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Imaging maculopathy in post-mortem human eyes

Christine A. Curcio *

Department of Ophthalmology, University of Alabama School of Medicine, Birmingham, AL, USA

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Abstract

Age-related maculopathy (ARM) remains a poorly understood degeneration. To discover new pathways using contemporary genomics, proteomics, and immunohistochemistry, validate emerging animal models, and validate new imaging modalities, human tissues obtained from donor eyes will be essential to ARM research for the foreseeable future. Because fundus appearance is the clinical diagnostic *lingua franca*, laboratory investigators adapted these standards to the distinctive appearance of post-mortem tissues in order to identify and stage ARM in donor eyes. Post-mortem tissues offer unique advantages and limitations relative to pre-mortem tissues for imaging studies. One fellow eye can be used for imaging and the other for correlative laboratory studies, if some degree of disease stage asymmetry between eyes is acceptable. Histological verification is a necessary, albeit challenging, step in validating a grading system.

Keywords: Ageing; Degeneration; Drusen; Electron microscopy; Fundoscopy; Histochemistry; Maculopathy

1. Background

Age-related maculopathy (ARM), the major cause of vision loss in the elderly, is a poorly understood degeneration. Animal models, genetically and surgically induced, abound for choroidal neovascularization, the principal sight-threatening complication (Ambati, Ambati, Yoo, Ianchulev, & Adamis, 2003), but models replicating the early stages of the disease remain an elusive goal, in part because biochemical models of drusen biogenesis are poorly developed. To discover new biochemical pathways using contemporary genomics, proteomics, and immunohistochemistry, validate emerging animal models, and validate new imaging modalities, human tissues obtained from donor eyes will be essential to ARM research for the foreseeable future. It is instructive to note the experience of research in other age-related diseases. Forty years after the characterization of cholesterol-enriched lesions in coronary artery disease, 20 years after the isolation of tau-protein from Alzheimer brain, and the current widespread availability of animal models and in vitro systems for both diseases, high-impact studies using human tissues are still being published in atherosclerosis and Alzheimer research. Because imaging plays a key role in identifying and staging eyes for subsequent analysis, this topic is appropriate for a neuro-imaging conference. This article will briefly address how maculopathy can be visualized in post-mortem eyes and summarize results pertaining to lesion formation obtained through such studies in my laboratory. It is predicated on the concept that even as retinal imaging approaches previously unimagined levels of technical refinement, histopathology remains an important adjunct approach. Intended for the basic or clinical investigator with access to human eye tissue, this article will not comprehensively review ARM histopathology, nor will it provide detailed clinical information on selected ARM cases.

* Tel.: +1 205 325 8632; fax: +1 205 325 8634.
E-mail address: curcio@uab.edu.

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2. Definitions

The human macula, defined epidemiologically (Klein et al., 1991) and anatomically (Polyak, 1941), is ~6 mm in diameter, centered on the fovea, and contained within the vascular arcades. It subserves the central 21° of visual angle. The retinal layers most directly involved in early and late ARM are the retinal pigment epithelium (RPE), Bruch's membrane (BrM), choriocapillaris (ChC), and secondarily impacting on the photoreceptors (Ph). The latter cells, in turn, are segregated within the image plane of the macula into a small cone-dominated fovea surrounded by a large rod-dominated parafovea. BrM, the inner wall of the choroid, a vascular bed with the body's highest blood flow, is a 5-layer connective tissue consisting of the basal laminas of the RPE and ChC on the outside, an elastin layer in the middle, and two collagenous layers between (Marshall, Hussain, Starita, Moore, & Patmore, 1998). Early ARM is typified by the presence of soft drusen (focal extracellular deposits with sloping sides) and an abundance of basal deposits. The latter are diffuse lesions located either between the RPE and its basal lamina (basal laminar deposit, consisting of basement membrane-like material) or, like drusen, between the RPE basal lamina and the inner collagenous layer of the BrM (basal linear deposit, consisting of membranous debris). Choroidal neovascularization in ARM patients consists primarily of in-growth of ChC vessels into a natural cleavage plane external to the RPE (Grossniklaus & Green, 2004). Extensive and sharply defined atrophy of RPE (geographic atrophy) can occur as an end-stage of a non-exudative degeneration or concomitantly with neovascularization.

3. Clinical grading systems

To achieve twin goals of objectivity and reproducibility for ARM diagnosis and staging, clinical researchers now rely on standard fundus photographs rather than clinical examination. Features common to clinical ARM grading systems were derived from those developed for diabetic retinopathy (DRSRG, 1981; ETDRS, 1991). These include the use of standard lighting conditions that emphasize drusen or subtle alterations in RPE pigmentation, a fovea-centered grid which defines standard subfields for assignment of lesion location, standard circles (based on choroidal vessel diameter) which can be used to measure diameter and area, and on-going reliability assessment by cross-checking individual graders and by periodic re-grading of a standard test photograph set. Although reliable, these grading systems still await histological validation, a challenging goal, because few ARM eyes come to histopathology. To date only two studies have illustrated micrographs of lesions previously graded using accepted clinical standards (Curcio, Medeiros, & Millican, 1998; Sarks, Arnold, Killingsworth, & Sarks, 1999).

Population-based epidemiologic studies e.g., (Klein, Klein, & Linton, 1992; Mitchell, Smith, Attebo, & Wang, 1995; Vingerling et al., 1995) rely on the Wisconsin ARM Grading System or the related International System, which defines an early and late stage. Clinical studies and clinical trials following the lead of the N.E.I.-funded Age-related Eye Disease Study (AREDS) (2001) will increasingly utilize the AREDS grading system. This formulation resembles the WARMGS in lesion definition, but differs from the WARMGS in that four stages of maculopathy are assigned rather than two. A progression between the first three stages are implied but not proven by this scheme.

4. Previous literature on ARM clinicopathologic correlation

A literature search[1] reveals roughly 130 studies since 1974 (half of which appeared since 1998) that directly examined eyes from known ARM patients with light or electron microscopic tissue methods. These investigations can be divided into several main genres, as illustrated by the following: (1) extensive series of eyes from a single hospital population, supplemented by clinical information with pre-mortem imaging (Sarks, 1976; Sarks et al., 1999), and derivative small sub-series (Penfold, Killingsworth, & Sarks, 1984); (2) extensive series of eyes with clinical information including pre-mortem imaging from eye pathology laboratories working closely with local eye banks (Bressler, Silva, Bressler, Fine, & Green, 1994; Green & Enger, 1993; Green & Key, 1977); (3) extensive series of clinically undocumented eyes from eye pathology laboratories working closely with local eye banks (Biswas & Raman, 2002; Kliffen, Mooy, Luider, Huijmans, & Kerkvliet, 1996; Loeffler & Lee, 1986; Spraul & Grossniklaus, 1997; van der Schaft et al., 1992); (4) extensive series of eyes from eye pathology laboratories working with autopsy services (Gartner & Henkind, 1981; Hoshino, Mizuno, & Ichikawa, 1984); (5) extensive series harvested from local eye banks for research purposes, with varying degrees of clinical documentation (Chong et al., 2005; Curcio, Presley, Millican, & Medeiros, 2005; Olsen & Feng, 2004); (5) series of varying sizes gleaned from an eye bank network coordinated through a non-profit organization, foundation, or individual laboratory (Bhutto et al., 2004; Hahn, Milam, & Dunaief, 2003; Kamei & Hollyfield, 1999; Marmorstein et al., 2002). To date there has been little move towards standardizing ARM histopathologic

[1] PubMed; June 23, 2005; age-related macular degeneration histopathology; abstract in English; human or non-human primate.