Clinicopathologic Correlation of Successfully Treated Choroidal Neovascularization Lying Within the Notch of a Large Serous Retinal Pigment Epithelial Detachment

We report the histopathologic features of a successfully treated serous retinal pigment epithelial detachment (RPED) with accompanying choroidal neovascularization (CNV) in a 74-year-old woman with age-related macular degeneration (AMD). These findings were correlated with antemortem fluorescein and indocyanine green (ICG) angiographic studies. Histopathologic studies showed that the serous RPED represented a separation of the retinal pigment epithelium (RPE) and its basal lamina from the remainder of the Bruch membrane with no intervening CNV. Laser photocoagulation had successfully closed the accompanying sub-RPE (Gass type 1, presumed intra-Bruch) choroidal neovascular membrane. The RPED resolved, leaving a fairly well-preserved RPE monolayer, which reapposed the Bruch membrane, allowing retention of very good vision for 21 months. Additionally, in an area of drusen resorption, only small calcific deposits remained and there was no remaining basal laminar deposit.

Only a limited number of previous reports describe histopathologic correlative studies with recent fluorescein and ICG angiography in eyes with CNV associated with AMD. In this study, we report, to our knowledge, the first such case of an eye successfully treated with laser photocoagulation for a serous RPED with CNV and resorption of accompanying drusen.

Report of a Case. A 74-year-old woman with AMD had a 2-month history of blurred central vision in her right eye. The vision in her left eye had been poor for 10 years because of exudative AMD. Her medical history was remarkable for hypertension, coronary artery disease, peripheral vascular disease, and colon cancer. She did not smoke.

On examination, visual acuity was 20/30 OD with no scotomata or metamorphopsia by Amsler grid testing. Visual acuity OS was counting fingers at 4 ft. Funduscopic examination results of the right eye disclosed a sharply circumscribed, dome-shaped detachment of the macular RPE, with a shallow overlying sensory retinal detachment. Large drusen were seen throughout the posterior pole, and there was a small patch of geographic atrophy temporal to the fovea within the area of detached RPE. Examination results of the left eye revealed disciform macular scarring, exudation, subretinal fibrosis, RPE migration, and hyperplasia (Figure 1). The fluorescein angiogram of the right fundus revealed a well-circumscribed area of early hypo-fluorescence with progressive hyperfluorescence in the later phases corresponding to the RPE elevation seen clinically. Along the nasal border of the lesion, a notched area was present in which there was delayed filling and irregular late hyperfluorescence. Results of ICG angiography demonstrated well-demarcated hypofluorescence corresponding to the RPED in the early and late phases. Within the nasal notch of the RPED, an expanding area of focal hyperfluorescence was present (Figure 2).

Figure 1. Fundus photograph from a 74-year-old woman with a sharply circumscribed, dome-shaped elevation of the retinal pigment epithelium in the right eye with overlying serous retinal detachment (arrowheads) and a nasal notch (white arrowhead). Large drusen are scattered throughout the posterior pole, and a small patch of geographic atrophy is located temporal to the fovea (arrow). The left eye (OS) shows disciform macular scarring, exudation, subretinal fibrosis, retinal pigment epithelium migration, and hyperplasia.
well-defined notch superior to the border of the RPED shows stippled leakage in the later fluorescein phases and staining in the late ICG angiography phases.

Argon green laser photocoagulation (175 applications; 200-µm spot size; 0.2-second duration burns up to 220 mW) was applied to the focal area of the presumed CNV at the nasal border of the RPED. Additionally, isolated laser applications were placed along the margin of the RPED (Figure 2).

The patient returned 1 month later. Visual acuity was 20/40 OD, and the macula was flat. Fluorescein and ICG angiographic study results revealed no leakage from the CNV and no hyperfluorescence in the area of the RPED (Figure 3). The patient returned at 3, 5, and 8 months with no evidence of CNV or RPED recurrence.

Fifteen months after treatment, visual acuity was 20/25 OD. Fundus examination results revealed a flat macula with a photocoagulation scar nasal to the fovea. When compared with pretreatment photographs, drusen were fewer in the posterior pole (Figure 4).

Twenty-one months after laser photocoagulation and 5 months after her most recent examination, the patient died following treatment for recurrent colon cancer.

Results. The eyes were enucleated 3 hours post mortem and fixed 13 hours thereafter in 4% buffered formaldehyde. The paraffin-embedded serial sections were cut parallel to the pupil, optic nerve, and macula plane, and the slides were stained with hematoxylin-eosin. Using a microscope fitted with a calibrated reticule, histopathologic features were measured and plotted to yield a 2-dimensional cylindrical projection of the optic disc and macula (Figure 5). This cartographic method has been described previously. The histopathologic and angiographic correlates are summarized in the Table.

We studied the following regions: resolved RPED (Figure 6), successfully photocoagulated CNV (Figure 7), photocoagulation scars, and resorbed drusen (Figure 8).

In the region of resolved RPED, a mildly disrupted RPE monolayer apposed the Bruch membrane. The neurosensory retina was thinned, and the photoreceptor nuclear density was reduced. One to 3 layers of cell nuclei were found in the outer nuclear layer of this eye compared with 7 to 9 layers found in previously studied normal-aged retinas. A thin layer of hypocellular eosinophilic fibrous tissue was beneath the RPE. This material was different than its basal laminar deposit because it lacked the anteroposterior striated appearance described by Sarks and Sarks. This region did not exhibit any distinguishing angiographic characteristics. There was no transmission defect to suggest RPE atrophy. During tissue processing, serial sections did not include the region superior to the RPED. Therefore, no histopathologic commentary could be made about the corresponding area of stippled leakage in the later fluorescein phases and staining in the late ICG phases.

Good histopathologic correlation was seen with the clinical and angiographic findings of successfully treated CNV. Hypocellular fibrous tissue was found beneath the RPE and its basal lamina. This
treated CNV is a sub-RPE (Gass type 1, presumed intra-Bruch) membrane, which communicates with the choroid via 2 endothelium-lined breaks in a layer presumed to be the outer layer of the Bruch membrane (Figure 9). This region corresponded to hypofluorescence in early and late phases with no leakage in both fluorescein and ICG angiography.

The regions of photocoagulation at the nasal notch and at the margin of the RPED were characterized by thinning of the neurosensory retina with destruction of the inner nuclear, outer plexiform, and photoreceptor layers. There was hyperplasia of the retinal pigment epithelial cells. Fibrocellular tissue was found beneath the retina and in the inner choroid, along with destruction of adjacent choroidal vessels. This area corresponded to well-
demarcated hypofluorescence in early phases with staining of the edges in the late phases on the fluorescein angiogram. On the ICG angiogram, the photocoagulation scars corresponded with well-demarcated hypofluorescence in both the early and late phases.

Examination of the area of drusen resorption disclosed separation of the Bruch membrane into an inner layer (RPE basal lamina) and an outer layer, whose elastic layer was undulated. Calcification was evident in this presumed intra-Bruch space. No basal laminar deposit was present in this area. This region displayed no distinguishing angiographic features.

**Comment.** Serous PEDs from the Bruch membrane have distinctive clinical and angiographic features and often contribute to loss of central vision in patients with AMD.\(^{11,12}\) Serous PEDs have been qualified as avascular or vascularized to denote the absence or presence of associated CNV.

Avascular serous PEDs, sometimes referred to as drusenoid PEDs, presumably form as soft drusen progressively accumulate, enlarge, and coalesce. These elevations of RPE typically develop slowly and initially may cause milder complaints of

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**Correlation of Histopathologic Features With Angiographic Findings**

<table>
<thead>
<tr>
<th>Ophthalmoscopic Finding</th>
<th>Map Color</th>
<th>Histologic Findings</th>
<th>Fluorescein Finding</th>
<th>Indocyanine Green Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolved RPED</td>
<td>Pale blue</td>
<td>Mildly disrupted RPE monolayer apposes Bruch membrane; thinned neurosensory retina; reduced photoreceptor nuclear density</td>
<td>No discerning features</td>
<td>No discerning features</td>
</tr>
<tr>
<td>Photocoagulated CNV</td>
<td>Pink Green</td>
<td>Thin hypocellular eosinophilic fibrous tissue underlay the RPE hypocellular fibrous tissue between RPE and basal lamina (intra-Bruch; Gass type 1)</td>
<td>Early and late hypofluorescence</td>
<td>Early and late hypofluorescence</td>
</tr>
<tr>
<td></td>
<td>Red spots</td>
<td>Perforation from choroid through outer layer of Bruch membrane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photocoagulation scar</td>
<td>Purple</td>
<td>Thinned neurosensory retina; destruction of inner nuclear, outer plexiform, and photoreceptor layers; RPE hyperplasia; fibrocellular tissue beneath retina and in the inner choroids</td>
<td>Early hypofluorescence; late staining of edges</td>
<td>Early and late hypofluorescence</td>
</tr>
<tr>
<td>Resorbed drusen</td>
<td>Yellow rings</td>
<td>Bruch membrane separation into inner layer (RPE and basal lamina) and outer layer (elastic layer, choriocapillaris basal lamina); calcification in intra-Bruch space</td>
<td>No discerning features</td>
<td>No discerning features</td>
</tr>
</tbody>
</table>

Abbreviations: CNV, choroidal neovascularization; RPE, retinal pigment epithelium; RPED, retinal pigment epithelial detachment.
blurring and metamorphopsia. Angiographic results outline these lobular or scalloped lesions as the material beneath the RPE stains with fluorescein. The late staining may be irregular depending on the density of the material beneath the RPE. In the absence of CNV, vision loss may be minimal or progress slowly. Occasionally, the detachment may spontaneously flatten.13,14

With vascularized RPEDs, patients tend to experience acute vision loss as they develop sharply demarcated, dome-shaped elevations of the RPE, often accompanied by elevation of the overlying neurosensory retina. In AMD, serous RPEDs are usually accompanied by angiographic evidence of CNV and constitute approximately 15% of eyes with neovascularization (M.L.K., unpublished data, 1998). If the detachment occurs at the edge of the CNV, a reniform detachment results. In these lesions, the sub-RPE material within the dome stains slowly and unevenly. Irregular early hyperfluorescence and evidence of late staining may or may not occur in the area of CNV that lies in the notch.13,14

In 1984, Gass13 presented the concept that notched serous RPEDs

Figure 6. In the region of resolved retinal pigment epithelial detachment, the photoreceptor nuclear density is attenuated (arrowhead). Hypocellular, eosinophilic fibrous tissue remains between the retinal pigment epithelium and its basal lamina and the presumed outer layers of the Bruch membrane (arrows). A mildly disrupted retinal pigment epithelial monolayer has reapproximated the Bruch membrane (hematoxylin-eosin, original magnification ×100 [A]; original magnification ×200 [B]).

Figure 7. The photocoagulated choroidal neovascularization (asterisk) resides between the plane of the retinal pigment epithelium (arrowhead) and the presumed outer layers of the Bruch membrane (arrow). Note the scarring of the inner choroid, absence of choriocapillaris, and loss of retinal pigment epithelial cells and outer nuclear layer as a result of laser photoacoagulation (hematoxylin-eosin, original magnification ×200).

Figure 8. Resorbed soft drusen. Sub–retinal pigment epithelium (presumed intra-Bruch) calcification present in areas where drusen resorbed (arrows). No basal laminar deposit is seen. The outer nuclear layer is attenuated (arrowheads) (hematoxylin-eosin, original magnification ×200).
are often caused by occult, flat sub-RPE CNV lying within the notch outside the margin of the serous RPED and reported the case of successful treatment of these lesions with focal laser directed to the area of the notch with or without laser of the margin of the RPED. He also demonstrated the clinical and histopathologic findings of flat, focal, occult sub-RPE CNV lying within the notch causing a large hemorrhagic RPED. Since then, the term notched serous RPED has gained wide usage in describing these commonly occurring, potentially treatable lesions.

For the last 20 years, the value of laser photocoagulation in such cases has been unclear. Investigators have reported that laser treatment is of no value. Other reports that if the CNV is identified and treated, flattening of the RPED will occur and vision can be preserved, as happened in this case. A basic assumption in treating such eyes is that the adjacent CNV is confined to an area identified on fluorescein or ICG angiography and not also located under the serous RPED. This study illustrates the histopathologic basis for successful treatment of CNV associated with a serous RPED, which is the absence of CNV in the area under the collapsed RPED. To our knowledge, only 2 other clinicopathologic cases of serous RPED with cartographic reconstruction have been reported. In both cases, the serous RPEDs were not treated and were represented histopathologically as a serous separation of the RPE and its basal lamina from the remainder of the Bruch membrane. Frank et al in 1973 correlated the fluorescein angiographic and histopathologic features of drusen, serous RPED without CNV, and serous neurosensory detachment in a patient with AMD. In 1976, Small et al reported a patient (case 2) with a serous RPED accompanied by an adjacent subfoveal CNV and correlated the fluorescein angiographic features with the histopathologic features also using cartographic reconstruction. In this patient, the subfoveal CNV, composed of fibrovascular tissue, resided beneath the RPE within a split in the Bruch membrane (Gass type 1) and was adjacent to serous separation of the RPE.

By correlating both fluorescein and ICG angiographic features with histopathologic characteristics and cartographic reconstruction, we demonstrated in this case that identification and ablation of extrafoveal CNV with argon laser treatment allowed the adjacent serous RPED to resolve, enabling the patient to maintain a visual acuity of 20/25 OD.

Another unique feature of this study was the histopathologic findings of resorbed drusen. Although resorption of drusen has been recognized clinically following laser photocoagulation, no information has been reported describing the histopathologic findings in an eye in which this has occurred.

In this eye, soft drusen were characterized by a localized RPED with underlying amorphous eosinophilic material and basophilic calcifications. Areas of drusen resorption were identified using cartographic correlation. In these areas, calcification was present within the Bruch membrane and no basal laminar deposit was evident (Figure 9). There was also sepa-
tion of the presumed inner and outer layers of the Bruch membrane with an undulating contour. Although the separation may be an artifact of tissue processing, it does suggest the prior presence of some material in areas where drusen have resorbed. Additionally, in this region, the outer nuclear layer is attenuated indicating photoreceptor loss.

The phenomena of disappearing neighboring drusen after flattening both vascularized and non-vascularized RPEDs is seen frequently. This observation was partly responsible for the interest in using focal photocoagulation of some drusen to clear the macula of drusen. In this case, it is unclear whether disappearance of drusen was as a consequence of the development and flattening of the RPED itself or due to photocoagulation at the nasal notch and at the margin of the RPED. Histopathologic clues to resorption of drusen seen in this study have implications for trials such as the Complications of Age-related Macular Degeneration Prevention Trial in which a standardized grid of laser photocoagulation is applied to the macula in hopes of reducing drusen and preventing CNV. Although there are no clinical features that correspond to basal laminar deposits, it is almost certain basal laminar deposits were present in the area of resorbed drusen. Basal laminar deposits were present elsewhere, primarily nasal to the optic nerve head. This suggests that resorption of clinically apparent drusen may serve as a marker for resorption of basal laminar deposits. The RPE in the area of drusen resorption remained intact. Although there was some reduction in the thickness of the outer nuclear layer, there was clearly an intact photoreceptor-RPE complex in the area of drusen resorption.

In conclusion, when correlated with both fluorescein and ICG angiographic findings, this study illustrates histopathologic evidence for 2 important points. Eyes with serous RPED and adjacent CNV may be successfully treated if the CNV can be completely identified and photocoagulated. With closure of the CNV, the serous RPED can resolve, the RPE monolayer is relatively preserved, and vision can improve if the CNV is outside the fovea. Serous RPEDs probably develop because of a cleavage plane between the elastic portion of the Bruch membrane and the RPE and underlying basal laminar deposits. Fluid leaking out of adjacent CNV is able to dissect along this cleavage plane resulting in the serous RPED. Closure of the CNV with laser allows the resolution of the RPED (Figure 11). In areas of resorbed drusen, there is a relatively normal relationship between the RPE and the overlying photoreceptors.

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2. Chang TS, Freund KB, de la Cruz Z, Yannuzzi LA, Green WR. Clinicopathologic correlation

Figure 11. Diagrammatic representation. An extrafoveal sub–retinal pigment epithelium (RPE) (Gass type 1, presumed intra-Bruch) choroidal neovascularization adjacent to a serous RPE detachment was treated with laser photocoagulation. In this case, successful treatment resulted in closure of the choroidal neovascularization, resolution of the RPE detachment, relative preservation of the RPE monolayer, and preservation of good vision for 21 months.
of choroidal neovascularization demonstrated by indocyanine green angiography in a patient with retention of good vision for almost four years. 


26. Small ML, Green WR. Involvement results were unremarkable. The remainder of the ocular examination results were unremarkable. An otolaryngologic consultation provided findings of erythematous nares, congestion, a deviated nasal septum, and polyps in the left nasal cavity. An orbital computed tomographic (CT) scan revealed extensive sinus soft tissue opacification with sinus expansion and multifocal erosion with lytic destruction of bone along the paranasal sinuses. In

Allergic Fungal Sinusitis With Unilateral Eye Involvement

We describe 2 patients with ocular signs and symptoms who were subsequently diagnosed as having allergic fungal sinusitis (AFS). This disease is characterized primarily by chronic rhinosinusitis, nasal polyposis, allergic mucin, and the presence of fungal organisms according to a culture and/or histologic examination. Clinical features are those associated with chronic rhinosinusitis, which include facial pressure, nasal obstruction, and rhinorrhea. Proptosis, ptosis, and diplopia are the most common ocular symptoms; however, these conditions rarely represent the initial manifestation of the disease. The nasal mucus specimens of patients with AFS are designated as allergic mucin because of the abundance of eosinophils and their degradation products within the mucus. Although standardized treatment for AFS is not well defined, surgical debridement and systemic corticosteroid therapy are commonly recommended.

The typical patient with AFS is young and immunocompetent with a history of asthma or atopy. Orbital involvement in AFS is caused by the direct extension of sinus inflammation and can result in compressive ocular symptoms. Although well described in the medical literature, AFS has rarely been described with ophthalmic involvement. We found only 5 such patients discussed in the ophthalmologic literature and take this opportunity to add our case series to this list.

Report of Cases. Case 1. A 15-year-old African American boy came to our clinic with mild proptosis, pain and tearing of the left eye, and a history of having been “elbowed” in that eye 4 months previously (Figure 1). Medications included ibuprofen, fexofenadine hydrochloride, and an artificial tear preparation. Medical and family histories were noncontributory. His visual acuity was 20/20 OU. Slight hypoglobus and 5-mm proptosis were present in the left eye. The remainder of the ocular examination results were unremarkable. An otolaryngologic consultation provided findings of erythematous nares, congestion, a deviated nasal septum, and polypos in the left nasal cavity. An orbital computed tomographic (CT) scan revealed extensive sinus soft tissue opacification with sinus expansion and multifocal erosion with lytic destruction of bone along the paranasal sinuses. In

Figure 1. A 15-year-old African American boy with proptosis, hypoglobus, and mild blepharoptosis of the left eye.


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