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The Role of Imaging in the Diagnosis and Monitoring of Wet AMD: Expert Insights

PART ONE OF TWO: INITIAL DIAGNOSIS

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The Role of Imaging in the Diagnosis and Monitoring of Wet AMD: Expert Insights

Part One of Two: Initial Diagnosis

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries.¹ The natural history of AMD is characterized by the progression from early disease, through the intermediate stage, and finally to the two advanced forms of AMD: dry AMD, also known as geographic atrophy, and neovascular or wet AMD.^{2,3}

Recent advances in retinal imaging technology have led to marked improvements in the diagnosis of wet AMD and the detection and quantification of markers of disease progression.⁴ Imaging in one form or another is now an important part of a retina specialist's everyday clinical practice.

This roundtable from ARVO 2019 gathered a panel of leading retina specialists to discuss the current use of imaging in the management of wet AMD, including the different imaging modalities currently available and their impact on diagnosis, and to provide insights into the role of imaging for clinical decision-making. Personal perspectives and clinical pearls were shared through the presentation of patient cases submitted by the retina specialists.

The resulting discussions will be published in two parts, with this, the first part, focusing on the use of imaging in the initial diagnosis of wet AMD.

The Importance of Early Detection

Rishi P. Singh, MD: Undiagnosed wet AMD can result in rapid deterioration in vision. Studies show that choroidal neovascularization (CNV) can grow at an estimated average rate of 10 $\mu\text{m}/\text{day}$,⁵ and a meta-analysis has demonstrated that in untreated wet AMD, VA can worsen by 3 lines at 12 months.⁶ The same study also demonstrated that wet AMD developed in the fellow eye in approximately 27% of patients within 4 years.⁶ This evidence speaks to the importance of early detection in wet AMD.

How do your patients with wet AMD present? Are they symptomatic at the time of initial presentation? Does it affect how you manage them if they're not symptomatic?

Jeffrey S. Heier, MD: The goal is, ideally, to catch these patients before they are symptomatic. We know that outcomes are associated with lesion size and baseline VA, so the earlier we can detect the disease, the better off the patients are.

Nancy M. Holekamp, MD: If I'm able to make a firm diagnosis of wet AMD, it doesn't matter to me if patients are symptomatic or asymptomatic, because if they're not currently symptomatic, they may be shortly without some form of intervention. However, it can be hard to convince people who are asymptomatic about the need for close monitoring.

Michael Singer, MD: In patients who are asymptomatic, I'll use imaging to help patients understand that their disease is serious, especially if they have hemorrhage so that they can actually see the bleeding. Sometimes patients are also more motivated if there is a family history of wet AMD or if a friend has had the disease.

Initial Patient Presentation

Dr. Singh: Do most patients come in to see you with a diagnosis of new onset wet AMD, or are they unaware that they have wet AMD when they first see you?

Dr. Heier: There's really two groups: those patients that are referred to me for wet AMD, who usually have been told their acute vision loss is due to wet AMD, and those who we've been following for AMD, whether with intermediate or high-risk drusen in one or both eyes, or for management in their fellow eye for neovascular disease. It's not uncommon to detect CNV in those patients, often before they're symptomatic, because we're following them regularly.

Dr. Holekamp: About 60% of my new patient referrals come from optometry and 40% from general ophthalmologists; most referrals already have a diagnosis of macular degeneration.

Dr. Singer: If patients are referred to me from another doctor, they generally have a basic understanding of the concept of wet AMD, but before we discuss next steps we have a much more in-depth conversation so they understand not only what the disease is, but also how long they will need to be under medical supervision for and how important it is that they stay motivated and committed to attending their clinic visits.

Dr. Singh: What is the time commitment for an initial office-based evaluation?

Dr. Singer: With all the tests we perform, it probably comes close to 2 hours.

Dr. Heier: Our time is usually 2 to 3 hours.

Dr. Holekamp: We prepare patients and tell them it will take at least 2 hours for a first evaluation in our office.

Fluid as a Component of Wet AMD Disease Activity

Dr. Singh: In both clinical studies and clinical practice, the presence of retinal fluid is used as a marker of disease activity in wet AMD.^{7,8} Retinal fluid detected with OCT includes intraretinal fluid, subretinal fluid, and subretinal pigment epithelium fluid.⁷⁻⁹ Considering these three different compartments of fluid, which, if any, are the most concerning to you as a clinician?

Dr. Singer: Intraretinal fluid is the most concerning to me. Studies show that intraretinal fluid seems to be much more of a prognostic indicator than the other fluids. Nevertheless, I take all fluid seriously in my initial clinical decision-making.

Dr. Heier: Similarly, I don't really differentiate between the different types of fluid initially. My initial management is always the same.

Dr. Holekamp: Any fluid I see at baseline receives the same consideration.

Current Imaging Strategies for Diagnosing Wet AMD

Dr. Singh: The imaging modalities used in evaluating and managing wet AMD can include color fundus photography (CFP), fluorescein angiography (FA), fundus autofluorescence (FAF), indocyanine green angiography (ICGA), OCT, and more recently, OCT angiography (OCT-A).⁴

CFP has been the historical standard for recording abnormalities in the fundus and is still used in clinical trials of AMD today.^{4,10} CFP is useful in finding landmarks, evaluating serous detachments of the neurosensory retina and retinal pigment epithelium, and determining the etiology of blocked fluorescence.¹⁰ FA is used to detect the presence of and determine the extent, type, size, and location of CNV, as well as monitor persistence or recurrence of CNV.^{4,10} FAF is generally used for the delineation and quantitation of areas of GA.⁴ ICGA allows for the visualization of choroidal circulation and is useful in differential diagnosis.¹⁰ OCT is an important modality for diagnosing and managing wet AMD and can be used to evaluate retinal fluid and measure central retinal thickness.¹⁰ OCT-A allows the detection of blood flow based on motion contrast and can be used for detailed characterization of neovascularization in wet AMD. Compared with conventional dye-based angiography, it is noninvasive.⁴

What are the initial imaging modalities you might use when diagnosing a new case of wet AMD?

Dr. Heier: All of our patients with AMD receive OCT. In addition, every patient with suspected or newly diagnosed wet AMD also has FA to avoid any confusion with other conditions such as small branch retinal vein occlusions or cystoid macular edema. We also perform OCT-A on most of our patients. We don't tend to use CFP as we don't think it is necessary; plus it would require using a separate piece of equipment.

Dr. Holekamp: On a typical wet AMD patient, we use CFP, OCT, and FA. With those three tests alone, I can definitively rule in or rule out wet AMD. It's very rare for me to perform ICGA at an initial visit, and since our OCT machine provides near infrared that shows any associated geographic atrophy, I don't think that FAF is needed if the focus is wet AMD and not advanced dry AMD. CFP does require the use of a different camera, but the images are great for patient education and motivation when they can compare images of their affected and unaffected eyes and see bleeding in their own retina.

Dr. Singer: We perform FA, CFP, and OCT in the vast majority of cases. I will only perform ICGA at an initial visit if I'm running into questions; sometimes it helps, but most of the time it's not of great value. By the time the patient has gone through the

initial three modalities, they have had enough testing and are probably fatigued.

Dr. Singh: We use CFP and OCT as standard. I use OCT rather than CFP for teaching purposes as I find that patients are easily able to see the difference between a normal OCT and an image from their affected eye. I don't use FAF in the initial phase of the evaluation unless I suspect central serous retinopathy. I don't tend to use FA on the initial visit as I prefer not to perform this sort of invasive and potentially allergy-provoking procedure in a satellite office setting.

Dr. Singh: When you perform FA, are you looking for a particular lesion type as a prognostic indicator during the initial visit?

Dr. Singer: Results from clinical trials report that smaller lesion sizes have a better prognosis,¹¹ so I like to catch lesions early when they are small, and the patient still has good vision. When a patient has a larger lesion that is not as obviously well-defined, I'm less optimistic about the long-term prognosis although it doesn't radically change my clinical approach.

Dr. Heier: We now see that patients with all types of different lesions (e.g. retinal angiomatous proliferation or polypoidal choroidal vasculopathy) can be successfully managed.

Dr. Singh: What does OCT-A add in terms of diagnostic benefit?

Dr. Heier: It can help when there's a question of whether you're actually dealing with a choroidal neovascular process; sometimes the FA shows hyperfluorescence, and it is difficult to determine if there is subtle leakage or staining. OCT-A can help to reveal if a neovascular complex is present, and the technique has the benefit of being noninvasive.

Case 1: Routine Imaging of a Patient Presenting With Likely Wet AMD

Nancy M. Holekamp, MD

Case overview:

- A 65-year-old white female presented with a BCVA of 20/50 in the right eye.
- Color fundus photography (CFP) revealed the presence of a very large peripapillary membrane with a substantial amount of hemorrhage and drusen in the temporal macula (Figure 1).
- OCT on presentation showed fluid encroaching on the fovea (Figure 2).
- Fluorescein angiography (FA) was also performed on presentation (Figure 3).



Figure 1. CFP at presentation.

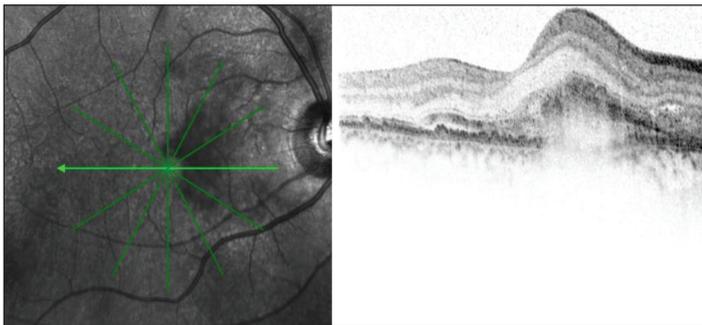


Figure 2. OCT at presentation.

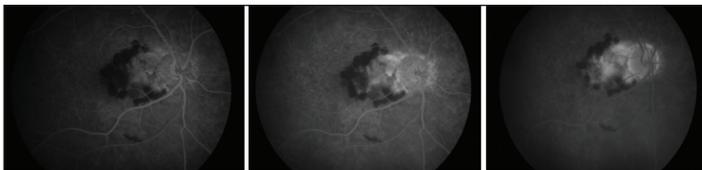


Figure 3. Intravenous FA at presentation. Left to right: early, mid, and late phases.

Discussion:

Nancy M. Holekamp, MD: The purpose of this case is to demonstrate the imaging that I would do routinely on a first-time patient who presents with possible wet age-related macular degeneration (AMD). CFP reveals that this patient has a large peripapillary choroidal neovascular membrane, which I believe is associated with macular degeneration because of the drusen that are visible in the temporal macula. Peripapillary lesions are always large by the time they become symptomatic, so here we're dealing with advanced disease.

I also routinely perform OCT and FA at baseline. With OCT images, it is important to have multiple sections through the entire macula in order to be able to clearly diagnose a problem.

Rishi P. Singh, MD: What other features do you look for in

the images that you take—for example fibrosis in the CFP or hyperreflective material on the OCT?

Dr. Holekamp: On more than 80% of my new wet AMD patients I get a CFP of the fellow eye to confirm bilateral drusen. I also think that detecting fibrosis is incredibly important to the overall visual prognosis as its presence is damaging to central vision. However, I'm a little less certain of what hyperreflective material on OCT tells us about the prognosis.

Jeffrey S. Heier, MD: I agree that this is a case where the color photograph really does help, as it's not clear on the OCT that there is a lot of fluid present.

Case 2: Subretinal Hemorrhage in Wet AMD

Jeffrey S. Heier, MD

Case overview:

- This patient had been followed for active wet age-related macular degeneration (AMD) in the right eye for 6 years; the patient also had dry AMD in the left eye.
- VA was 20/40 in the right eye (Figure 1) and 20/25 in the left eye (Figure 2).
- After another year of follow-up, the patient developed wet AMD in the left eye with no change to VA (Figure 3).
- Approximately 6 months later, the patient developed a new subretinal hemorrhage in the right eye (Figure 4), while the left eye remained dry.

Discussion:

Jeffrey S. Heier, MD: This patient with wet AMD was characteristic of those we see in our clinic. She had wet AMD in the right eye, with a lot of subretinal fluid and a low-lying fibrovascular pigment epithelial detachment but good VA of 20/40 maintained over 6 years. We were following the patient carefully when, over the course of 1 year, she also developed wet AMD in the fellow eye. The right eye then suddenly developed a new subretinal hemorrhage. However, her vision remained quite good as the hemorrhage was extrafoveal, with subretinal fluid occurring centrally. With continued intense monitoring and management over the course of 20 months, the hemorrhage has gradually resolved although trace intraretinal fluid remains (Figures 5 and 6).

Rishi P. Singh, MD: When you review these OCT scans what parameters do you look at?

Dr. Heier: Each one of my patients gets a volume scan. I don't

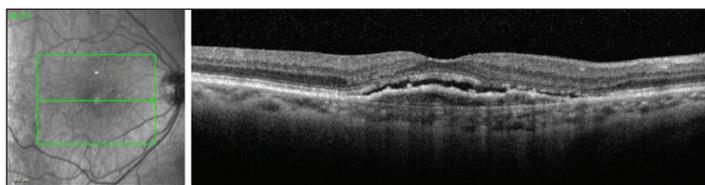


Figure 1. OCT after 6 years of follow-up for wet AMD (right eye).

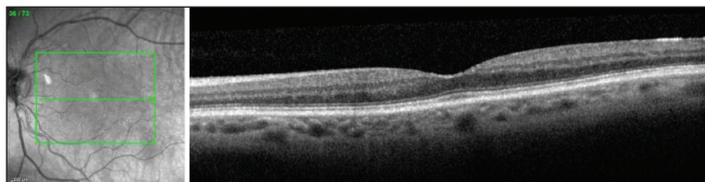


Figure 2. OCT after 6 years of follow-up for dry AMD (left eye).

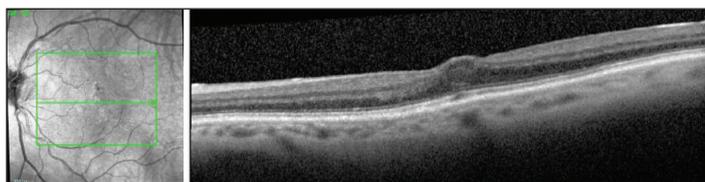


Figure 3. OCT after 7 years of follow-up; conversion to wet AMD (left eye).

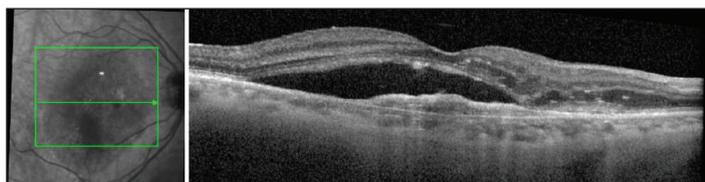


Figure 4. Development of subretinal hemorrhage in the right eye.

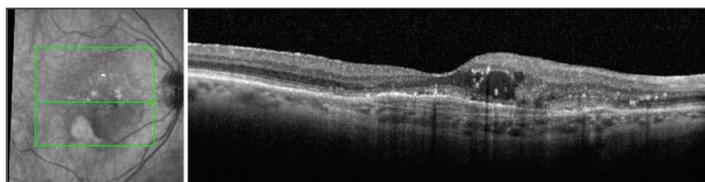


Figure 5. One month following the discovery of a subretinal hemorrhage in the right eye.

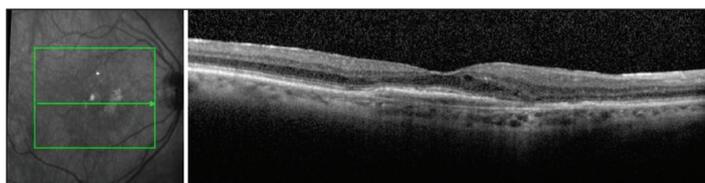


Figure 6. OCT taken 20 months after the discovery of a subretinal hemorrhage in the right eye.

look at the maps or at central retinal thickness. To me, the value of OCT is in providing a qualitative assessment of how the macula looks—a volume scan shows me not just central fluid but fluid throughout the macula.

Nancy M. Holekamp, MD: Was this patient symptomatic when she progressed to wet AMD in the left eye? You caught it very early.

Dr. Heier: What is interesting is the patient came into the clinic and initially reported no change in her vision, but when

I showed her the OCT showing the fluid in her left eye, she admitted that she had noticed a change but hadn't wanted to say anything. However, even if she had been asymptomatic, it is important to monitor closely for disease activity because the key is to catch it early. From clinical trials we know that at least 80% of patients can be prevented from losing 15 letters or more from baseline for at least 2 years with close follow-up and maintenance.^{12,13}

Case 3: CSCR Converting to Wet AMD

Michael Singer, MD

Case overview:

- A 64-year-old female diagnosed with chronic central serous chorioretinopathy (CSCR) in the left eye for 6 months.
- VA was 20/20 in the right eye and 20/25 in the left eye (Figures 1 and 2).

Discussion:

Michael Singer, MD: We had followed this case for 6 months and tried several noninvasive options. Since there was no response to these therapies, we decided to perform photodynamic therapy (PDT) in the patient's left eye. The patient called 2 days later stating that her vision had abruptly decreased, and her VA was found to be 20/40 in the left eye. Upon imaging we saw that the apparent CSCR had converted from a single hotspot to a leaking lesion, and the disease was now presenting more like wet age-related macular degeneration (AMD) (Figures 3 and 4).

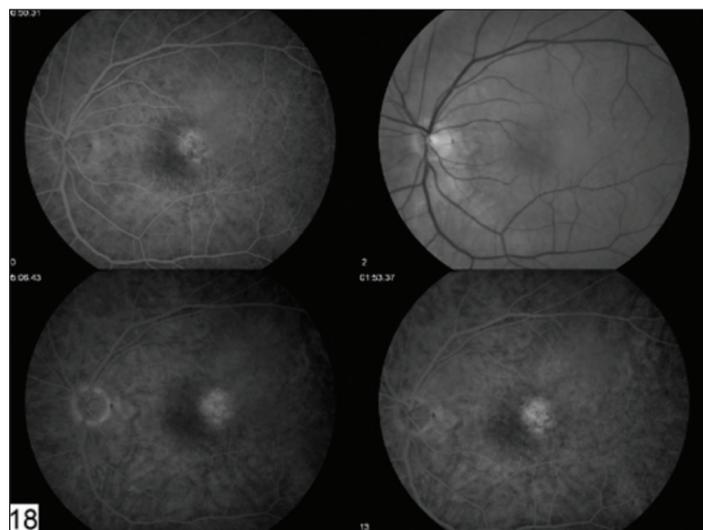


Figure 1. Fundus autofluorescence at presentation.

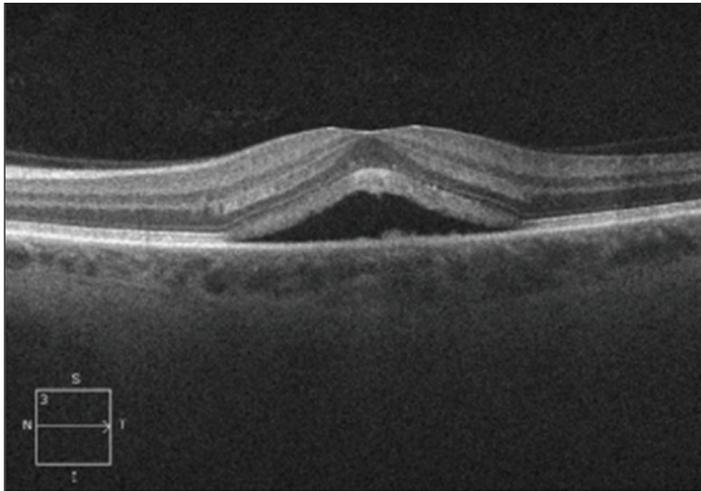


Figure 2. OCT at presentation.

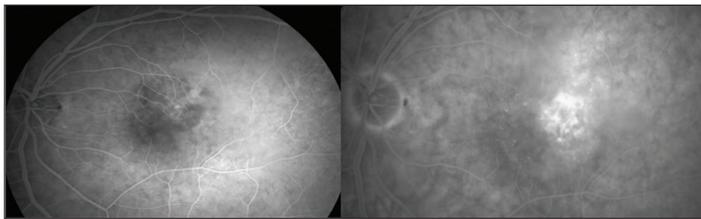


Figure 3. Two days after PDT.

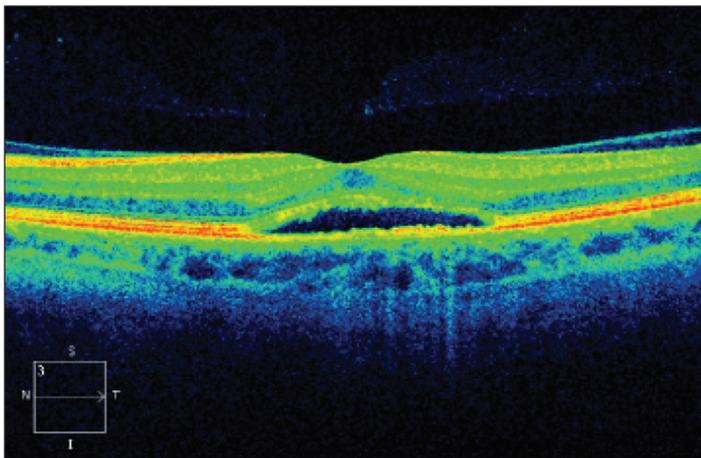


Figure 4. OCT 2 days after PDT.

Jeffrey S. Heier, MD: OCT-A can be particularly helpful in patients with CSCR as it can reveal the presence of a neovascular complex. While this doesn't necessarily mean that there is leakage, it provides insight into the fact that a case may not be typical CSCR.

Nancy M. Holekamp, MD: To me, the patient's age of 64 years is the clue that the case was going to be challenging. In a patient diagnosed with CSCR in their 60s or 70s, the clinician needs to be aware of the potential for conversion to wet AMD. CSCR in older people requires close monitoring.

Case 4: Non-Subfoveal Lesion in Wet AMD

Rishi P. Singh, MD

Case overview:

- A 74-year-old woman presented with decreased VA in the right eye for 3 weeks.
- There was a previous history of dry age-related macular degeneration (AMD) in both eyes.
- BCVA was 20/60 in the right eye and 20/20 in the left eye.
- Color fundus photography revealed a yellow lesion with pre-retinal hemorrhage present which might indicate a retinal angiomatous proliferation (RAP) lesion type and a large area of subretinal fluid (Figure 1).
- OCT on presentation showed a bilobular subretinal pigment epithelium area with intraretinal fluid present (Figure 2).
- OCT angiography on presentation showed a RAP lesion (Figure 3).

Discussion:

Rishi P. Singh, MD: The most interesting aspects of this case were



Figure 1. Color fundus photography at presentation.

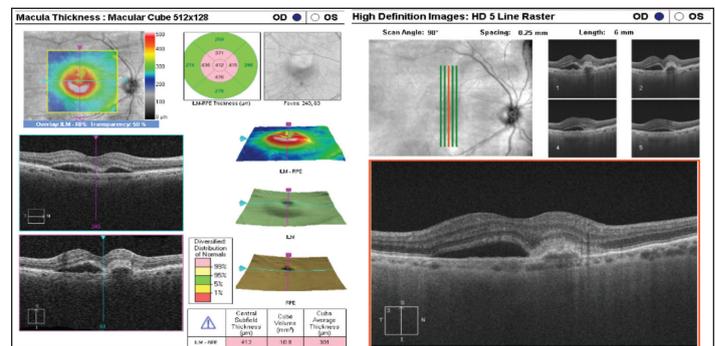


Figure 2. OCT at presentation showing subretinal pigment epithelium and intraretinal fluid.

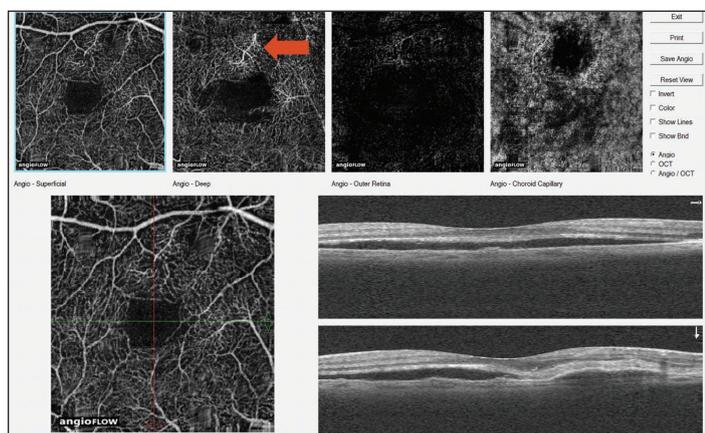


Figure 3. OCT angiography at presentation. The arrow indicates retinal angiomatous proliferation lesion.

the location of the fluid, concentrated along the superior arcades, and the lesion type as a truly non-subfoveal lesion. In addition, OCT-A nicely highlighted a RAP lesion that was present as well.

Michael Singer, MD: Knowing the natural progression of wet AMD, we need to closely monitor these types of lesions even though they are not centrally located. It's a more difficult discussion to have with our patients, but the concept of keeping long-term vision is important to them. They come to understand that there's a defect somewhere in their vision, even though it's not in their central vision, and it's going to worsen if it is ignored.

Nancy M. Holekamp, MD: In my experience with RAP, the prognosis is so much better if it's identified early. When lesions are larger and with more exudation, then they become far more challenging to manage.

Conclusion

Dr. Singh: Let's summarize the pearls of today's discussion on how we initially diagnose and manage a patient with wet AMD.

Dr. Singer: We all know that, in wet AMD, early diagnosis results in a better prognosis for the patient. Imaging plays an important part in making this possible and is thus invaluable in the management of wet AMD.

Jeffrey S. Heier, MD: We have to remember that while we all typically rely on OCT in our day-to-day practice, in those patients who are not typical or not characteristic of wet AMD, other imaging modalities such as CFP, FA, ICGA or OCT-A can really help to continue our understanding and inform our clinical decision-making.

Dr. Holekamp: We are becoming much more sophisticated in our understanding of fluid and the fluid compartments. We've moved beyond just talking about wet or dry retinas to really taking a closer look. ■

References:

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ.* 2004;82:844-851.
2. Ferris FL, 3rd, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology.* 2013;120:844-851.
3. Holz FG, Schmitz-Valckenberg S, Fleckenstein M. Recent developments in the treatment of age-related macular degeneration. *J Clin Invest.* 2014;124:1430-1438.
4. Holz FG, Sadda SR, Staurenghi G, et al. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from Cclassification of atrophy consensus meetings. *Ophthalmology.* 2017;124:464-478.
5. Klein ML, Jorizzo PA, Watzke RC. Growth features of choroidal neovascular membranes in age-related macular degeneration. *Ophthalmology.* 1989;96:1416-1419;discussion 20-21.
6. Wong TY, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology.* 2008;115:116-126.
7. Arnold JJ, Markey CM, Kurstjens NP, et al. The role of sub-retinal fluid in determining treatment outcomes in patients with neovascular age-related macular degeneration—a phase IV randomised clinical trial with ranibizumab: the FLUID study. *BMC Ophthalmol.* 2016;16:31.
8. Wykoff CC, Clark WL, Nielsen JS, et al. Optimizing anti-VEGF treatment outcomes for patients with neovascular age-related macular degeneration. *J Manag Care Spec Pharm.* 2018;24:53-515.
9. Ying GS, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. *Ophthalmology.* 2013;120:122-129.
10. AAO Retina/Vitreous Panel. Preferred practice pattern guidelines. Age-related macular degeneration. AAO. 2015. Available at www.aao.org/ppp. Accessed January 2, 2019.
11. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology.* 2012;119:1175-1183.
12. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology.* 2009;116:57-65 e5.
13. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355:1419-1431.