sarcoma (AIDS) can mimic subconjunctival hemorrhage

Telangiectasia

Rendu-Osler-Weber, Louis-Bar, Fabry's disease, Sturge-Weber

Microaneurysms

Diabetes, hypertension, arteriosclerosis, carotid occlusion
Sickle hemoglobinopathy (Paton's sign), in Hb SS disease, comma-shaped

Conjunctival inflammation

Common indications for penetrating keratoplasty (or DSEK)

Endothelial Decompensation (PK or DSEK)

* **Fuchs dystrophy**
Descemet thickened with guttate excrescences

Aphakic bullous keratopathy (ABK)
Descemet membrane thin without guttae, marked endothelial atrophy
Pseudophakic bullous keratopathy (PBK)
Descemet membrane thin without guttae, marked endothelial atrophy
Keratoconus
Old herpetic keratitis
Acute keratitis
Old interstitial keratitis
Corneal dystrophies other than Fuchs -extremely rare!!

Lamellar Corneal Surgery Specimens
DSEK specimens (Descemet stripping endothelial keratectomy)
Embed and section or flat preps- sheets of Descemet membrane
Fuchs- irregular in caliber, guttae, variable endothelial atrophy, pigment in endothelium
PBK- No guttae, more severe endothelial loss
Failed DSEK – thin lamella of posterior stroma, Descemet membrane, endothelial atrophy
PK post DSEK- endothelial graft usually firmly adherent
DALK (Deep anterior lamellar keratopathy)
For keratoconus or anterior pathology
Thick lamella of anterior stroma; posterior stromal tissue; air bubbles in stroma ("pneumatic artifact")
Presence of Descemet membrane on posterior lamella indicates conversion of DALK to PK