COLOR CHANGES OF THE FUNDUS, A LITERATURE REVIEW

by

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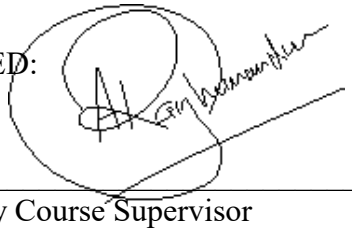

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COLOR CHANGES OF THE FUNDUS, A LITERATURE REVIEW

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ABSTRACT

The purpose of this literature review is to develop an analytical model of the pathological presentations of the fundus using published information. In order to create a comprehensible organization of retinal lesions, articles and books concerning histology of the retina were evaluated, and reports were used to form a logical model. The review is to serve as a guide for those learning the diseases of the fundus, as a methodical approach to understanding diverse color appearances indicative of possible retinal pathology. Various fundus diseases were assessed by their color presentations throughout the retinal layers, and arranged into five categories including the following: (1) white, (2) gray, (3) yellow, (4) black, and (5) red. The gathered published information was developed into a comprehensive color-based classification of commonly seen retinal pathology.

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CHAPTER 1

INTRODUCTION

Retinal pathology may present as five main colors in the fundus: (1) white, (2) gray, (3) yellow, (4) black, and (5) red. Categorizing various color appearances may assist the examiner in identifying the etiology of the presentation. In some instances, the presentation of a lesion may not always be the true color of the source, but appear differently due to its location. This holds true when evaluating a hemorrhage in the retina. A subretinal hemorrhage may be viewed as gray-green secondary to the overlying pigment epithelium, whereas a hemorrhage that is more anterior will be viewed as bright red. Several other color changes of the fundus can be evaluated and better understood based on their content, location, and physiological presentation.

CHAPTER 2

DISCUSSION

The collagen content of fibrous connective tissue creates a white appearance of the retina. As an example, the sclera may become visible upon fundus examination in the case of pathologic myopia. The ocular expansion resulting in thinning and weakening of the sclera appears as an abnormal out pouching known as a posterior staphyloma.[1] Breaks in Bruch's membrane frequently seen in pathologic myopia are referred to as lacquer cracks, and present as a white crisscrossing network of thin lines within the retina. These lines in the retina serve as a significant risk factor for the development of a choroidal neovascular membrane.[1] A benign and more common example of collagen accounting for a white appearance in the fundus is a scleral crescent, in which the retinal and choroidal tissue fails to follow the course of the sclera at the optic nerve.

When the neurosensory retina is damaged, tissue repair is accomplished by gliosis, a process by which glial cells migrate and proliferate over a break on the inner retinal surface. This is most often recognized as an epiretinal membrane after the development of a posterior vitreous detachment.[1] The innate contractile properties of these glial cells cause wrinkling of the internal limiting membrane, and extensive membrane formation and contraction can result in an opaque white macular pucker.

Nonglaucomatous optic neuropathies may lead to a white appearance of the optic disc. Optic disc pallor, indicating optic atrophy, may be caused by compression of the optic nerve by a mass lesion. In the case of chronic papilledema or arteritic anterior ischemic optic neuropathy, the entire extent of the disc may appear pale due to loss of vascular supply to the optic nerve. Conversely, toxic optic neuropathy resulting from

alcoholism or substance use presents as whitening of only the temporal aspect of the disc.

Inflammatory diseases such as sarcoidosis contribute to white appearances in the fundus due to glial proliferation and the accumulation of lymphocytes.[1] Intermediate uveitis involves inflammation occurring at the pars plana and the peripheral retina, in which snowball opacities appear in the vitreous. This "snowbanking" of vitreous collagen and lymphocytic infiltrates may be associated with sheathing around retinal vessels, known as "candle-wax drippings" also seen in sarcoidosis. The affected vessels become cuffed with perivascular inflammatory infiltrate, and the retinal vasculitis can be confirmed with leakage on fundus fluorescein angiography.[2]

Focal infarcts of the retina cause whitened areas of ischemia in several disease presentations including hypertensive retinopathy, diabetic retinopathy, and central and branch retinal vein occlusions. Infarcts may follow the course of the nerve fiber layer and appear as fluffy patches, which are referred to as cotton-wool spots. These lesions represent axoplasmic debris resulting from the interruption of axoplasmic transport due to vascular or mechanical abnormalities.[3]

Central nervous system myelin is a white finding in the retina that is produced by oligodendrocytes for rapid axonal propogation. Myelinated retinal nerve fiber layers obscure underlying vessels, and appear sharply demarcated with feathered borders. Typically, normal myelination progresses from the optic chiasm to the optic nerve and halts at the lamina cribrosa.[4] If the myelination continues forward beyond the extent of the disc, most often congenitally, the white nerve fibers will be visible upon funduscopic examination.

Finally, when calcium develops in the fundus, it presents as a white finding,

unless it presents deeper within the retinal tissues. For example, optic nerve head drusen may be difficult to identify by the color presentation since the concretions of calcium are buried within the nerve head. Rather, the drusen can be recognized by the distorted appearance of the optic disc margins. In contrast, calcified drusen at the level of Bruch's membrane appear ophthalmoscopically as white due to the attenuation of the overlying retinal pigment epithelium (RPE).[5]

Calcium soaps may manifest as small whitish-yellow refractile granules suspended throughout the vitreous humor. This common degenerative condition is known as asteroid hyalosis, and has been associated with systemic diseases such as systemic hypertension, diabetes, and atherosclerotic vascular disease.[6,7] Although this fundus finding may impair the quality of ophthalmoscopy, the fatty calcium globules are benign and rarely cause visual disturbances.[6]

Choroidal nevi may present as gray lesions in the retina secondary to accumulation of melanocytes in the choroid. The nevus is the most common primary intraocular tumor, however most nevi are not detectable until after childhood due to the lack of pigmentation at an early age.[1] These choroidal nevi present with slightly indistinct borders and occasionally appear to have a halo surrounding the slate-gray central zone. Although rare, a choroidal nevus may evolve into a malignant melanoma and should be monitored for possible transformation indicated by several risk factors including orange pigment (lipofuscin) within the lesion.

Edema within the retina presents as a gray-white opacification. A common source for an edematous retina is attributed to the leading cause of blindness in American adults—diabetic retinopathy. The weakening of blood vessel pericytes secondary to

uncontrolled diabetes results in leaky retinal vessels that exude extracellular fluid and swell the macula. Diabetic macular edema is the most common etiology for loss of vision in people with diabetic retinopathy. In the case of blunt trauma to the eye, the retina may also develop swelling due to disruption of the photoreceptors.[5] This gray-white opacification is known as commotio retinae and more specifically Berlin's edema when it occurs in the macula. Early retinal necrosis caused by a central retinal artery occlusion is also seen clinically as a gray-white finding in the fundus. The acute ischemia of the retina causes a metabolic disturbance within the inner retinal tissue, resulting in intracellular edema and whitening secondary to the lack of vascular supply.[5]

Finally, breaks in Bruch's membrane can result in the development of subretinal neovascular membranes, further leading to a choroidal hemorrhage with a gray-green appearance.[8] The hemorrhages appear to be gray-green rather than red due to the overlying pigment of the RPE. Several ocular conditions including choroidal rupture, presumed ocular histoplasmosis, angioid streaks, pathologic myopia, and age-related macular degeneration are associated with the development of these subretinal hemorrhages.[8]

Yellow changes in the fundus are usually attributable to lipid accumulation within the outer plexiform layer.[5] Depending upon the amount of lipid content present, exudates appear as yellow or yellow-white. Exudation in the retina results from chronic vascular leakage secondary to damaged blood vessel walls. The buildup of high molecular weight proteins and lipoproteins can be visualized in Coats' disease, a condition characterized by retinal telangiectasias and aneurysms.[8] A star-shaped macular exudate presents in the case of neuroretinitis as well as advanced hypertensive retinopathy. These exudates that

accumulate in the macula have a star configuration due to the obliquely oriented outer plexiform layer at this location.[5] Thus, the exudates appear to radiate away from the fovea like spokes of a wheel.

Cholesterol may appear in the fundus in the form of a hollenhorst plaque within a retinal artery. Cholesterol emboli can be identified as refractile yellow plaques often localized to the bifurcation of an artery due to a narrowed lumen.[9] Upon ophthalmoscopy, the plaque may appear to be larger than the width of the blood vessel, giving the appearance that it is wrapped outside of the vessel. This is due to the fact that the column of blood appears to be narrower than the blood vessel itself. The dislodged cholesterol embolus originates from aorto-carotid atheromatous plaques and typically results in a branch retinal artery occlusion.[9] On occasion, the hollenhorst plaque may be small and seen intravascularly without blockage of blood flow to the adjacent retina.[1]

The bilateral abnormal accumulation of lipofuscin in the macula is the classic clinical presentation of Best's disease (Vitelliform macular dystrophy). These round solitary yellow lesions of the RPE are recognized as having an "egg-yolk" appearance. When the vitelliform cyst liquefies and becomes absorbed, it is referred to as a pseudohypopyon due to its layered appearance.[10] A "scrambled egg" appearing lesion may develop in the later stage of the disease if the macular cyst ruptures.[8]

Ophthalmoscopic presentation of Stargardt's disease and Fundus Flavimaculatus reveals subretinal yellow flecks scattered throughout the posterior pole. Unlike the typical round appearance of drusen near the macula, these lesions are more linear or pisciform in shape, and follow the distribution of the vessels. The presentation of the bilateral yellow flecks results from the accumulation of a lipofuscin-like byproduct at the level of the RPE

with subsequent photoreceptor dysfunction.[1]

The retinal pigment epithelium usually accounts for black color changes of the fundus. The pigmented tissue may present as physiologic hypertrophy present at birth, known as congenital hypertrophy of the RPE (CHRPE). These jet-black lesions may present as unilateral or bilateral round areas of pigmentation with well-defined edges. The margins of the CHRPE frequently appear as "a narrow zone of granular gray pigmentation or depigmentation".[1] With age, partial depigmentation of the lesion may occur, resulting in discrete atrophic foci (lacunae) that can expand and coalesce over time.[1] Relative to a choroidal nevus, a CHRPE can be viewed ophthalmoscopically as a darker lesion with more distinct edges due to its superficial location in the retina. In some presentations, unilateral, multifocal clustered lesions can be identified as bear tracks of the fundus. This is characterized by several, flat, gray to black lesions that are grouped together in one area.[1] Less commonly, bilateral, multifocal pigment epithelial lesions may manifest as irregularly shaped and widely separated throughout the fundus.[1] These concerning CHRPE lesions are associated with familial adenomatous polyposis (FAP) of the colon.

Unlike the congenital presentations of pigment epithelium hypertrophy previously cited, the RPE is capable of responding to mechanical trauma or inflammation by hyperplasia.[8] As an example, while fresh laser burns appear white or gray, older photocoagulation scars appear pigmented as a response to injury.[8] Hyperplasia of the RPE adjacent to the treatment zone occurs secondary to the heat generated from the laser. When injury presents in the form of a retinal break, the RPE may become hyperplastic in reaction to the damage. The pigment epithelium can invade the retinal tissue surrounding

the break, forming tight adhesions between the attached and detached retina. This demarcation line indicates a long-standing condition (typically about 3 months), and serves as a seal preventing liquefied vitreous from entering beneath the retina and causing further detachment. Similarly, lattice degeneration may also stimulate RPE hyperplasia. Lattice is a linear band of peripheral retinal thinning located near the ora serrata. As the layers of the retina atrophy, RPE hyperplasia occurs surrounding the lesion.

In the case of ocular toxoplasmosis, the condition presents as a focal necrotizing retinochoroiditis with disruption of the retinal pigment epithelium. The large majority of toxoplasmosis cases are congenital, accounting for approximately 80% of presentations.[1] Active lesions present as focal, white, inflammatory infiltrates that can spill over into the vitreous and cause a "headlights in the fog" appearance resulting from severe vitritis. The inflammation can extend beyond the neurosensory retina, RPE, and choroid, and permit a direct view of underlying sclera. Once the inflammation resolves, retinochoroidal scars are left behind with black RPE clumps surrounding the primary infection.[1] Later reactivations of the lesions can manifest adjacent to old inactive scars.

Black pigment clumping can present in the peripheral retina in more than one retinal condition. In the case of retinitis pigmentosa (RP), the most common hereditary retinal dystrophy, ophthalmoscopy reveals deposition of retinal pigment with the appearance of "bone spicules". This pigmentation results from RPE cells budding off and settling within the neurosensory retina. Reticular degeneration is another example in which aggregation of pigment can be seen within the retinal periphery. This condition "is characterized by a reticular pigmentation that forms a polygonal, netlike arrangement of hyperpigmented lines forming geometric patterns in the peripheral fundus."[11] In studies

of reticular degeneration, all of the pigment deposits have been confined to the peripheral retina, whereas the dispersion may progress toward the posterior pole in the case of retinitis pigmentosa.

Red presentations in the fundus typically result from blood in an atypical location. The blood may present outside of the retinal vasculature as in the case of a preretinal or vitreous hemorrhage. It may also manifest intravascularly in the form of neovascularization. Aside from the abnormal presentation of blood, retinal holes may also account for a red finding in the fundus.

Endothelial vascular damage can result from any atherosclerotic, hypertensive, inflammatory, or thrombophilic conditions.[9] Along with the abnormalities of the blood vessel walls, venous compression by the arteries results in turbulent blood flow, and ultimately intravascular thrombus formation.[9] When a blood clot develops, it may lead to occlusion of the veins and subsequent hemorrhages within the retina due to the backup of blood. This presentation is referred to as a branch retinal vein occlusion (BRVO) when hemorrhages occur in one quadrant or a central retinal vein occlusion (CRVO) when they involve all four quadrants.

Vein occlusions encompass one of several retinal vascular disorders that can result in neovascularization. Other conditions that may present with this complication include diabetic retinopathy, retinopathy of prematurity (ROP), ocular ischemic syndrome, and sickle cell retinopathy. In all of these disorders, formation of new abnormal blood vessels is up regulated by vascular endothelial growth factor (VEGF) in the incidence of retinal ischemia. VEGF released into the circulation stimulates the growth of new vessels that lack endothelial tight junctions. Due to the weakness and

preretinal location of these neovascular vessels, vitreous traction may cause shearing of the vessels and result in formation of intraocular hemorrhages.

The appearance of a hemorrhage depends on its location in the fundus. A preretinal hemorrhage is confined between the internal limiting membrane and the posterior hyaloid face. It appears as very red and usually takes on a boat shape. Although the vitreous is normally an avascular structure, a vitreous hemorrhage may result secondary to ruptured neovascular vessels that have grown through the hyaloid face. It presents very differently from a hemorrhage involving the retina in that the vitreous itself appears to be red and cloudy. If the hemorrhage is severe, it will completely obscure the view of the fundus.

We have previously cited the gray-green appearance of a subretinal hemorrhage secondary to the overlying pigment epithelium, further reiterating that location of a hemorrhage affects its ophthalmoscopic appearance. In contrast, an intraretinal hemorrhage manifests as a bright red color that takes on the shape of the cells found throughout the particular retinal layers. A more superficial retinal hemorrhage within the nerve fiber layer of the posterior pole will present as flame-shaped due to the orientation of the nerve fibers.[5] In the case of deeper retinal hemorrhages, they may appear as dots or blots attributing to the perpendicular orientation of the retinal cells within this layer.[5]

Aside from blood presenting in the fundus, retinal holes can also account for red color changes. An atrophic retinal hole manifests in areas of sensory retinal degeneration secondary to vascular insufficiency.[7] The red appearance of the round lesion is due to the increased view of the underlying choriocapillaris. On occasion, a white cuff of subretinal fluid or black pigment will surround the atrophic hole.[7]

CHAPTER 3

CONCLUSION

The 5 color changes found in the fundus include white, gray, yellow, black, and red. Each of these variations in retinal presentation represents several different etiologies. White color changes can be attributed to numerous causes including gliosis of the damaged neurosensory retina, the collagen content of the normal sclera, and inflammatory diseases involving the accumulation of lymphocytes. However, in the case of black retinal presentations, the only attributable source is the disruption and migration of the RPE, most notably in response to injury or inflammation of the fundus. It is crucial to understand the various etiologies for color changes in the fundus in order to appropriately identify retinal pathology upon ophthalmoscopic evaluation.

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