CHANGES OF THE RETINA & CHOROID (FUNDUS SPOTS)

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INTRODUCTION

Color, location and appearance can generally distinguish changes of the retina and choroid. The differential diagnosis frequently involves the overall clinical picture, which includes associations, patient's history and health status. However, like optic nerve head abnormalities, proper observation and recognition of anatomical correlation are the first step towards a diagnosis.

PERTINENT STRUCTURAL ANATOMY & PHYSIOLOGY

SENSORY RETINA

The sensory retina is composed of the retinal layers extending from the internal limiting membrane to the photoreceptor cell layer.

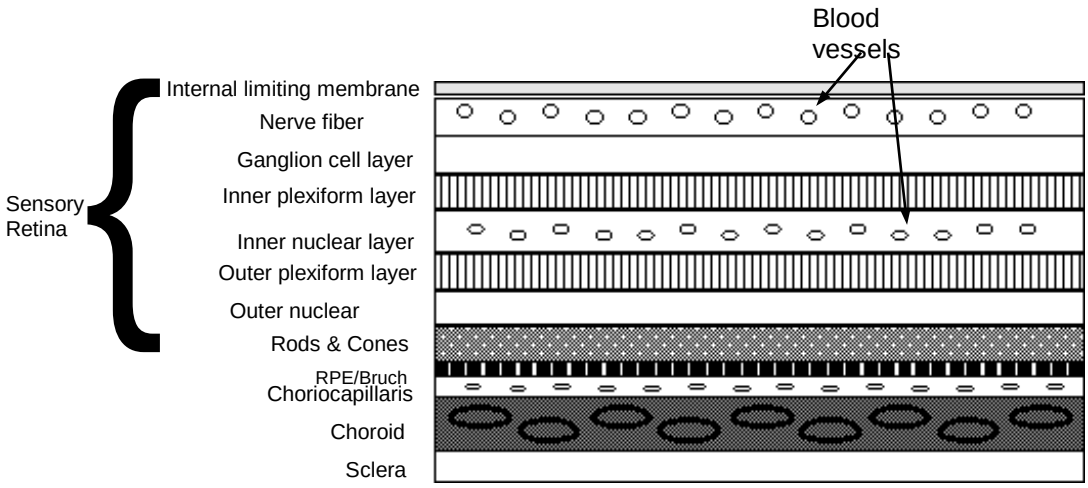

Figure 1: *Retinal layers of the sensory retina*

The foveal region is structurally different. At the center, the 0.35mm foveola contains only cone photoreceptors and is ~ 90µm compared to 350µm at the perifovea. The nerve fibers and ganglion cells are displaced and stacked radially to allow incident light to fall on the cone cells and their cell bodies without interference. The retinal thickness increases therefore as the fovea unfolds up the "clivus" where the "stacked" outer plexiform forms the layer of Henle. These oblique axons with accompanying Muller cell processes form the Henle fiber layer.

RETINAL PIGMENT EPITHELIUM (RPE)

The RPE is a uniform single layer of cells situated between the sensory retina & Bruch's membrane (a specialized matrix for RPE and blood flow from the choriocapillaris). The cells are cuboidal & hexagonal shaped and are **heavily pigmented by melanin granules** in the cytoplasm. The ratio of RPE cell to rod/cone cells is 1:20 in the periphery and 1:1 in the macula.

The sensory retina is **loosely attached** to the RPE with no true bond and is easily detached from it under the proper influence. The RPE however is bound tightly to Bruch's layer (membrane). RPE cells are also bound tightly to one another with *zonula occludens*. Together with Bruch's membrane, these attachments form **the outer blood-retinal barrier** and act to block fluids of the "swamp-like" choroid & choriocapillaris. Only when breaks between them occur is fluid allowed to leak underneath the retina.

The RPE functions to hold structures together. It maintains the health of outer retinal layers, processes and transports metabolites and ion exchanges in the visual cycle, regenerates retinal pigment and discards the photoreceptors' outer segment "garbage" by phagocytosis. The RPE also serves to absorb stray light and neutralize the effects of short wavelength light.

BRUCH'S MEMBRANE

Bruch's Membrane is a 5-layer membrane composed—from in to out—of the basement membrane of the RPE, the inner collagenous zone, the elastic layer, the outer collagenous layer and the basement membrane of the choriocapillaris.

Bruch's membrane functions with the RPE as the outer blood-retinal barrier and supportive system to the retina. Because of the close association to each other, the 2 are often commonly referred to as the **RPE-Bruch Complex.**

The RPE-Bruch complex is crucial to various pathological processes and breaks within it are responsible for a number of pathological processes that affect the retina. **Breaks** allow **leakage of fluids** and the growth of new vessels **(neovascularization)** from the underlying choroid & choriocapillaris under the RPE or loosely bound sensory retina.

CHORIOCAPILLARIS

The choriocapillaris is the **capillary bed** of the choroidal system adjacent to Bruch's membrane. It is vascularized by the short posterior, long posterior & anterior ciliary arteries (does not supply the choroid) and drains into the vortex veins. The vasculature is **highly fenestrated and sponge-like**, allowing blood to freely leak into the choroidal space. To supply for the high-energy demand of macula, it is **most dense beneath the macula.**

CHOROID

The choroid lies between the retina and the sclera and has dense network of choroidal blood vessels. It is composed of larger blood vessels, nerves, melanocytes, immune system cells and support tissue (fibroblasts, collagen). The choroidal vessels are also **highly fenestrated and leaky, allowing blood to circulate freely.** Through diffusion, it supplies nutrition to the **RPE and outer 1/3 of retina.** It also serves to "cool" the retina by dispersing heat created by the light absorption of the RPE and the metabolic activity of the retina.

SCLERA

The sclera is a tough layer of dense connective tissue consisting of collagenous fibers and networks of elastic fibers that serves to maintain the shape and integrity of the intraocular content.

PERTINENT VASCULAR ANATOMY & PHYSIOLOGY

There are two sources of blood supply to the retina: (1) the central retinal artery, which supplies the inner retina and (2) the choroidal blood vessels, which supply the outer retina. The outer 1/3 of the retina is supplied by the choroidal-choriocapillaris system. Branches of the central retinal artery (CRA) and cilioretinal artery supply the inner 2/3 of the retina. The inner arteries lie in the nerve fiber layer (NFL) or ganglion cell layer and have strong adhesions to the internal limiting membrane.

Two capillary networks exist in the retina. A **superficial network** that runs in the superficial NFL and ganglion cell layer and a **deep network** that runs in the inner nuclear layer. The superficial network is **post-arterial** and is most often affected in **arterial-based diseases** (e.g. HTN). The deep network is **pre-venular** and is most often affected in **congestive venous-based diseases** (DM, vein occlusion).

Three areas of the retina are **devoid of capillaries**. The **foveal avascular zone** (FAZ) is a 0.50mm diameter zone centered on the fovea that is free of vessels to minimize interference and allow maximal acuity. The **ora zone** is a ~1DD area near and around the ora where the retinal vessels don't reach. Finally, the **perivascular zone** is a small area around the vessels themselves, particularly the large arteries, where capillaries do not exist.

This **inner blood-retina barrier** is formed by the normal retinal vessels that are strong barriers to perfusion of blood components and do not leak readily.

RED SPOTS IN THE FUNDUS

HAEMORRHAGES

Hemorrhages are ocular manifestations of underlying vascular or blood disease. The type of haemorrhage (a.k.a. hemes) may indicate the different disease processes involved. Recognizing these with ophthalmoscopy is the first step towards correlating them with possible aetiologies.

Sub-RPE

Sub-RPE hemes, as the name suggests, occur under the RPE. Usually large and round, they appear dark (gray-greenish in color) because of the filtering quality of the overlying RPE and because of their size and density. Sub-RPE haemorrhages occur mostly secondary to subretinal or choroidal neovascularization.

Subretinal haemorrhages

Subretinal hemes occur between the RPE & sensory retina. Similar to sub-RPE hemes, they usually occur as a result of subretinal or choroidal neovascularization. They are differentiated from sub-RPE by their deep red color since they are above the RPE.

"Dot & Blot" haemorrhages (a.k.a. deep retinal hemes)

Dot & blot hemes are small and round hemes that derive from the deep pre-venular capillary bed. They take on the small round shape because they occur in the inner nuclear and outer plexiform layers and are therefore restricted by the surrounding structural elements. They are seen most often in the posterior pole. **Diabetes mellitus** (DM) is the most common aetiology.

Superficial retinal haemorrhages (a.k.a. flame-shaped hemes)

Superficial retinal hemes usually involve the NFL, especially near the optic disc. Because they occur within the striated nerve fiber layer, they assume a typical flame shape. Derived from the post-arterial capillary bed, they are most often caused by arterial-based diseases.

Pre-retinal haemorrhages (a.k.a. Sub-hyaloid or retrogel hemes)

Pre-retinal hemes occur between the ILM and superficial NFL. They are typically large and red, being very superficial, and assume a flat-topped sideways "D" appearance due to gravity and the ILM restriction. They may be caused by a number of aetiologies such as trauma, hypertension, DM, acute posterior vitreous detachment, etc.

Intravitreal haemorrhages (a.k.a. intragel hemes)

Intravitreal hemes are usually large, red clumps of blood that float within the vitreous and often move with eye movements. Trauma & diabetes are the 2 most common causes.

Full thickness haemorrhages

Full thickness hemes involve all layers of the retina and appear as dark brown patches of blood. Full thickness hemes are usually a feature of severe retinopathy (e.g. vein occlusions, diabetes).

VESSEL ANOMALIES

Microaneurysm

Microaneurysms are sac-like dilations of a blood vessel that appear like a lump or saccule on the wall of vessels. They are 50-100 microns in size and are very hard (almost impossible) to see with ophthalmoscopy. They are best seen with fluorescein angiography, appearing like Christmas lights throughout the affected area.

Microaneurysms occur in the **deep capillary bed** usually in relation to conditions creating venous stasis. They occur in areas of **hypoxia** and represent a vascular response to the weakening of capillary wall. They are permeable and allow serous fluid to leak into the retina. Diabetes is the most frequent cause of microaneurysms.

Macroaneurysm

Macroaneurysms are an isolated dilated area of a **major retinal arterial branch** (usually within 3 bifurcations) that results from focal damage to a vessel wall. Their occurrence is associated with vascular diseases such as hypertension, arteriosclerosis, retinal emboli and cardiovascular disease. Macroaneurysms leak and can cause oedema, exudation and haemorrhages.

Collateral vessels

Collateral vessels represent the development of new blood vessels within the framework of an existing vessel network. Collateralization is an attempt by the vascular system to create a detour to move blood around an area with closed or reduced blood perfusion. Naturally, they develop near zones of ischemia which are often indicated by the presence of cotton wool spots (CWS). They occur in diseases that obstruct blood flow such as vaso-occlusive conditions, compressive diseases, end-stage glaucoma, etc.

Collateral vessels may be single or multiple and occur at the retinal or ON level. They are initially **capillary-capillary** connections but may evolve into **vein-vein** connections after venous occlusions, into **artery-artery** after artery occlusions, or even into **artery-vein** connections after capillary bed shutdown. Collaterals typically **do not leak.** They are **beneficial** in that they drain or bring blood to compromised areas.

Note that artery-vein connections that occur without capillary bed occlusion may be congenital or acquired and are referred to as **optociliary shunt vessel.**

Intra-Retinal Microvascular Abnormalities (IRMA)

IRMA are shunt vessels, a variation of collaterals that occur in **diabetes**. IRMA represent an attempt at redirecting blood in areas of non-perfusion. They are a cross between dilated capillaries and early new vessels and actually look like intraretinal neovascularization. IRMA indicate hypoxia and are considered to be the germination bed for neovascularization. They are one of the defining features of the severe non-proliferative diabetic retinopathy.

Neovascularization (NV)

NV is a complex reaction to hypoxia, which results in the growth of new vessels in an attempt to provide oxygenated blood to ischemic areas. NV may develop from viable retinal vascular beds on the retinal surface, on the ONH, on the iris and in the AC angle.

New vessels represent a direct threat to vision because they are **abnormal**, **fragile and leaky**. They can lead to retinal oedema, bleeding, fibrosis and retinal detachment.

YELLOW / WHITE SPOTS IN THE FUNDUS

HARD EXUDATES

Hard exudates result from the breakdown of retinal vessels and are comprised of **blood fluids, lipids & small molecules (blood soup!).** Exudates are shiny white to yellow deposits with generally sharp borders. Usually found in the posterior pole, they may appear as isolated spots, confluent patches or rings. Since they indicate “leakage”, they may be associated to clinically noticeable retinal thickening. They usually affect the **pre-venular deep capillary bed** in association to impeded venous drainage. They are usually deposited in the **outer plexiform layer** but may extend from the NFL to the outer nuclear layer.

Hard exudates represent a distinctive sign of retinal vascular compromise that is characteristic of venous-based congestive disease. They are, however common in diabetes and hypertension.

COTTON WOOL SPOTS (CWS)

CWS are edematous nerve fibers that result from capillary non-perfusion (infarct) within the NFL. NF ischemia causes interruption of axoplasmic flow resulting in the build-up of material within axons, which in turn results in **NF swelling.** CWS formation is mostly related to **arterial-based** diseases that affect the superficial capillary bed. CWS are sometimes called “soft exudates”, but the term is inaccurate, may lead to confusion and is being dropped.

CWS are whitish feathery “spots” with indistinct borders. Because the NF layer is superficial, underlying vessels and details may be obscured by dense CWS. CWS are usually located within 3DD of disc where the NFL is the thickest. They **do not occur within the foveal avascular zone (FAZ)** given that the FAZ is perfused by the choriocapillaris. CWS are generally transient and resolve in 5-7 weeks.

DRUSEN

Drusen are a **product of RPE metabolism.** Seen as fine yellow dots in the retina, they represent lipofuscin granule "residual bodies" that are composed of mucopolysaccarides and lipids from denatured mitochondria, cytoplasmic debris, pigment granules and photoreceptor remnants. In other words, they are retinal **"garbage"!**

Drusen may represent an altered state of retinal metabolism and may be associated to conditions of "sick" RPE. They are encountered in **RPE-Bruch complex diseases** (e.g. dystrophy, degeneration), in conditions of **vascular compromise** that cause alterations in the RPE metabolism (e.g. vasculopathies or retinopathies) and in conditions that cause **zone hypoxia by obstruction** (e.g. space occupying lesions).

Drusen are extruded between the RPE and Bruch's membrane. When large and fluffy, drusen may progress to affect the health and architectural integrity of the overlying retina. They may **focally reduce the adhesion of the RPE to Bruch's membrane** or they may cause **breaks** in Bruch's membrane allowing seepage and/or infiltration under the RPE and sensory retina.

Bilaterality and symmetry is the rule with drusen with respect to size, location, number and density. Several types of drusen can be identified. The **hard drusen** are small, well-defined deep yellow deposits that represent hyaline deposits between the inner and outer collagenous layers of Bruch's. The hard drusen are not likely to cause breaks in Bruch's and have little clinical significance. The **soft drusen** are large and fluffy with blurry edges that represent deposits between the basement membrane of the RPE and the inner collagenous layer of Bruch's. The soft drusen are noticeable in older individuals and are clinically more apt to produce complication. The **basilar laminar drusen** are multiple fine yellow spots usually observed in young patients that represent hyaline thickening of the basement membrane of the RPE. When thick, they may exacerbate obstruction of nutrient exchange. The **calcific drusen** are a glistening fine discreet yellow dot that results from long-standing drusen that have aged and calcified. Finally the **mixed variety drusen** represent a combination of the above types.

RPE WINDOW DEFECT

An RPE window defect is a well-defined focal white-yellow area in the fundus where **the melanin of RPE cells is absent.** The **RPE cells are present** but they are white. As a result, underlying choroid details are not visible and overlying retinal details (e.g. vessels) are highly contrasted against the defect.

VASCULAR SHEATHING

Vascular sheathing is perceived in the fundus as a whitened thickened vessel wall. Sheathing may be a congenital thickening of vascular walls which is usually found within 2DD of the optic nerve and is continuous with the ON vessels. Alternatively, it can be acquired as a result of vasculopathies and inflammatory conditions that affect both arteries (e.g. in arteriosclerosis) or veins (e.g. long-standing venous obstructive diseases).

RETINAL EMBOLI

A retinal emboli is a white-yellow "plug" that is observed in retinal vessels usually at the level of bifurcations. It can derive from many sources but arises most frequently from eroding carotid sinus lesions, eroding cardiac vegetation or from self-injected matters. Retinal emboli have a strong association with significant cardiovascular disease and may precipitate vaso-occlusive retinal disease.

Retinal emboli may be of several types with different ophthalmoscopic appearances:

The **cholesterol type** is shiny yellow-orange, originates from vascular plaques and is often noted at bifurcations. The **calcium type** is gray-white, originates from cardiac plaques and artificial heart walls and lodges itself in unbranched arterioles. The **platelet type** is a long, dull white arteriolar plug that originates from carotid plaques and from blood diseases. The **fibrin type** is not easily seen since it often lodges at the lamina cribrosa causing central artery occlusions. It represents a thrombus that originates after acute mitral insufficiency. Finally the **talc or cornstarch type** are fine shiny yellow-white dots that occur in the posterior pole capillaries from self-injected products in drug users.

DARK SPOTS IN THE FUNDUS

CONGENITAL HYPERTROPHY OF THE RPE (CHRPE)

CHRPE are brown to black flat lesions that are 1 to several DD in size, usually round and most often found in the peripheral retina. They have well defined margins sometimes with a distinctive depigmented halo that is **pathognomonic** of the lesion. Chorioretinal atrophy, in the form of punched-out holes through which the choroid is visible, frequently develops in the lesion producing **lacunae** and giving the area a **"Swiss cheese"** appearance.

CHRPE is the result of a congenital **increase in size** of the RPE cells. Because the larger cells contain more melanin granules, the involved area is darker. The halo is produced by adjacent pigment epithelial cells that are almost devoid of melanin granules. These lesions are benign and stable, except for slight enlargement over time and the development of lacunae.

Grouped pigmentation such as **"Bear Tracks"** is a variation of CHRPE which presents like a series of animal footprints on the retina. The "footprints" are grouped in clusters and usually extend in a **wedge shape** from the posterior pole into the periphery.

RPE HYPERPLASIA

RPE hyperplasia represents an "invasion" of the retina by **replicating** RPE cells. RPE cells replicate in response to any form of insult to the retina and/or its supportive components (e.g. inflammation, laser treatment, neovascularization, retinal breaks or holes, trauma, vitreo-retinal traction). RPE hyperplasia is often called **reactive hyperplasia** because it indicates an attempt by the retina to repair damages. The pigment formation indicates that offensive process has been ongoing for ~ 90 days.

Unlike RPE hypertrophy, RPE hyperplasia is dark black in color, has numerous irregular patchy areas and keeps company to an ocular condition or previous history.

BENIGN CHOROIDAL MELANOMA (A.K.A. CHOROIDAL NEVUS)

A choroidal nevus is a melanotic gray-green to brown choroidal mass that results from the accumulation of melanocytes within the choroid. Characteristically flat or slightly raised (< 2mm) with a gradual elevation from the choroid, it is usually 0,5-2DD in size (95%) with well-defined small areas of overlying orange pigment, drusen and RPE alterations. Occasionally a very shallow overlying sensory retinal detachment may be seen due to the underlying altered RPE-Bruch complex. The choroidal nevus is a benign lesion that shows no growth but it may convert to a malignant choroidal melanoma, which is characteristically bigger, more elevated, "uglier and meaner".

CHOROIDAL NEOVASCULARIZATION (A.K.A. SUBRETINAL NEOVASCULARIZATION)

Choroidal neovascularization (CNV) represents growth and proliferation of new vessels under the retina usually **between the RPE and Bruch's membrane** but also **under the sensory retina**. The area of new vessel growth, termed **NV net,** appears gray-green because of its usual sub-RPE location. The new vessels are abnormal and leaky and the NV net is often accompanied by turbid fluid. CNV is serious in that it may progress to RPE and sensory retinal detachment, fibrosis and severe vision loss.

CNV is a severe complication that arises from any condition where there is a **break in Bruch's membrane and a hypoxic status.** The break allows entry into the underlying sub-RPE space; the hypoxic status provides the stimulus to new vessel proliferation.