ABSTRACT

We report an unusual case of acute recurrent bilateral multifocal choroidal neovascularization that was associated with histologically proven membranoproliferative glomerulonephritis type II and did not resolve with laser photocoagulation. Early development of subretinal neovascular membranes with widespread retinal pigment epithelial changes in this condition may herald poor prognosis despite laser ablation of the neovascular tuft.

CASE REPORT

Occurrence of Atypical Acute Bilateral Multifocal Choroidal Neovascularization in Membranoproliferative Glomerulonephritis Type II

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Membranoproliferative glomerulonephritis (MPGN) is a group of diseases characterized histologically by alterations in the basement membrane and proliferation of glomerular cells. Based on distinct ultrastructural and immunofluorescence findings, primary MPGN can be divided into 2 major types: type I and type II.[1] In type II, MPGN of electron-dense material of unknown origin is deposited in the glomerular basement membrane proper.[1] Ocular histopathologic changes originally reported in patients with MPGN type II described dense deposits in the basement membrane of the ciliary epithelium and throughout the inner collagenous layer of Bruch membrane that simulated drusen.[2-4]

In patients with a long history of renal disease, more numerous and larger subretinal nodules as well as atrophic changes were found.[5] Clinical observations suggest that the occurrence and progression of retinopathy in these patients is a slow process with vision usually not affected.[5] Thus far, the association of subretinal neovascular membranes is described in only 4 cases with a history of renal disease longer than 15 years.[6] We report an unusual case of acute bilateral multifocal choroidal neovascularization in a patient with type II MPGN that progressed during a period of 3 months to visual loss despite laser therapy.

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Materials & Methods

Complete eye examinations of the patient included measurement of visual acuity, pupillary reaction, Goldmann applanation tonometry and perimetry, and detailed ophthalmoscopy, as well as fundus photography and fluorescein and indocyanine-green angiography.

Renal biopsy tissue, fixed in a phosphate-buffered 4% formaldehyde and 1% glutaraldehyde solution, was divided into 2 pieces. One piece was osmicated, dehydrated in ascending grades of ethanol, and was finally embedded in epoxy resin for transmission electron microscopy. The other piece of tissue, after initial fixation and alcohol dehydration, was embedded in paraffin wax. Sections 6 to 8 μm in thickness were cut from the paraffin block for routine histologic and immunofluorescence staining.

For immunostaining, deparaffinized and rehydrated sections were mounted on polylysine coated slides and incubated with a goat polyclonal antibody against human complement C3 (1:8 dilution, Sigma, St. Louis, Mo). Visualization of the primary antibody was performed by using the fluorescein-conjugated rabbit anti-goat IgG (1:64 dilution, Sigma), and epifluorescence microscopy. Replacement of the primary antibody with normal nonimmune goat serum served as a negative control.

Ultrastructural evaluation of the biopsy was carried out on ultrathin sections stained with uranyl acetate and lead citrate specimen by using a Hitachi 600 electron microscope (Tokyo, Japan).

Results

The patient, a 45-year-old white man, had a 2-week history of rapid deterioration in vision. He had no prior ocular disease and had an unremarkable family history. The patient was on hemodialysis for advanced renal disease and received antihypertensive therapy with minoxidil and nifedipine for more than 6 months. Eighteen months earlier, severe systemic hypertension heralded the onset of acute renal failure. Subsequently his renal function did not improve and chronic renal failure with nephrotic syndrome ensued, which necessitated hemodialysis. At that time serum complement levels (C-3 and C-4) were normal; however, the patient exhibited persistently elevated glucose levels despite insulin therapy. He was awaiting renal transplantation.

Ocular examination. The patient had corrected visual acuity of $20/30^{-3}$ in the right eye and 20/40 in the left eye. On ocular examination, pupils, visual fields, applanation tonometry, and slit-lamp evaluation of the anterior segment were all unremarkable and the ocular media were clear. Biomicroscopic examination of the fundus revealed bilateral, multifocal, symmetrical peripapillary subretinal hemorrhages (Fig 1). A small subretinal hemorrhage with serous elevation of the overlying neurosensory retina was noted immediately above and temporal to both foveae. A larger area of subretinal hemorrhage was evident above the right fovea. Biomicroscopic examination with a contact fundus lens revealed scant, ill-defined, small yellow deposits at the level of the retinal pigment epithelium (RPE). There was no evidence of peripapillary chorioretinal scarring or stigmata of age-related macular degeneration. The peripheral retina was unremarkable. Blood pressure was well controlled with medication.

Fluorescein angiography revealed the presence of a well-defined juxtafoveal choroidal neovascular membrane measuring about 1000 μm in diameter above the right fovea (Fig 2A). A larger neovascular membrane was evident in a symmetrical position in the left eye (Fig 2B). There were multiple areas of transmitted hyperfluorescence above and below the left optic nerve and a small amount of fluorescein leakage temporal to the right optic nerve. In the right eye, hyperfluorescence was partially blocked below the optic nerve that was thought to represent an additional choroidal neovascular membrane. Indocyanine-green angiography did not reveal any neovascular activity (Fig 3).

The patient underwent argon laser photo ablation (50–100 μm in size, 0.3–0.4 W, 0.2 sec, 92 spots) of the left juxtafoveal neovascular membrane; 2 weeks later

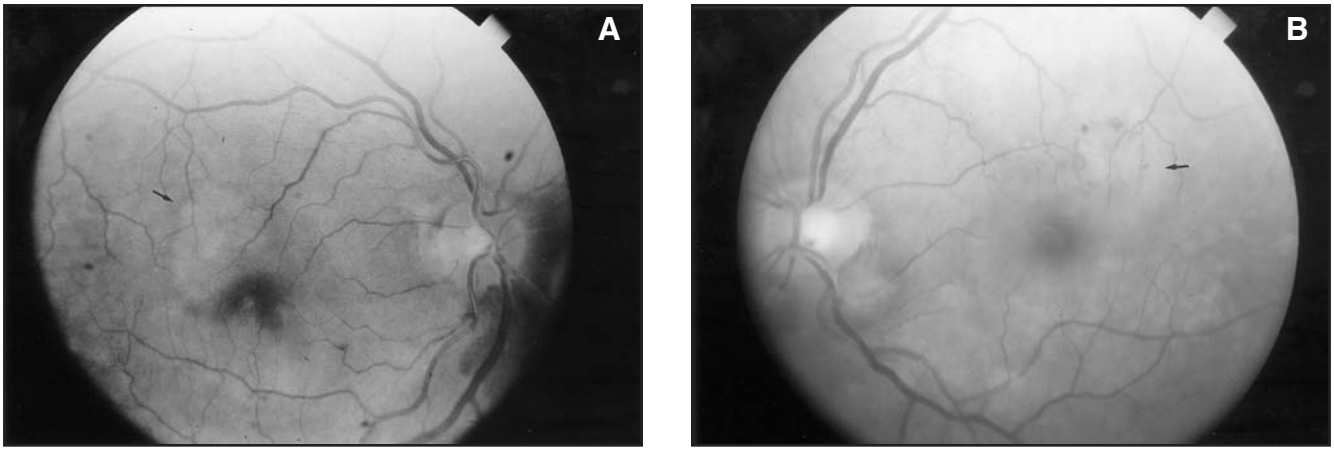

Fig 1.—Fundus photograph of posterior pole showing bilateral peripapillary hemorrhage with subretinal serous fluid above and temporal to both foveae. Ill-defined subretinal yellow lesions were seen in right (A) and left (B) eyes on fundus biomicroscopy (arrows).

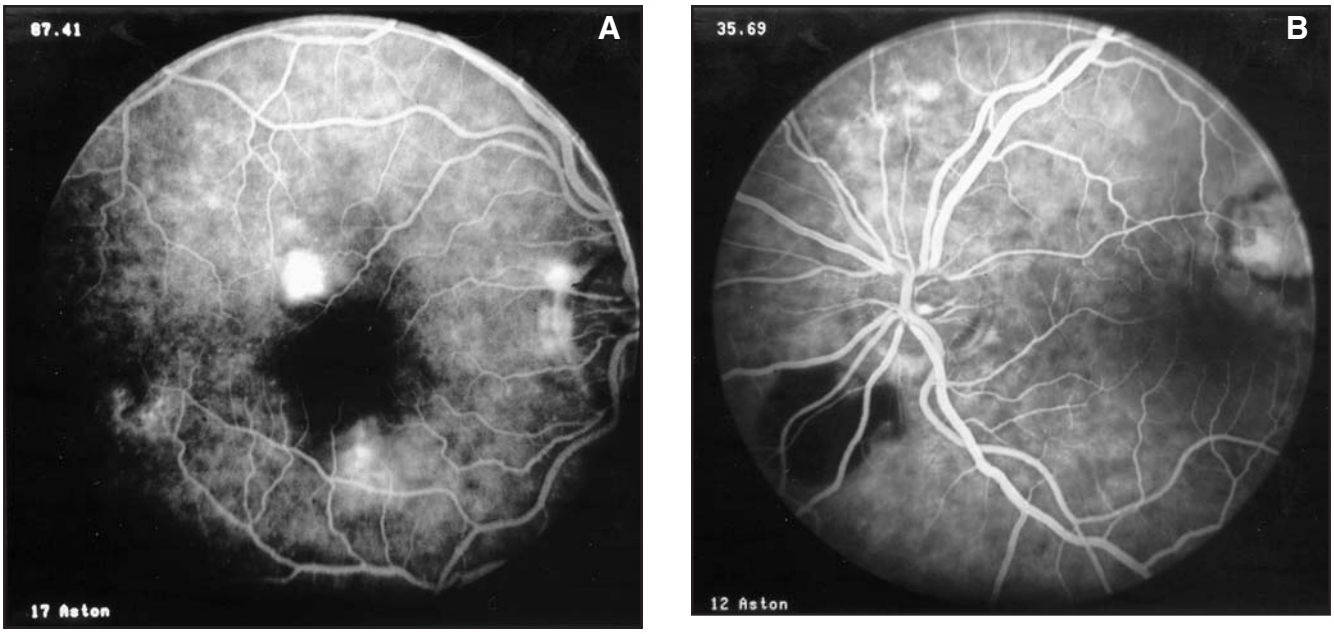

Fig 2.—Digital angiogram of (A) early venous phase in the right eye showing well-defined choroidal neovascular membrane, and (B) late venous phase in the left eye with larger, symmetric neovascular membrane. Note also the transmission of hyperfluorescence temporal to and below the right fovea as well as at the temporal edge of the nerve.

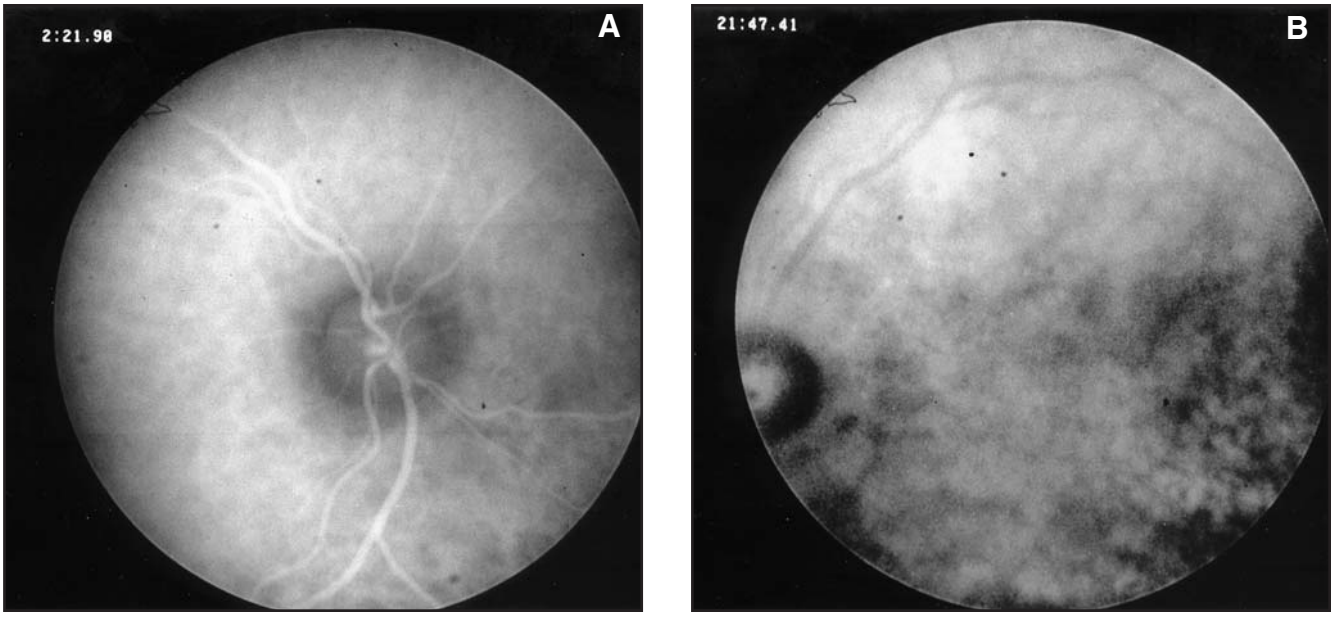

Fig 3.—Late-phase indocyanine-green digital angiogram of (A) left and (B) right eyes.

he complained of decreased vision in the right eye. On examination, visual acuity was 20/40 in the right eye and $20/60^{+2}$ in the left eye. The neovascular membrane in the right eye had enlarged and was treated with argon green laser (50–100 μm in size, 0.3–0.4 W, 0.2 sec, 124 spots).

Two weeks later, visual acuity had decreased to 20/100 in the right eye and 20/400 in the left eye. Repeat fluorescein angiography at this time demonstrated recurrent neovascularization in the parafoveal region of the right eye and early disciform scarring of the lesion in the left eye with foveal involvement (Fig 4). Repeat focal laser photo ablation (50-100 μm in size, 0.3–0.4 W, 0.2 sec, 144 spots) of the right neovascular membrane was performed with krypton red laser. Two weeks later, the patient's visual acuity had diminished to 20/400 in the right eye and counting finger in the left eye. Examination revealed subfoveal neovascularization in the right eye and a disciform scar in the left fovea.

Histopathology and immunofluorescence staining. Histologic examination of the renal biopsy specimen revealed proliferation of mesangial cells, increased mesangial matrix, and a markedly thickened basement membrane (Fig 5). The lobular architecture of the glomerulus was accentuated. Complement C3 immunofluorescence staining demonstrated a positive reaction product in the peripheral capillary wall and

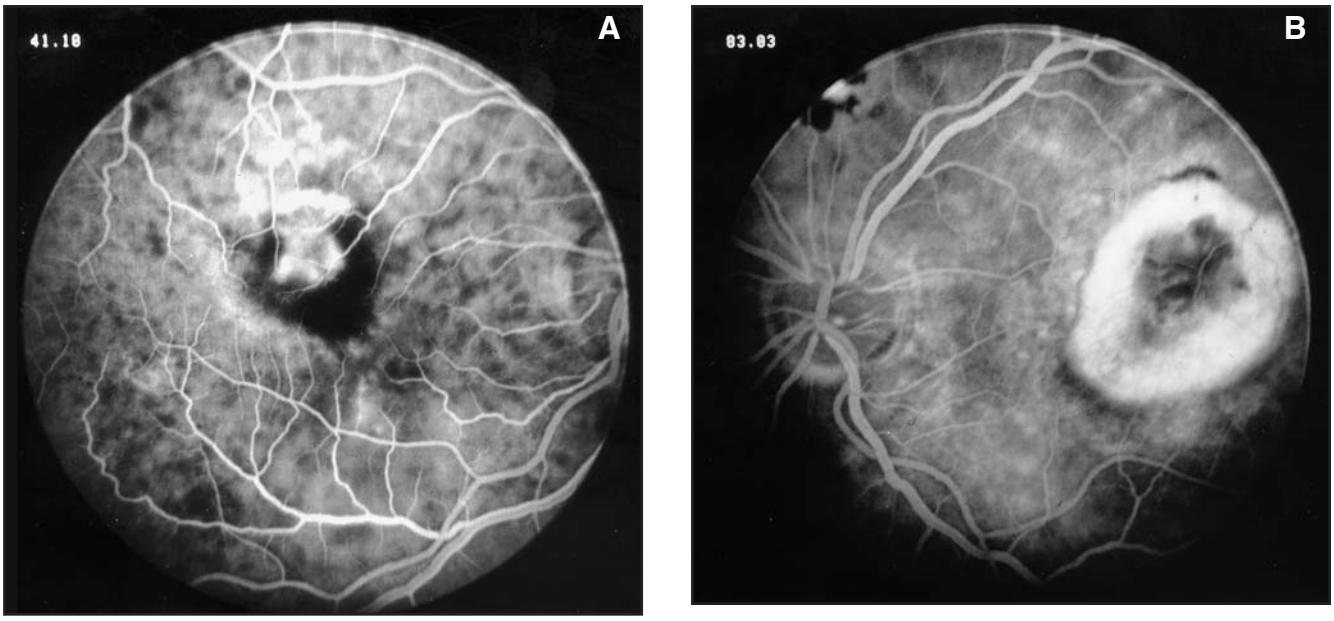

Fig 4.—Digital fluorescein angiogram showing venous phase of both eyes, with (A) recurrent choroidal neovascular membrane in the right eye and (B) disciform changes in the left fovea.

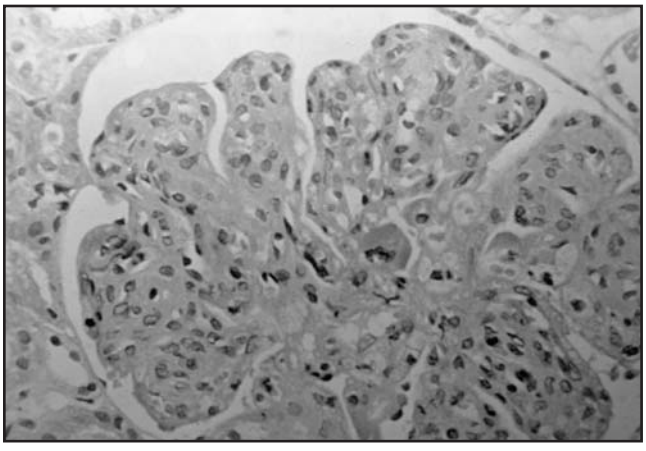

Fig 5.—Light micrograph of kidney demonstrating hypercellular, lobulated glomerulus with thickened capillary walls (hematoxylin-eosin, × 850).

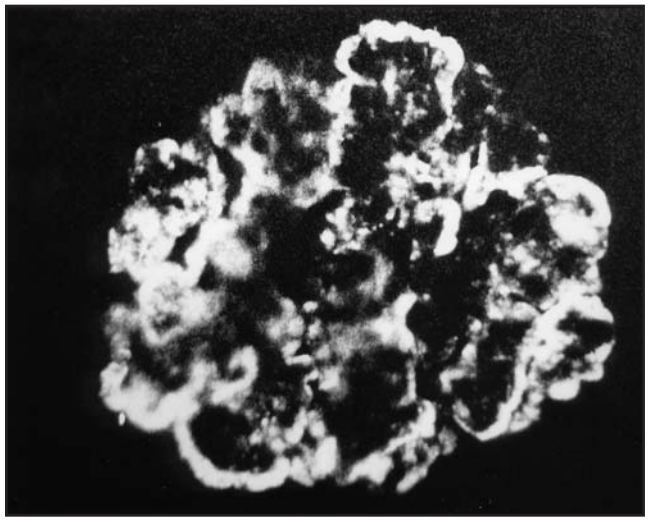

Fig 6.—Immunostaining for complement C3 revealing positive staining around peripheral capillary walls and mesangium (× 700).

mesangium (Fig 6). The negative control did not show staining of any structure.

Ultrastructurally, an irregular, ribbonlike, electron-dense, homogeneous structure was observed in the glomerular basement membrane proper (Fig 7).

Discussion

Choroidal neovascularization in association with renal disease is an unusual finding.[7] Most retinal complications associated with renal dysfunction involve microvascular changes of the retinal blood vessels secondary to the attendant systemic hypertension. Other vascular causes of acute renal failure, such as periarteritis nodosa, Wegener's granulomatosis, or thrombotic thrombocytopenic purpura can produce retinal vasculitis, tortuosity, or thrombosis.[7] Changes seen with hemodialysis are also usually vascular in origin and include central retinal vein occlusion, cortical blindness, and anterior ischemic optic neuropathy.[8-10]

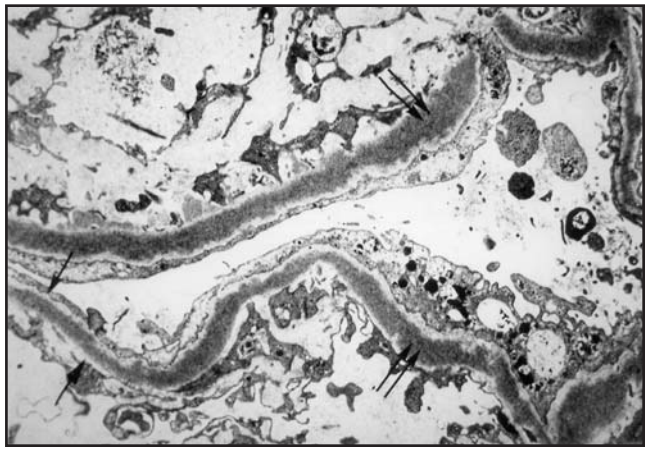

Fig 7.—Transmission electron micrograph of the kidney, showing homogeneous electron-dense deposits within basement membrane proper (double arrows) (× 54,000).

The pathologic changes revealed by light microscopy as well as by immunofluorescent staining of the renal specimen indicate that our patient has MPGN type II (dense deposit disease). The electron-dense deposits that were observed within basement membrane proper further confirm the diagnosis.[1] Patients with MPGN type II have been noted to manifest partial lipodystrophy that includes variable glucose intolerance,[1] as was found in our patient. However, our patient did not display low levels of serum complements as has been described in association with some cases of MPGN type II.[5]

Previously, Leys et al[5,6] described a series of patients with chronic MPGN type II who developed subretinal neovascular membranes in the course of the illness. Their 4 patients, who had biopsy-proven MPGN type II, had fundus findings similar to each other that consisted of extensive pigment epithelial abnormalities and a varying number of small drusen-like subretinal deposits. In addition, 3 of the 4 patients demonstrated alterations of the electro-oculogram with reduced Arden ratios between 150% and 160% (light-peak to dark-trough ratio). Pigment epithelial disease is not reported in any other glomerulopathies or in MPGN type I.[2,11] The ocular histopathologic findings in association with MPGN type II include electron-dense deposits in the inner collagenous layer of Bruch membrane, which resemble deposits found in the glomerular basement membrane.[3,4]

A recent report of central serous retinopathy in MPGN type II confirms the propensity of such patients to develop disease related to dysfunction of the RPE and Bruch membrane.[12] Unusual causes of choroidal neovascularization not associated with age-related macular degenerative changes include acute multifocal posterior placoid pigment epitheliopathy, rubella retinopathy, chorioretinal folds, photocoagulation, chronic papilledema, and hyaline bodies of the optic nerve.[13] Idiopathic choroidal neovascularization of the macula has been ascribed to a forme fruste of the ocular histoplasmosis syndrome when seen in young patients. However, the visual prognosis in patients with idiopathic choroidal neovascularization is usually good.[13] The rare and ill-defined condition known as the pseudo-inflammatory macular dystrophy of Sorsby[14] has an autosomal dominant mode of inheritance and is manifested by hemorrhagic, rapidly progressive disciform lesions of the macula, followed by pigmentary changes in the peripheral retina.

Our patient suffered from chronic renal failure and developed rapidly progressive and destructive, symmetrical choroidal neovascular membranes in association with diffuse, scattered RPE changes. The widespread and aggressive nature of the ocular disease in a relatively young person indicates a global defect in the RPE or its subjacent structures.

We believe that our patient represents an atypical form of choroidal neovascularization due to MPGN type II. The rapid onset from the time of diagnosis is unusual, but this appears to correlate with the advancement of the subretinal neovascularization despite laser treatment. Our case contrasts with those patients who had long-standing renal dysfunction prior to the onset of neovascular complications and, when treated with laser, responded well.[5,6] The scant amount of clinically detectable dense deposits appears to conform with the finding of Leys et al,[5] who noted an absence of subretinal nodules in 2 patients early in the course of their disease. Diffuse RPE changes on fluorescein angiography documented in the previous report were also found in our patient.

Patients with MPGN type II are at risk of significant complications due to associated retinal pigment epithelial dysfunction. In addition, the typical ophthalmic findings may be helpful in aiding the diagnosis of the patient's underlying renal disorder. The early development of subretinal neovascular membranes may herald a poor prognosis despite laser treatment.

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