AMD: A Relatively Manageable Disease

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1. **Introduction**
    a. AMD is the leading cause of blindness in the developed world in persons >50yo & 3rd leading cause of blindness worldwide
    b. Characterized by pathologic alterations of the outer retina, RPE, Bruch's membrane and choriocapillaris complex including drusen, RPE abnormalities, geographic atrophy, and choroidal neovascularization (CNV).
    c. Approximately 80% nonexudative form & 20% exudative form, however, neovascularization accounts for 90% of severe central vision loss from AMD
    d. Geographic atrophy (GA) affects 5-8 million people worldwide (~20% of people with AMD), and almost 1.5 million in US
    e. Due to a growing proportion of older adults in the United States population, the prevalence of AMD is expected to increase to 22 million by the year 2050
        i. Number of cases of advanced AMD is expected to increase from 1.7 million in 2010 to 3.8 million in 2050
2. **AMD staging/classifications & definitions**
    a. No AMD
    b. Early nonexudative (AREDS category 2)
    c. Intermediate non-exudative (AREDS category 3)
        i. Defined as either 1) extensive medium sized drusen (63–124 µm in diameter), 2) at least one large sized druse (≥125 µm in diameter), or 3) non-central geographic atrophy
        ii. Risk for conversion to advanced AMD is approximately 18% within 5 years
            1. Risk increases to 26% if multiple large-sized drusen are present in both eyes
        iii. Among patients that already have neovascular AMD in the fellow eye, the risk for neovascularization in the eye with non-exudative AMD is very high, approximately 42% at five years
    d. Advanced AMD- central GA and/or neovascularization
    e. Neovascular AMD
        i. Proliferation of new and abnormal blood vessels, usually originating from the choriocapillaris, that invade the subRPE and/or subretinal space through a disrupted Bruch's membrane
        ii. Lack a proper inner blood retina-barrier and may therefore leak out fluid and/or blood
        iii. May be exudative or non-exudative
            1. Exudative neovascular membrane- defined as the presence of fluid or blood (or IVFA leakage) in combination with the presence of a neovascular complex found with multi-modal imaging
        iv. Prompt treatment of exudative AMD is associated with better long-term visual outcomes, and many cases of severe loss can actually be prevented through early detection and referral

v. Types of CNV
    1. Type 1 (occult)- Sub-RPE neovascularization
        a. Most common type of CNV present in neovascular AMD and are found in 80% of cases
        b. IVFA: occult leakage patterns (late leakage of an undetermined source)
        c. OCT appearance: fibrovascular PED
        d. OCTA appearance: ill-defined network of vessels and are usually larger membranes with mature feeder vessels
        e. May poorly and incompletely respond to anti-VEGF therapy, and have a worse visual prognosis compared to type 2 CNV
    2. Type 2 (classic)- Sub-retinal neovascularization
        a. IVFA: classic leakage patterns of well-demarcated hyperfluorescence
        b. OCT appearance: subretinal hypereflective mass resting on top of the RPE and frequently has overlying intraretinal fluid
        c. OCTA appearance: well-defined complexes
    3. Mixed type 1 & type 2- partially located beneath the RPE and in the subretinal space
        a. May be subclassified as predominantly classic or minimally classic
    4. Type 3- Retinal angiomatous proliferation (RAP), characterized by deep intraretinal neovascularization that often anastomoses with a sub-RPE neovascular membrane

f. Geographic atrophy (GA)
    i. Defining lesion of atrophic AMD
    ii. Atrophy of the RPE, photoreceptors, and choriocapillaris (in the absence of neovascularization)
        1. "Atrophy" refers to irreversible tissue loss of attenuation
    iii. OCT definition: Complete RPE and Outer Retinal Atrophy (cRORA) = Zone of RPE loss/attenuation & overlying PR degeneration ≥ 250μm in diameter, with homogenous choroidal hyper-transmission
    iv. Approximately 2.5 yrs from first appearance to foveal involvement
    v. In eyes with incident non-central GA, 4-year risk of central involvement was 57%
    vi. Extrafoveal, multifocal & bilateral progress quicker

3. Multimodal imaging technologies

a. Color fundus photography (CFP)
    i. CFP or ophthalmoscopy superior for detecting hemorrhage
    ii. Low sensitivity in detecting early GA and not an ideal way track its enlargement over time
b. Structural OCT
    i. generally considered standard of care in the evaluation of AMD
    ii. Can greatly facilitate the clinician's ability to detect the earliest neovascular and exudative AMD possible
    iii. Useful in detecting new or recurrent neovascular disease activity and guiding therapy
    iv. Important when reviewing OCT data to scan through the entire cube looking for fluid and RPE elevation, rather than just one central raster B-scan
c. Enhanced depth imaging OCT (EDI-OCT) & swept source OCT
d. OCT Angiography (OCTA)
    i. Provides high resolution, detailed images of CNV complexes that allows the clinician to assess their shapes and morphologic patterns
    ii. Allows the clinician to directly visualize the choroidal neovascular membranes themselves, not just the secondary effects such as fluid
    iii. Only imaging modality that can directly image high risk non-exudative neovascular membranes

iv. Can be of great value in differentiating vascularized from non-vascularized PEDs
v. when performed periodically in eyes clinically graded as having intermediate stage non-exudative AMD it may enhance detection of early neovascularization

e. Fundus autofluorescence (FAF)
    i. One of the primary methods used to detect, monitor, and quantify GA lesions
    ii. More sensitive for GA detection than CFP
    iii. GA is dark (hypo-autofluorescent) and well demarcated on FAF
f. Intravenous fluorescein angiography (IVFA) & indocyanine green angiography (ICG)
    i. Invasive, dye injection required
    ii. Can add value in detecting and classifying neovascular membranes as well as determination the degree of exudative activity
    iii. ICG especially important in the diagnosis of polypoidal choroidal vasculopathy

4. Utility of multimodal imaging in AMD

a. Identify eyes at high risk for progression to advanced disease
b. Drusen subtype classification
    i. Hard drusen- most benign
    ii. Soft drusen
        1. OCT appearance: round, mound-shaped elevations of the RPE from Bruch's membrane that are filled internally with drusenoid material that is homogenous (uniformly reflective) and relatively dark (hypo-reflective).
    iii. Subretinal drusenoid deposits (reticular pseudodrusen)
        1. OCT appearance: nodular, hyper-reflective deposits that rest on the anterior surface of the RPE
        2. Eyes with a combination of both soft drusen and subretinal drusenoid deposits, are at highest risk for conversion to neovascular AMD
c. Earlier detection of neovascularization
    i. Non-exudative neovascular membranes
        1. Characterized by the presence of a well-defined neovascular complex via OCTA in a treatment naïve eye that has no signs of exudation via ophthalmoscopy, such as exudates or hemorrhages, and no fluid on structural OCT imaging
        2. Present in approx. 10% of eyes with intermediate AMD, and that have already become exudative in the fellow eye
        3. Pose a greater risk for future exudative conversion
d. Earlier detection of treatable exudation
    i. Presence of exudation is the main factor in determining whether anti-VEGF therapy is indicated
e. Morphologically classify neovascular membranes (size and shape)
f. Assess treatment response to anti-VEGF therapy and need for retreatment in neovascular/exudative AMD
g. Predict future GA development
    i. High risk OCT biomarkers for future GA development
        1. Nascent GA (AKA Incomplete RPE and Outer Retinal Atrophy (iRORA)= impending GA, subsidence of the OPL & INL and a hypo-reflective wedge, signal hypertransmission into the choroid with corresponding attenuation/disruption of the RPE
        2. Subsidence of inner nuclear layer (INL) and outer plexiform layer (OPL)- appear to sink toward the RPE in an area of outer retina loss
        3. External limiting membrane (ELM) descent
        4. ELM and/or photoreceptor ellipsoid zone (EZ) loss

5. Hyporeflective wedges- triangular, hyporeflective regions with the base adjacent to Bruch's membrane and the apex extending internally to the inner aspect of the OPL
6. Intraretinal hyperreflective foci- characterized by discrete, punctate lesions in a single or clustered distribution that are of equal or greater reflectivity than that of the RPE. Often observed overlying drusen.
7. Drusen with hyporeflective cores- probably correspond to reflectile drusen
8. Refractile drusen & hyperreflective crystalline deposits (sub-RPE plaques)- hyperreflective linear lesions usually located within the sub-RPE space and correspond to highly reflective lesions
9. Drusenoid pigment epithelial detachment (PED) collapse

h. Predict progression of GA
    i. OCT features predicting GA progression
        1. RPE/Bruch's membrane complex splitting
        2. OCTA-impairment of choriocapillaris flow is present immediately surrounding GA lesions and the greater the degree of greater flow impairment = faster GA enlargement
    ii. FAF features predicting GA progression
        1. Prognostic value of GA Phenotypic FAF patterns based on the degree of surrounding hyper-autofluorescence
        2. No abnormality (0.38 mm2/yr)
            a. Focal -(0.81 mm2/yr) single or individual small spots of ↑ FAF adjacent directly to margin of GA
            b. Banded (1.81 mm2/yr)- ↑ FAF adjacent directly to margin of GA in an almost continuous ring shape
            c. Diffuse (1.77 mm2/yr)- ↑FAF at the margin and elsewhere
            d. Diffuse Trickling (3.02 mm2/yr)- diffuse pattern + high intensity at margin that seeping towards the periphery

5. Features suggestive of neovascular or exudative AMD

a. Fluid at any level
    i. OCT is superior to ophthalmoscopy in the detection of fluid
    ii. Can be intraretinal, subretinal (serous macular retinal detachment), or subRPE (serous PED)
    iii. With OCT imaging fluid is hyporeflective or dark
b. Hemorrhage (subretinal, subRPE, intraretinal)
    i. Ophthalmoscopy and CFP are superior to OCT in hemorrhage detection
    ii. Must be large to be detected by OCT
    iii. On OCT blood is hyperreflective and may block light transmission posterior to it
c. RPE detachment (PED)- separation of the RPE from Bruch's membrane
    i. Fibrovascular
        1. Associated with exudative and/or neovascular AMD
        2. Result from a type 1 neovascularization complex
        3. Clinically appearance- mostly opaque area of RPE elevation often with an irregular surface contour that may contain a mix of blood, fibrotic tissue, and fluid
        4. OCT appearance- variable (nonhomogenous or non-uniform) internal reflectivity which may include horizontally oriented multilaminate hyperreflective sheets; elevation of the RPE is often irregular in contour or the PED is multilobulated
    ii. Hemorrhagic
        1. Associated with exudative and/or neovascular AMD

2. Clinical appearance- round or oval-shaped dark-green colored elevations of the RPE with discrete borders

iii. Serous
1. Result from serous fluid accumulation between the RPE and Bruch's membrane
2. Clinical appearance- well-demarcated, dome-shaped, yellowish-orange elevations of the RPE
3. OCT appearance- a smooth dome-shaped elevation of the RPE and are internally dark; Bruch's membrane is often visible at the base of the PED as a thin hyperreflective line
4. While serous PEDs may be associated with nonexudative AMD, they are more often a manifestation of exudative AMD and should greatly raise suspicion for the presence of neovascularization until proven otherwise
5. Often requires evaluation with IVFA to look for treatable neovascular source

iv. Drusenoid
1. Associated with intermediate stage non-exudative AMD and formed by coalesced soft drusen
2. Clinically appearance- yellow–white areas of RPE elevation with possibly scalloped borders and intralesional spots of hyperpigmentation.
3. OCT appearance: round elevations of the RPE filled with homogeneous and uniformly mildly hyperreflective drusenoid material

d. Grey-green subretinal/subRPE thickening (fundoscopy)
i. Subretinal/sub-RPE fibrovascular proliferation

e. Exudate (OCT or fundoscopy)
i. May be intraretinal or subretinal
ii. Via OCT it is hyperreflective and often associated with posterior shadowing
iii. Exudate alone does not indicate that a neovascular membrane is currently active and must be accompanied by fluid to be considered active

f. Fibrovascular disciform scar & RPE tear

6. Other diagnostic technologies

a. Macular pigment optical density (MPOD)
i. Low macular pigment optical density is a risk factor for AMD
ii. Can ↑ MPOD measure with carotenoid supplementation

b. AMD home monitoring systems
i. Notal vision Foresee home preferential hyperacuity perimeter
1. Need for home monitoring between routine office visits to detect early conversion from intermediate to neovascular AMD; Early detection and prompt treatment of neo improves the visual outcomes
2. FDA approved home preferential hyperacuity perimeter (PHP) that augments in-office exams
3. Prescription only for patients with intermediate nonexudative AMD in at least one eye and BCVA 20/60 or better
4. Each test result is compared to a normative database and the pt's personal baseline; Clinician is alerted if significant change
5. AREDS 2 HOME Study
a. Foresee Home identified 64% of converters
b. Functional vision (≥20/40) at conversion was maintained in 94% of patients using Foresee Home vs 62% without
6. ALOFT Study (Analysis of the Long-term visual Outcomes of ForeseeHome Remote Telemonitoring)
a. Large retrospective review of clinical data from 2010 to 2020 (3,334 eyes)
b. 52% of conversions detected by system alert

c. Median acuity measures of converters at: 1) Baseline 20/30 2) Initial conversion 20/39 3) Final follow-up 20/32
d. 82% of eyes that converted had functional vision (≥20/40) at final follow up

iii. Mobile applications

7. Management

a. Nutritional supplementation
   i. Consider AREDS 2 beginning at intermediate nonexudative stage
      1. AREDS-2 Supplement Formula
         a. Zinc oxide (80mg or 25mg)
         b. Cupric oxide (2mg)
         c. Vitamin C (500 mg)
         d. Vitamin E (400 IU)
         e. Lutein (10 mg)
         f. Zeaxanthin (2 mg)
   ii. AREDS decreases conversion to neovascular/exudative AMD but provides little benefit on GA development & progression

b. Photobiomodulation
   i. Valeda Light Delivery System- First FDA approved therapy for Dry AMD using Photobiomodulation in Nov 4th 2024
   ii. LIGHTSITE III 24-month study
      1. ~200 patients across multiple completed and enrolled trials
      2. 9 sessions over 3-5 weeks, repeated every 4 months for a total of 2 years
      3. Met the predetermined primary efficacy BCVA endpoint at Month 21 (mean letter difference of 3.8 letters, p = 0.0036) with a statistically significant difference between the PBM group versus Sham
      4. A mean letter difference of 4.3 letters (p = 0.0024) was maintained at Month 24.
      5. Within group analysis showed improved BCVA with a mean > 5 letter gain in PBM eyes from:
         a. Month 13 (LS mean 6.0 letters) (p = < 0.0001)
         b. Month 21 (LS mean 6.2 letters) (p < 0.0001)
         c. Month 24 (LS mean 5.6 letters) (p < 0.0001)
   iii. Post Hoc Analysis on Treatment Benefit on Incident GA
   iv. Incidence of New GA:
      1. Incident GA Significantly Higher in the Sham Group at Month 24, p = 0.007
      2. Sham group: 12/50 (24.0%)
      3. PBM group: 6/87 (6.8 %)

c. Anti-VEGF Updates
   i. Faricimab
      1. Anti-VEGF agent FDA approved in Jan 2022
      2. Dual mechanism of action: Not only a VEGF-A inhibitor but also inhibits angiopoietin-2
      3. Phase III TENAYA and LUCERNE clinical trials
      4. Through week 48, faricimab up to Q16W offered durable vision gains and meaningful anatomic improvements that were comparable with aflibercept Q8W
   ii. High dose aflibercept
      1. 8mg dose vs standard dose of 2mg
      2. Phase 3 studies Pulsar and Photon
         a. Pulsar: At week 48, 83% of aflibercept 8mg patients maintained ≥12-week treatment intervals
         b. Similar safety profile to aflibercept 2mg

iii. Port delivery system- voluntarily recalled. No new devices being implanted

d. Complement inhibition therapy for GA
    i. Treatment slows progression, does not halt GA enlargement
    ii. Administered via intravitreal injection monthly or every other month
        1. Pegcetocoplan
            a. C3 Inhibitor- FDA approved Feb 2023
            b. Phase 3 RCTs DERBY & OAKS, GALE extension crossover
            c. Combined data: 19% reduction in lesion growth with monthly injections compared to sham at 24 months for central GA
            d. Combined data: 26% reduction in lesion growth with monthly injections compared to sham at 24 months for noncentral GA
            e. In 24 month post hoc analysis of extrafoveal lesions only (≥250 µm away from foveal center), treated patients demonstrated:
                i. Preservation of 5.6 letters (more than one line on ETDRS chart) in BCVA compared to sham.
                ii. A 4.1 point benefit in vision-related quality-of-life outcomes, as measured by the NEI-VFQ-25.
            f. Adverse effects:
                i. Dose dependent increased risk for progression to neovascular AMD
                ii. Intraocular inflammation
                    1. OAKS & DERBY 24 months: 28 cases (0.24% per injection) with no occlusive vasculitis or retinitis reported
                    2. Real world data: 7/29/23 Apellis reports 7 cases of confirmed retinal vasculitis, 4 of which occlusive; estimated rate of occurrence 1 per 10,000 injections
                iii. Ischemic optic neuropathy: OAKS & DERBY 24 months: 7 cases in monthly tx arm (1.7%)
        2. Avacincaptad Pegol (ACP)
            a. C5 Inhibitor- FDA approved Aug 2023
            b. Phase 3 RCTs Gather 1 & Gather 2
                i. Key difference in study design compared to DERBY & OAKS: only extrafoveal GA within 1500 µm from the foveal center included, fellow eye CNV excluded
            c. Gather 1: 35.4% reduction with ACP 2 mg compared to sham in mean change from baseline in GA area over 12 months
            d. Gather 2: 17.7% reduction in mean GA growth over 12 months with ACP 2 mg compared to sham
            e. Post hoc analysis: 56% reduction in the risk of vision loss with ACP 2 mg compared to sham over the first 12 months of treatment for the combined GATHER1 and GATHER 2 data. No longer significant at 24 months.
            f. Adverse Events
                i. Neovascular/exudative AMD: 12 month Gather 1 9% tx vs 2.7%sham, 12 month gather 2 6.7% tx vs 4.1% sham
                ii. Intraocular inflammation: One case of mild self-resolving vitritis in Gather 1
                iii. Ischemic optic neuropathy: Single case of ION in the ACP 2mg group in GATHER 1 at 18 months

8. Case discussions

9. Conclusion

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