Clinicopathologic Correlation of Progressive Fibrovascular Proliferation Associated With Occult Choroidal Neovascularization in Age-Related Macular Degeneration

The development of fibrous tissue in patients with occult choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD) is one of the major determinants of vision loss. Usually this process is slow with the development of disciform scarring that exceeds 50% of the lesion occurring in only 20% of eyes by 12 months.1 The typical time course is between 30 and 100 months of follow-up.2 Interestingly, in the absence of subretinal blood or classic CNV, no eyes with occult CNV developed more than 50% disciform scarring in a 9- to 12-month follow-up.3

In the present case, we describe clinicopathologic findings in a patient with AMD who developed progressive subretinal fibrovascular proliferation associated with occult CNV.

Report of a Case. A 76-year-old man had a 3-month history of vision loss and a visual acuity of 20/60 OD as well as turbid subretinal fluid in that eye (Figure 1A). The fellow eye demonstrated a visual acuity of 20/30 and the retinal examination findings in this eye showed drusen and pigmentary changes of the retinal pigment epithelium (RPE). On stereofluorescein angiography, leakage of undetermined origin at the level of the RPE consistent with a 4-disc area of occult CNV was identified in the right eye (Figure 1B and C). The right eye underwent a rapid and progressive fibrosis over the ensuing 6 months (Figure 1D-F) with visual acuity declining to 20/400. The patient underwent vitrectomy with removal of the subretinal neovascular fibrotic scar.

The surgical specimen measured $4 \times 3.5 \times 1.2 \text{ mm}$. Microscopic analysis of the neovascular complex demonstrated a well-demarcated lesion with a 2-component fibrous scar (Figure 2A). The overall thickness of the lesion was approximately 1200 µm with the subretinal and intra-Bruch's membrane components measuring 1100 and 100 µm, respectively. Fibroblastlike cells were evident throughout the extensive matrix of collagen. Many microvascular channels were prominent in the region external to the RPE and within the outer subretinal area. The innermost region of fibrosis was relatively acellular and contained few vascular structures.

DAPI staining for cellular nuclei demonstrated striking hyper-
cellularity in the subRPE component of the scar (Figure 2B). Many cells in this area were positive for CD68+, a macrophage marker (Figure 3A). The neovascular structures stained positively for CD34+, a marker for microvascular endothelium and hematopoetic stem cells (Figure 4A), and for von Willebrand factor (vWF) (Figure 4B), a marker for differentiated endothelial cells. Numerous individual cells identified as CD34+ cells were also located throughout the scar. Within the complex, multiple individual isolated cells were CD34+ but vWF negative, indicating possible immature endothelial cells (Figure 4A and B). Tissue stains for vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor were negative but strongly positive for platelet-derived growth factor (PDGF) B within neovascular en-
dothelial cells (Figure 3B). The VEGF from the subretinal fluid was below the detectable levels by enzyme-linked immunosorbent assay (Quantikine Human VEGF Immunoassay; R&D Systems, Inc, Minneapolis, Minn).

Comment. This patient demonstrated rapid fibrosis of an occult fibrous neovascular membrane. The histopathology of the present lesion contained microvascular channels, a prominent fibrotic response, hypercellularity of the tissue comprising both inflammatory and endothelial cells, and expression of PDGF B within vascular channels.

A hypercellular response was most prominent in that portion of the scar adjacent to the RPE. Part of the cellular responses appeared to be a prominent inflammatory component consisting of CD68+ macrophages. This finding suggests that these cells may participate in the evolution of fibrous neovascular membranes and support the inflammatory paradigm of CNV in AMD. The origin of vascular elements contributing to the subretinal fibrovascular membrane in AMD remains uncertain. In the present case, endothelial cells located within the microvascular channels were strongly positive for CD34+ and vWF. Many individual cells isolated within the fibrous matrix of this membrane were CD34+ but vWF negative. In addition, many endothelial marker positive cells were identified as isolated, individual cells rather than embedded in a neovascular channel. These findings, in this case, suggest that a cellular rather than a vascular invasion may have played a role in the pathogenesis of the neovascular structures. In addition, while vWF staining is specific to endothelial cells, CD34+ also serves as a marker for hematopoietic stem cells. Recently, work with stem cells has highlighted the capacity of these cells to differentiate into vascular elements both in vitro and in vivo under the influence of VEGF and PDGF. Whether this process occurs in the pathogenesis of CNV remains speculative.

Consistent with a previous report on cytokine production in CNV undergoing involution, this case exhibited a lack of VEGF expression both by immunohistochemistry and quantitative enzyme-linked immunosorbent assay. However, prominent PDGF staining was detected within the vascular channels. In summary, this surgically excised fibrovascular membrane demonstrates additional findings that add to our knowledge of the molecular biology of neovascular AMD.

Karl Csaky, MD, PhD
Judith Baffi, MD, PhD
Chi-Chao Chan, MD
Gordon A. Byrnes, MD
Bethesda, Md

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Corresponding author and reprints: Karl Csaky, MD, PhD, Bldg 10, Room 10N119, NEI/NIH, 9000 Rockville Pike, Bethesda, MD 20895-1857 (e-mail: kcsaky@helix.nih.gov).


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Blindness From Septic Thrombophlebitis of the Orbit and Cavernous Sinus Caused by Fusobacterium nucleatum

Fusobacterium organisms are obligate anaerobic gram-negative bacilli belonging to the family Bacteroidaceae. Of the 15 species recognized, Fusobacterium nucleatum and Fusobacterium necrophorum are the most frequently isolated species from clinical specimens. These species are most commonly found in the mouth and to a lesser extent in feces and the urogenital tract but rarely give rise to severe disease.1 We describe a previously healthy woman with a history of severe periodontal disease who developed septic thrombophlebitis of the orbit and cavernous sinus caused by F nucleatum. We are unaware of previous reports of septic thrombophlebitis of the orbit and cavernous sinus caused by F nucleatum.

Report of a Case. A previously healthy 55-year-old woman had a 1-month history of left-sided headaches that were treated with pain medications. Her medical history was notable for severe periodontal disease and a previous partial thyroidectomy for a benign mass. The patient subsequently developed severe left orbital pain.Computed tomography and magnetic resonance imaging of the orbits and brain were performed, and the findings demonstrated cavernous sinus enlargement and enhancement on the left side. Thoracoabdominal computed tomography and cerebrospinal fluid evaluation results were negative. Infectious and noninfectious inflammatory processes, including Tolosa-Hunt syndrome and granulomatous diseases, were considered in the differential diagnosis, and the patient was treated with antibiotics and high doses of steroids. One week prior to admission to our institution, she developed bilateral proptosis and intractable pain. She was referred to our institution for further evaluation and treatment.

On examination she had bilateral proptosis with severe periorbital edema and erythema with conjunctival hyperemia and chemosis. She was unable to open her eyes. Her visual acuity was counting fingers OU, but this could not be assessed reliably because of poor patient cooperation due to extreme pain. Extraocular motility was markedly limited in all fields of gaze bilaterally. The pupils measured 2 mm bilaterally with normal pupillary light reaction. Additional magnetic resonance images of the brain and orbits were obtained. Compared with the magnetic resonance images obtained 1 week earlier, there was now involvement of the right cavernous sinus (Figure 1). Proposis of both globes with reticulated abnormal enhancement of the retrobulbar fat in both or-