Age-Related Eye Disease Study

Objective: to evaluate the effect of high-dose supplements, macular carotenoids, and omega-3-fatty acid on the progression of AMD

Methods: patients randomized to receive various combinations of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (vitamin A, 15 mg), zinc (80 mg plus 2 mg copper), lutein (10 mg), zeaxanthin (2 mg), omega-3 long-chain polyunsaturated fatty acids (LCPUFA) in the form of docosahexaenoic acid (DHA) (350 mg) and eicosapentaenoic acid (EPA) (650 mg)

VEGF Inhibition Study in Ocular Neovascularization trial (VISION)

Objective: to evaluate intravitreal pegaptanib for subfoveal CNV due to neovascular AMD

Methods: 2 concurrent randomized, double-masked clinical trials, 1208 patients received either pegaptanib intravitreal injection (0.3 mg, 1.0 mg, or 3.0 mg) or a sham injection into study eye every 6 weeks for a total of 48 weeks. Patients were eligible for the trial if they were 50 years old or older and had subfoveal classic, minimally classic, and/or occult CNV due to wet AMD with a best-corrected visual acuity of 20/40 to 20/320 in the study eye.

Results: on average, patients treated with pegaptanib 0.3 mg and sham-treated patients continued to experience vision loss. However, the rate of visual acuity decline in the pegaptanib-treated group was slower than the rate in the patients who received sham treatment; 70% of patients treated with pegaptanib sodium injection (0.3 mg; $n = 294$) lost fewer than 15 letters of visual acuity compared with 55% in the control group ($n = 296$; $P < 0.001$); 10% of patients treated with pegaptanib sodium injection (0.3 mg; $n = 294$) had severe visual acuity loss (30 letters or more) compared with 22% in the control group ($n = 296$; $P < 0.001$). The beneficial effect was observed for all subtypes of neovascularization (NV). The beneficial effect was sustained for up to 2 years of follow-up

Conclusions: pegaptanib was better than sham and PDT for neovascular AMD

Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) Trial

Objective: pivotal phase III, multicenter, double- blind 24-month study, which compared monthly intravitreal injections of ranibizumab 0.3 or 0.5 mg or sham injections (n = 716) in patients with subfoveal occult only or minimally classic CNV due to wet AMD

Results: enrolled 716 patients with minimally classic and occult subfoveal CNV associated with AMD. The primary outcome was prevention of moderate visual loss (≤15 letters loss of vision), which was seen in 94.5% with ranibizumab 0.3 mg, 94.6% with ranibizumab 0.5 mg and 62.2% of patients receiving sham injections ($P < 0.001$). Vision improved by ≥15 letters for a significantly ($P < 0.0001$) greater number of ranibizumab-treated patients (24.8% for 0.3 mg and 33.8% for 0.5 mg) versus sham-treated patients (5.0%). Mean increases in VA from baseline were +6.5 letters for the ranibizumab 0.3 mg group and +7.2 letters for the ranibizumab 0.5 mg group, whereas sham-injected patients had a mean decrease of −10.4 letters. This benefit in VA in ranibizumab-treated patients was maintained through 24 months. At 24 months, 90% of ranibizumab-treated patients in the MARINA study lost less than 15 letters of visual acuity; 33% gained 15 or more letters of visual acuity ($P < 0.01$). Ranibizumab-treated patients exhibited a statistically significant improvement compared with sham-treated patients in all subgroups for all outcome measures.

Conclusions: ranibizumab was better than sham for occult with no classic and minimally classic CNV due to neovascular AMD

Anti-vascular endothelial growth factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in Age-related Macular Degeneration (ANCHOR) Trial

Objective: second pivotal phase III, multicenter, randomized, double-masked 24-month clinical trial, which compared ranibizumab with the active control verteporfin PDT in subfoveal predominantly classic CNV due to wet AMD

Results: enrolled 423 patients with predominantly classic subfoveal CNV associated with AMD. The primary outcome was prevention of moderate visual loss (≤15 letters loss of vision), which was seen in 94.3% with ranibizumab 0.3 mg, 96.4% with ranibizumab 0.5 mg and 64.3% of patients receiving PDT ($P < 0.001$). Vision improved by ≥15 letters in significantly more ranibizumab-treated patients (35.7% for 0.3 mg and 40.3% for 0.5 mg) than PDT-treated patients (5.6%; $P < 0.0001$). At 12 months, mean change in VA increased by +8.5 letters in the ranibizumab 0.3 mg group and by +11.3 letters in the 0.5 mg group, but decreased by −9.5 letters in the sham group ($P < 0.0001$)

Conclusions: ranibizumab was superior to verteporfin for treatment of predominantly classic CNV due to neovascular AMD

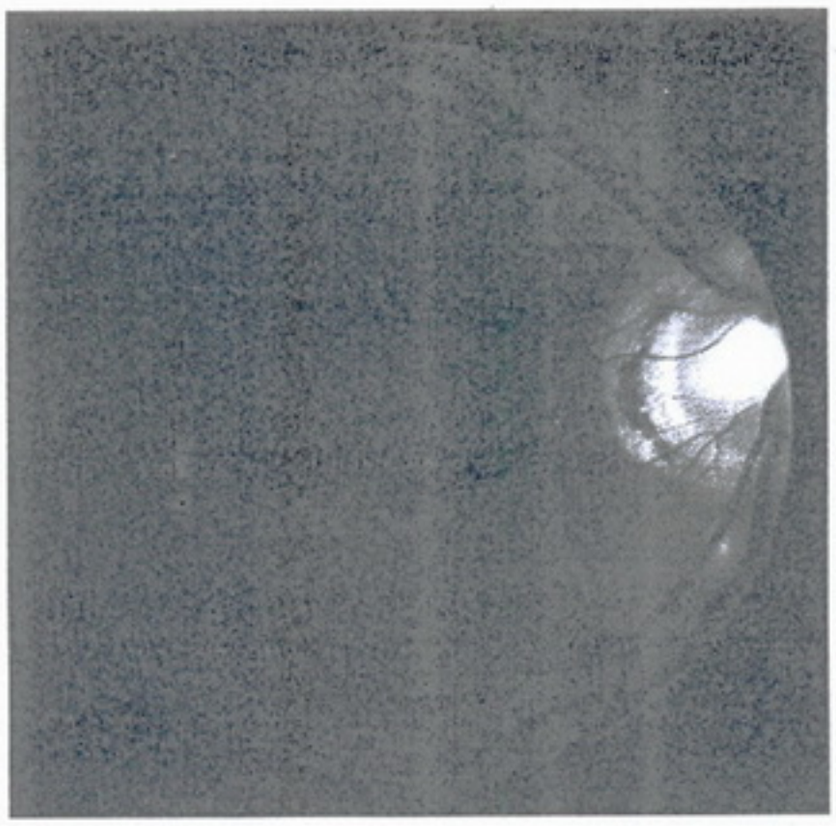


Figure 11-51. POHS demonstrating peripapillary scarring and macular, juxtafoveal choroidal neovascular membrane with surrounding subretinal hemorrhage. (From Noorthy RS, Fountain JS: Fungal uveitis. In: Yanoff M, Duker JS (eds) Ophthalmology. London, Mosby, 1999.)

Other Disorders Associated with Choroidal Neovascular Membrane (CNV)

Treatment for all CNV: consider laser only for extrafoveal lesions (MPS showed that laser treatment for juxtafoveal and extrafoveal CNV was beneficial); juxtafoveal and subfoveal lesions are treated with anti-VEGF agents or photodynamic therapy (see above)

Presumed Ocular Histoplasmosis Syndrome (POHS)

Due to *Histoplasma capsulatum,* a dimorphic fungus (mold in soil, yeast in animals and birds) endemic to Mississippi and Ohio River valleys; rare in Europe; rare among African Americans. Age of onset commonly 20–45 years; no sex predilection; 90% of patients with ocular signs have positive skin reaction (>5 mm) to intracutaneous 1 : 100 histoplasmin (test usually not used because it may incite macular disease)

Macular involvement associated with HLA-B7, HLA-DRw2; however, HLA typing is not commonly used

Primary infection involves inhalation of spores into respiratory tract and a self-limited flu-like illness; dissemination of the fungus then occurs to spleen, liver, and choroid. Primary choroidal infection causes granulomatous, clinically unapparent inflammation that resolves into a small, atrophic scar ('histo spot') that can disrupt Bruch's membrane

Findings: POHS consists of the triad of peripapillary atrophy, multiple punched-out chorioretinal scars ('histo spots,' may enlarge, 5–10% develop new spots), and maculopathy. No anterior or posterior segment cell; CNV can occur (different from that in AMD in that vessels penetrate Bruch's membrane and extend over RPE; a second layer of RPE forms [basal side up] and attempts to encircle the CNV) (Figure 11-51)

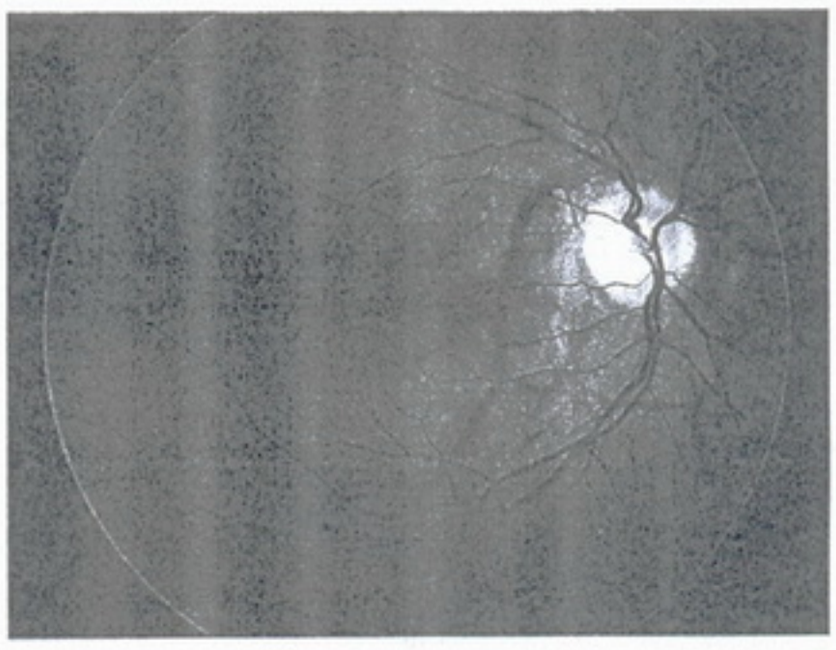


Figure 11-52. Peripapillary angioid streaks. (From Vander JF: Angioid streaks. In: Yanoff M, Duker JS (eds) Ophthalmology. London, Mosby, 1999.)

Risk of CNV: 1% with normal disc and macula; 25% risk over 4 years if not normal

CXR: calcifications

Angioid Streaks

Peripapillary linear cracks in thickened, degenerated, and calcified Bruch's membrane (Figure 11-52)

Subretinal hemorrhage can occur with minor trauma; patients should consider safety glasses

Etiology: 50% associated with systemic condition, 50% idiopathic

Mnemonic **PEPSI**:

- *Pseudoxanthoma elasticum* (PXE) (AR ≫ AD): female > male; peau d'orange appearance to retina; redundant skin with waxy, yellow, papule-like lesions ('plucked chicken' skin); increased elastic tissue; vascular malformations; abnormal mucosal vasculature may cause GI bleeds; may have optic nerve head drusen; angioid streaks present in 85%
- *Ehlers-Danlos syndrome* (fibrodysplasia hyperelastica) (AD): hyperextensible skin due to deficient collagen matrix; other eye findings include subluxed lens, high myopia, keratoconus, blue sclera, retinal detachment
- *Paget's disease:* increased bone production and destruction; increased serum alkaline phosphatase; prone to basal skull and long bone fractures; othcr bone disorders (acromegaly, calcinosis)
- *Sickle cell:* risk for autoinfarction of spleen and thrombotic episodes; other hematologic diseases (thalassemia, hereditary spherocytosis, acanthocytosis [Bassen-Kornzweig syndrome]); angioid streaks present in 1%
- *Idiopathic*: 50%

DDx: lacquer cracks in myopia

Pathologic Myopia

High myopia = Axial length >26 mm; > −6 D of myopia;
Pathologic myopia = Axial length >32.5 mm; > −8 D of myopia;

Approximately 2% of US population; female > male

CNV due to PM commonly occurs in young patients; bilateral common (12–40%)

Findings: long, oval disc, may be tilted, cup usually shallow; temporal crescent; posterior staphyloma; tigroid fundus with visible choroidal vessels; lacquer cracks (breaks in Bruch's membrane); Foerster-Fuchs' spot (macular hemorrhage); cataract; retinal holes and high risk of rhegmatogenous RD

Lacquer crack: sudden decrease in vision, metamorphopsia, often in teenagers; focal subretinal hemorrhage, dense, round, deep, and often centered on fovea; blood may obscure crack

Complications: CNV often near fovea (65%) worse prognosis; 60% with vision <20/200 at 2 years

Treatment: Same as CNV due to AMD

Other Causes of Macular CNV

Idiopathic, optic nerve head drusen, choroidal rupture, choroidal nevus, sympathetic ophthalmia, Vogt-Kayanagi-Harada disease, serpiginous choroiditis, other posterior uveitides (choroidal inflammation may enhance production of angiogenic factors; when coupled with RPE-Bruch's membrane disruption, CNV can develop)

Vascular Diseases

Damage to vessel walls causes leakage of serum and blood into plexiform layers, causing edema, exudates, and hemorrhages

Edema: histologically appears as clear cystoid spaces

Lipid: appears as yellow lesion; histologically, hard exudates are eosinophilic and PAS-positive

DDx: diabetes, hypertensive retinopathy, CNV, vein occlusion, parafoveal telangiectasia, Coats' disease, radiation retinopathy, CSR, trauma, macroaneurysm, papilledema, angiomatosis retinae

Microaneurysm: fusiform outpouching of capillary wall

Cotton wool spot: microinfarction of NFL (usually secondary to occlusion of retinal arteriole) with cessation of axoplasmic flow, mitochondria accumulate (resemble a nucleus, so lesion appears like a cell ['cytoid body'])

Hemorrhage: shape of intraretinal blood depends on layer in which it occurs (dot/blot in plexiform layer where cells are oriented vertically; flame-shaped/feathery border in NFL where cells are oriented horizontally)

Roth spot: white-centered hemorrhage

DDx: ischemia (anemia, anoxia, carbon monoxide poisoning), elevated venous pressure (birth trauma, shaken baby syndrome, intracranial hemorrhage), capillary fragility (hypertension, diabetes), infection (bacterial endocarditis, HIV), leukemia, collagen vascular disease

Neovascularization: growth of new vessels on vitreous side of ILM; new vessels grow along posterior hyaloid

Vascular tortuosity: may be congenital (arterial and venous) or acquired (venous)

DDx: hypertension, high venous pressure (occlusion), papilledema, high viscosity, AV fistula; associated with fetal alcohol syndrome, Peter's anomaly, optic nerve hypoplasia

Retinal Vasculitis

Involvement of retinal arterioles (arteritis), veins (phlebitis), or both (periphlebitis)

Findings: sheathing of vessels, hemorrhage

DDx: temporal arteritis, polyarteritis nodosa, lupus, Behçet's disease, inflammatory bowel syndrome, multiple sclerosis, pars planitis, Wegener's granulomatosis, Eales disease, sarcoidosis, syphilis, toxoplasmosis, viral retinitis (HSV, HZV), IV drug abuse, Lyme disease, tuberculosis

Cystoid Macular Edema (CME)

Intraretinal edema in honeycomb-like spaces; flower-petal pattern due to Henle's layer

Etiology: mnemonic DEPRIVEN

Diabetes
Epinephrine
Pars planitis
RP
Irvine-Gass syndrome
Venous occlusion
E_2 prostaglandin
Nicotinic acid maculopathy (does not leak)
Others: XRT, parafoveal telangiectasia, CNV (rare), juvenile retinoschisis (does not leak), Goldmann-Favre (does not leak), latanoprost (Xalatan), vitreous wick

Pathophysiology: abnormal perifoveal retinal capillary permeability; initial fluid accumulation may be within Müller's cells (rather than in spaces of outer plexiform and inner nuclear layers)

Findings: CME, optic nerve swelling, vitreous cell (Figure 11-53)

FA: multiple small focal fluorescein leaks early; late pooling of dye in cystoid spaces; classically, flower-petal ('petalloid') pattern; staining of optic nerve (Figure 11-54)

OCT: cystic intraretinal spaces (Figure 11-55)

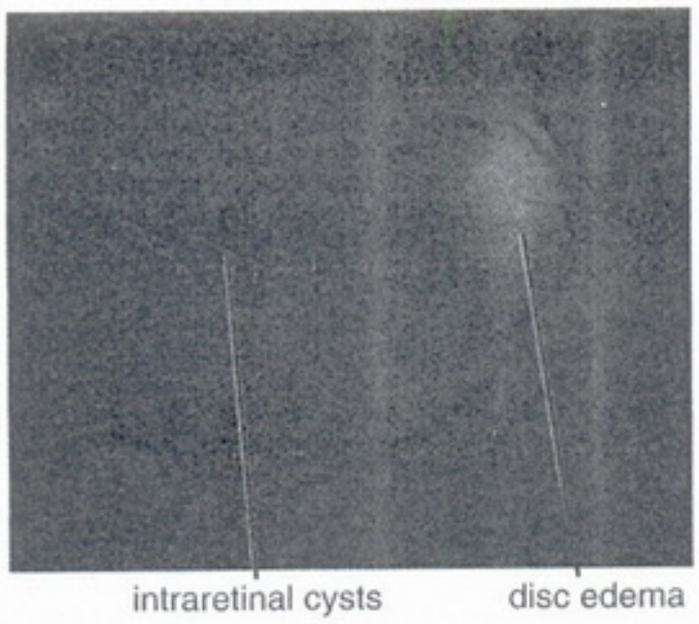


Figure 11-53. Cystoid macular edema with decreased foveal reflex, cystic changes in fovea, and intraretinal hemorrhages. (From Kaiser PK, Friedman NJ, Pineda R II: Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd edn. Philadelphia, Saunders, 2004.)

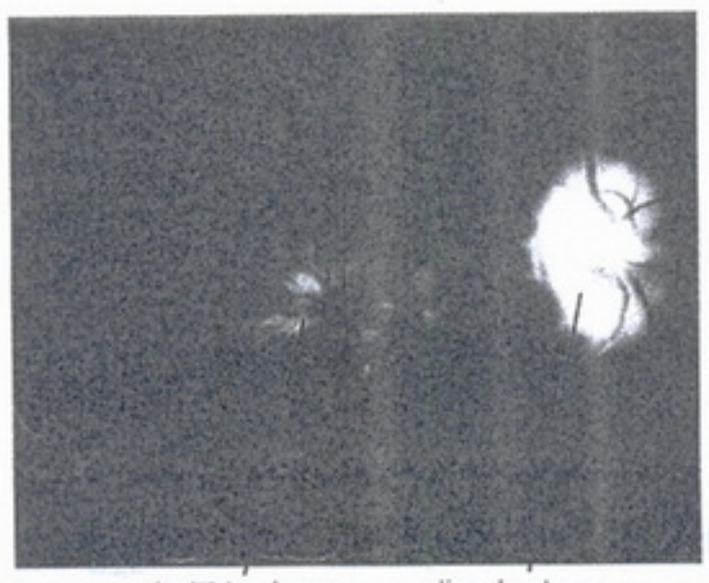


Figure 11-54. Fluorescein angiogram of same patient as in Figure 11-53, demonstrating characteristic petalloid appearance with optic nerve leakage. (From Kaiser PK, Friedman NJ, Pineda R II: Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd edn. Philadelphia, Saunders, 2004.)

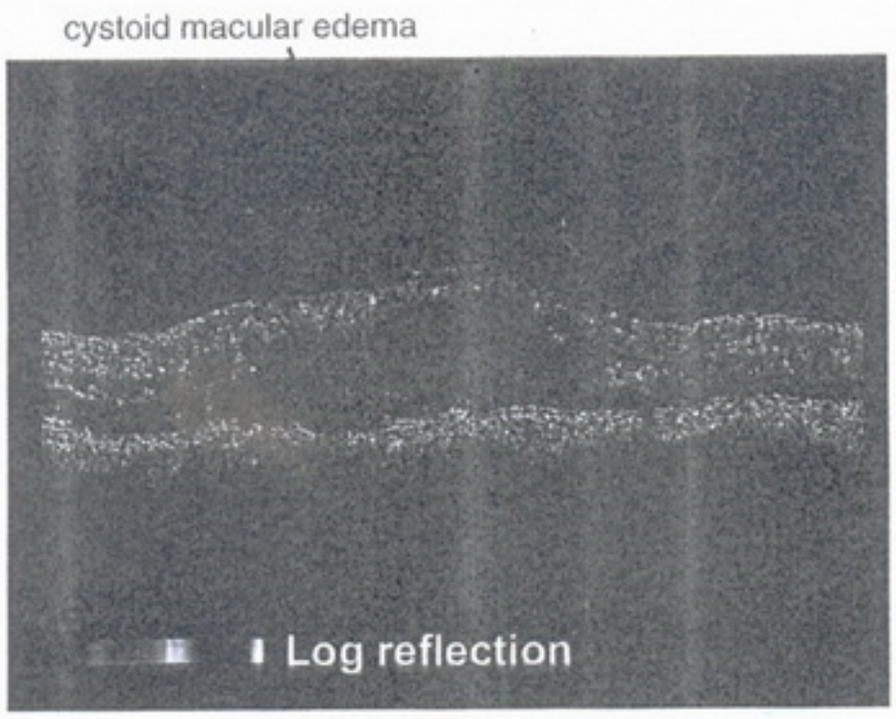


Figure 11-55. Optical coherence tomography of cystoid macular edema, demonstrating intraretinal cystoid spaces and dome-shaped configuration of fovea. (From Kaiser PK, Friedman NJ, Pineda R II: Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd edn. Philadelphia, Saunders, 2004.)

DDx of cystic macular changes (looks like CME clinically, but no fluorescein filling of cysts):

1. Juvenile retinoschisis
2. Goldmann-Favre
3. Some types of RP
4. Nicotinic acid maculopathy

Treatment: depends on etiology; focal laser treatment, topical steroids and NSAID, oral Diamox, sub-Tenon's or intravitreal steroid injection

Congenital Retinal Telangiectasia/Coats' Disease (Leber's Miliary Aneurysms)

(See Ch. 5, Pediatrics/Strabismus.)

Parafoveal/Juxtafoveal Telangiectasia (PFT, JXT)

Microaneurysmal and saccular dilation of parafoveal vessels

Classification:

Type 1: unilateral, male > female (10:1); onset during middle age; in spectrum of Coats' disease
- **TYPE 1A:** congenital; confined to temporal half of fovea; macular edema and exudation (lipid)
- **TYPE 1B:** idiopathic; capillary telangiectasia confined to 1 clock hour at edge of FAZ; minimal leakage on FA; occasional hard exudates; vision usually better than 20/25; can be treated with laser

Type 2A (most common): bilateral, acquired; male = female; 5th–6th decade of life; symmetric, involving area <1 DD; minimal macular edema; occasionally, superficial glistening white dots (Singerman's spots); right-angle retinal venules dive deep into choroid; eventual develop RPE hyperplasia; occasionally, yellow lesion measuring ⅓ DD centered on FAZ (pseudovitelliform macular degeneration); may develop macular edema that is due to ischemia (not amenable to laser treatment); ⅓ abnormal glucose tolerance test
- **FA:** parafoveal capillary leakage; risk of CNV

Type 3: bilateral, idiopathic; male = female; capillary occlusion predominates
- **TYPE 3A:** occlusive idiopathic
- **TYPE 3B:** occlusive idiopathic; associated with central nervous system vasculopathy

Structural abnormalities in types 2 and 3 are similar to diabetic microangiopathy (but no risk of NVE)

DDx: diabetes, vein occlusion, radiation retinopathy, Coats' disease, Eales' disease, Best's disease, sickle cell, Irvine-Gass syndrome, ocular ischemia

Complications: macular edema, exudates, CNV, intraretinal neovascularization, retinal–retinal anastamosis

Retinal Arterial Macroaneurysm (RAM)

May bleed, then autoinfarcts

Usually, elderly females; most common along temporal arcades; 10% bilateral

Mechanism: arteriosclerosis (fibrosis, thinning, decreased elasticity of vessel wall), hypertension (increased pressure on thin wall)

Findings: blood in every retinal layer, lipid exudate, artery occlusion downstream (especially following laser treatment), CME (Figure 11-56)

DDx of blood in every retinal layer (subretinal, intraretinal, and preretinal)**:** macroaneurysm, trauma, sickle cell retinopathy, choroidal melanoma, vein occlusion (rare), CNV (rare)

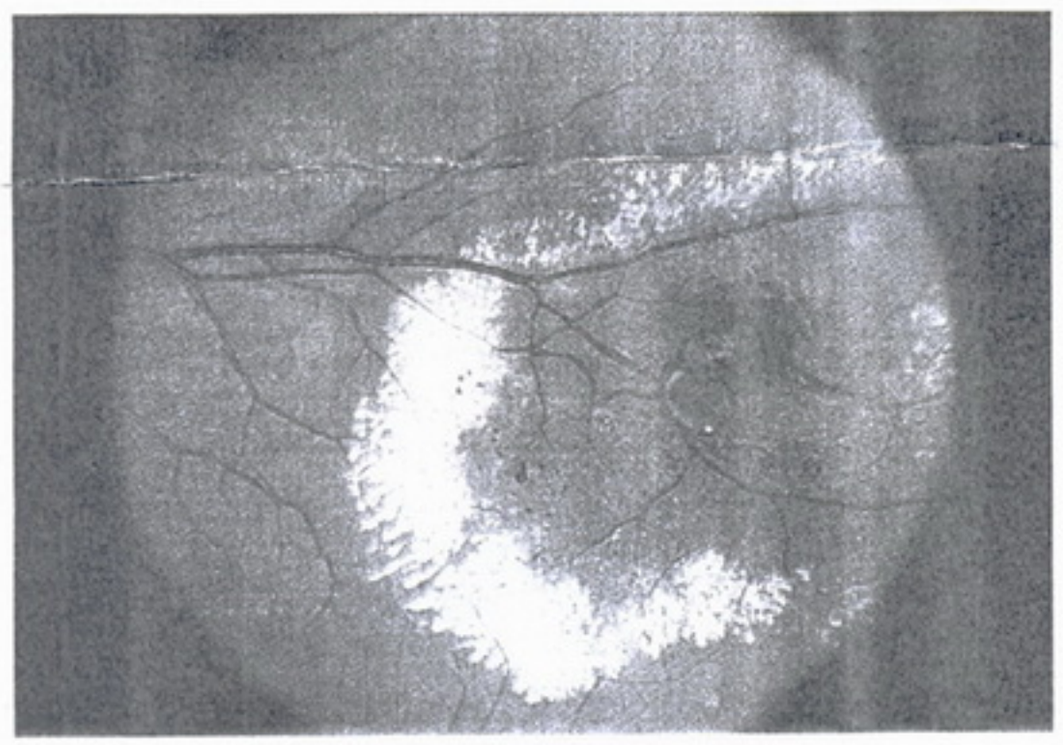
Pathology: overall thickening of vessel wall with hypertrophy of muscularis

Treatment: observation; consider focal laser (risk of hemorrhage)

Hypertensive Retinopathy

Focal or generalized vasoconstriction, breakdown of blood–retinal barrier with subsequent hemorrhage and exudate

Associated with microaneurysms or macroaneurysms



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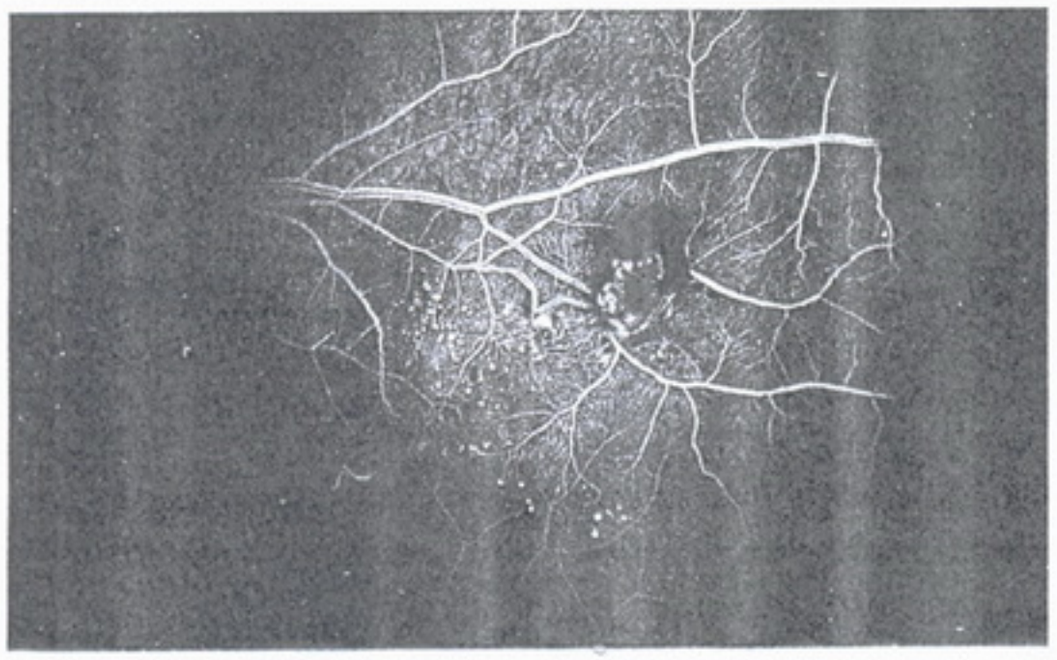

B

Figure 11-56. Macroaneurysm with surrounding dilated and telangiectatic capillary bed:. **A,** fundus photograph;, **B,** FA. (Courtesy Susan Fowell, MD. From Mittra RA, Mieler WF, Pollack JS: Retinal arterial macroaneurysms. In: Yanoff M, Duker JS (eds) Ophthalmology. London, Mosby, 1999.)

Classification systems:

Keith-Wagener-Barker Classification

GROUP I: minimal constriction and tortuosity of arterioles

GROUP II: Moderate constriction of arterioles; focal narrowing and arteriovenous nicking

GROUP III: Group II plus cotton wool spots, hemorrhages, and exudates

GROUP IV: Group III plus optic disc edema

Scheie Classification

GROUP 0: no visible changes

GROUP I: Diffuse arteriolar narrowing

GROUP II: Pronounced arteriolar narrowing and focal constriction

GROUP III: Grade II plus retinal hemorrhages

GROUP IV: Grade III plus optic disc edema

Findings:

Retinopathy: AV nicking, 'copper or silver wire' arterial changes, hemorrhages, exudates, cotton wool spots

Choroidopathy: fibrinoid necrosis of choroidal arterioles; may have Elschnig's spots (zone of nonperfusion of choriocapillaris; pale white or red patches of RPE), Siegrist streak (reactive RPE hyperplasia along sclerosed choroidal vessel), and exudative RD; due to acute hypertensive episode (pre-eclampsia, eclampsia, or pheochromocytoma); FA shows early hypoperfusion and late staining

Optic neuropathy: florid disc edema with macular exudate, linear flame hemorrhages

Pathology: thickening of arteriolar walls leads to nicking of venules; endothelial hyperplasia

Complications: retinal vein occlusion, retinal macroaneurysm, nonarteritic AION, ocular motor nerve palsies, worsening of diabetic retinopathy

Diabetic Retinopathy (DR)

Leading cause of new blindness in United States, adults aged 20–74 years

Classification:

Background or nonproliferative (BDR, NPDR): hemorrhages, exudates, cotton wool spots, microaneurysms (MA), intraretinal microvascular abnormalities (IRMA), venous beading (Figure 11-57)

Severe NPDR ('4-2-1 rule') (15% progress to PDR in 1 year):

Defined as any one of the following:

4 quadrants of hemorrhages/MAs

2 quadrants of venous beading

1 quadrant of IRMA (Figure 11-58)

Very severe NPDR (50% progress to PDR in 1 year):

Defined as 2 or more of the above

Proliferative (PDR): NV of disc or elsewhere (Figure 11-59)

High-risk proliferative (HR-PDR):

Defined as any one of the following:

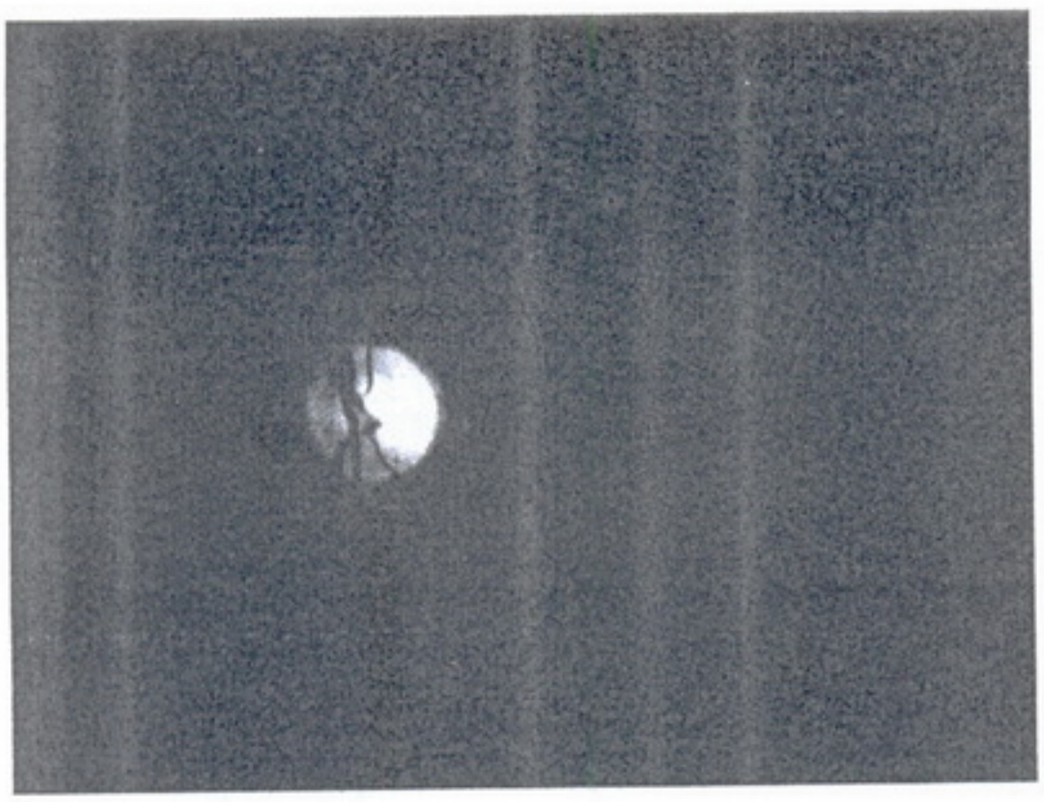

Figure 11-57. Nonproliferative diabetic retinopathy.

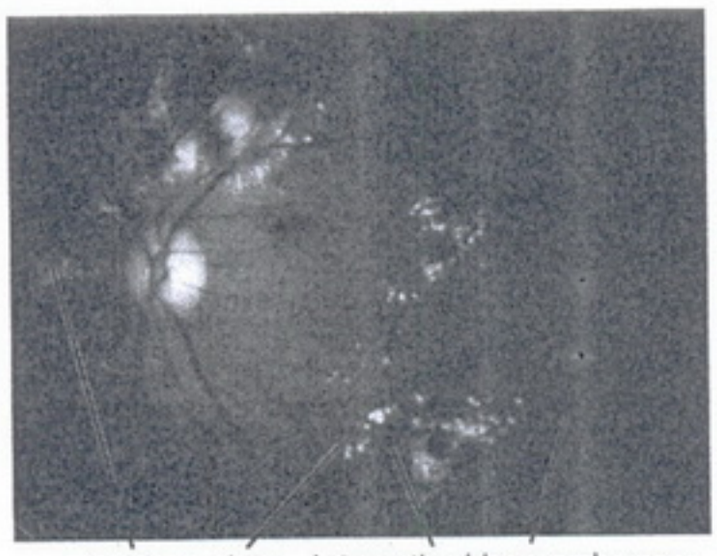

Figure 11-58. Severe nonproliferative diabetic retinopathy with extensive hemorrhages, microaneurysms, and exudates. (From Kaiser PK, Friedman NJ, Pineda R II: Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd edn. Philadelphia, Saunders, 2004.)

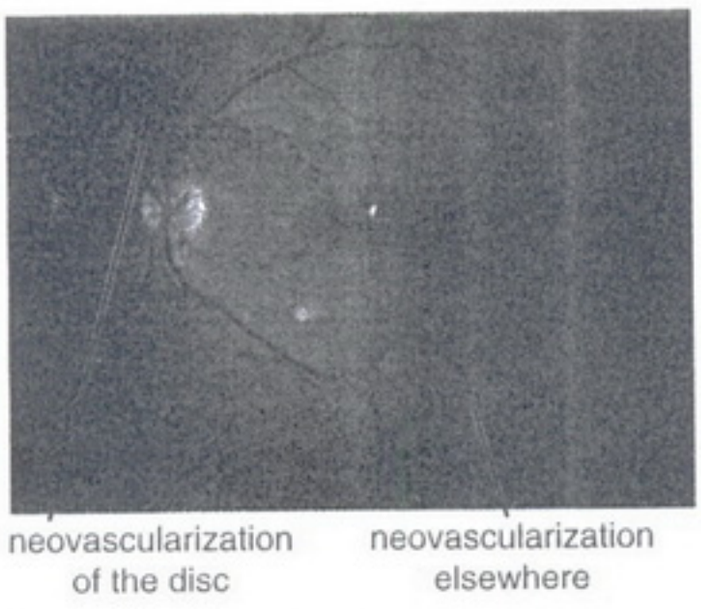

Figure 11-59. Proliferative diabetic retinopathy demonstrating florid neovascularization of the disc and elsewhere. (From Kaiser PK, Friedman NJ, Pineda R II: Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd edn. Philadelphia, Saunders, 2004.)

1. NVD ≥ ¼ to ⅓ disc area
2. Any NVD with vitreous hemorrhage
3. NVE ≥ ½ disc area with vitreous hemorrhage

Epidemiology:

Type 1 DM:

AT DIAGNOSIS: no BDR
AT 5 YEARS: 25% BDR, PDR rare
AT 20 YEARS: 98% BDR, 60% PDR, 30% CSME

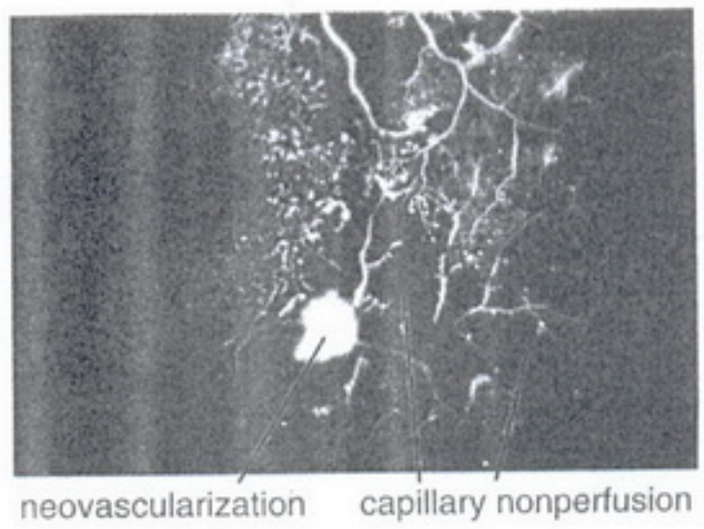

Figure 11-60. Fluorescein angiogram of a patient with proliferative diabetic retinopathy, showing extensive capillary nonperfusion, neovascularization elsewhere, and vascular leakage. (From Kaiser PK, Friedman NJ, Pineda R II: Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd edn. Philadelphia, Saunders, 2004.)

Type 2 IDDM:

AT DIAGNOSIS: 30% BDR
AT 5 YEARS: 40% BDR, 2% PDR
AT 20 YEARS: 90% BDR, 25% PDR, 40% CSME

Type 2 NIDDM:

AT DIAGNOSIS: 20% BDR
AT 5 YEARS: 30% BDR, 2% PDR
AT 20 YEARS: 50% BDR, 10% PDR, 20% CSME

Findings: cotton wool spots, lipid exudates (may appear as circinate exudate [ring of hard exudate surrounding leaky focus] or macular star [pattern reflects radial orientation of Henle's fibers]), hemorrhages (blot [outer plexiform layer], flame [tracks along NFL]), microaneurysms, IRMA (intraretinal microvascular abnormalities; shunts [arteriole to venule]), venous beading and loops, neovascularization (disc [NVD], elsewhere in retina [NVE], iris [NVI]) (Figure 11-60)

Clinically significant macular edema (CSME)

definition: one of the following:

1. Thickening within 500 µm of the foveal avascular zone (FAZ)
2. Hard exudate within 500 µm of the FAZ with associated thickening of adjacent retina
3. Zone of retinal thickening 1 disk *area* in size, any part of which is within 1 disk *diameter* of the foveal center

Asymmetric diabetic retinopathy is usually due to carotid disease (on either side)

Main cause of vision loss in NPDR: macular edema or ischemia

Main causes of vision loss in PDR: tractional RD (TRD), neovascular glaucoma (NVG), vitreous hemorrhage (VH)

Other sequelae:

Diabetic cataract: aldose reductase pathway converts glucose into sorbitol and fructose; causes osmotic effect; aldose reductase also converts galactose into galactitol (which causes cataracts in galactosemia)