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GA Perspectives: Foveal-Involving GA and Exudative AMD

Dr. Goldberg:
Thank you for joining me for this GA Perspective. This is a CME program provided by Evolve Medical Education. I'm Dr. Roger Goldberg. I'm a Vitreoretinal Specialist at Bay Area Retina Associates in Walnut Creek, California. And I'm volunteer faculty at the California Pacific Medical Center Ophthalmology Residency Program in San Francisco.

Patients with GA often report problems with the quality of their life and the quality of their vision, and yet, it's not often reflected in the visual acuity. This is a disease clearly where best corrected visual acuity or Snellen visual acuity is not a great indicator of the severity of the disease. Because oftentimes, particularly if the geographic atrophy doesn't involve the center of the fovea, the central macula, oftentimes patients can do very well reading the eye chart, picking out, you know, a black letter on a white background one letter at a time. But what happens is, when there's geographic atrophy that's surrounding the fovea, these patients are missing vision just off center. And so, they'll often report difficulties, for example, reading. Because when we look at a word, we can see the entire word all at once in our eyes scans it and moves on to the next word. But when you have to pick out each letter one at a time, it becomes very difficult to read or read for long periods of time, because it starts to get frustrating with how slowly your brain is acquiring that information.

It turns out that actually, surveys asking patients with geographic atrophy report lots of difficulties with what we might call activities of daily living. So, 50% of patients said they did not feel confident driving during the day. And nearly 90% of patients said they did not feel confident driving at night. In fact, I have a patient of mine in the Bay Area who isn't able to drive from Walnut Creek where I live into Oakland and San Francisco because there's a long tunnel there. And in the tunnel, even if it's daylight, he goes into the tunnel, and it's very dark. And he says he's basically night blind. His dark adaptation is so slow, that he really doesn't feel safe driving through that tunnel. It is lit but it's much darker than the outside environment. And it started to kind of impact his ability to do the things that he wants to do.

Finally, 82% of patients with geographic atrophy reported a worsening of their vision over the past year, compared to 25% of age-matched controls. So, these are the patients they might measure the same vision on the eye chart when you see them 6 months or a year later, but they come in and they say, ‘Doc, I think I'm getting worse.’ And there are certain of these phrases that you'll start to listen for and hear that should kind of raise the antenna of suspicion that says I better look at this patient a little bit more closely to see, one, is there geographic atrophy? And two, is that geographic atrophy showing signs of progression?

So, let me share a case. This is a 96-year-old, Caucasian female. I saw her here first in 2017. She lives alone. She actually gardens and cooks, but she's no longer driving. She loves to read. It's truly one of her hobbies. And I think kind of reading and often watching TV are two of the activities of daily living we often see are very important to patients kind of in this advanced age demographic. She's 20/300 in the right eye, and 20/63 in the left eye. So, in 2017 she had foveal-involving GA. Now, you can see here on the fundus autofluorescence, as well as the OCT, that there's areas of atrophy in the fovea, in the center of the macula, but she still has lots of good vision. Remember, this is her left eye which is her better-seeing eye, and this is the eye that's really helping to keep her functional. The fundus autofluorescence of course shows areas of hypo-autofluorescence as well as areas of hyper-autofluorescence. That hyper-autofluorescence at the edge we'll talk about shortly, but that's one of the risk factors for progression of geographic atrophy over time.

Here's the measurements of her geographic atrophy. And this is a tool that's available on most OCT systems. And I just freehand measure this, just tracing the outline of the atrophy on fundus autofluorescence. And it helps give me kind of a numerical way to follow patients. It can also be helpful for getting patients, of course, into clinical trials, which is probably why I had measured this patient's GA back in 2017, because at that point, we didn't have any treatment available to us for patients with geographic atrophy. Of course, that's different now.

So, what happened 4 years later? Well, now unfortunately, she's 20/200, she was untreated. And we see really extensive atrophy both on the fundus autofluorescence, as well as the infrared image, which is to the left of the OCT. And on the OCT itself, we see extensive hyper-transmission, which is a reflection of loss of the RPE. We see overlying loss of the photoreceptors on the OCT as well. And this patient, of course, has a very thin choroid. A thin choroid is another important risk factor for progression of geographic atrophy. So, this is someone certainly I wish I had had treatment available back in 2017, because this would have been a great patient to consider treatment to help slow the progression of geographic atrophy and hopefully preserve some vision and visual function in her better-seeing eye.

So, what are some risk factors for progression of intermediate AMD to geographic atrophy? Well, there are several baseline factors that are associated with progression of – progression both to geographic atrophy and then progression of geographic atrophy itself. What are some of those risk factors? Well, a high central

drusen volume, so lots of large drusen, particularly soft drusen in the central macula. Intraretinal hyperreflective foci, little kind of white dots that show up on the OCT in the retina is also a risk factor for progression. Subretinal drusenoid deposits, I think this is one of the more important ones where you see the drusen – our typical drusen are actually between the RPE and Bruch's membrane, subretinal drusenoid deposits are above the RPE, underneath the retina. And those are a risk factor for progression of GA and progression to GA. Hyperreflective drusen cores, so when the kind of the inside of the drusen is hyporeflective, or a little bit darker on the OCT, that can be a risk factor. Or what we call double-layer sign, this a really important sign to look for an exudative AMD, because it's basically a thin separation between the RPE and Bruch's membrane. So, normally those two layers are adherent to each other and you can't distinguish or see both the RPE and Bruch's membrane. Finally, a patient who has cRORA, or geographic atrophy in the fellow eye, we know that's also a risk factor for the study eye itself.

So, here's a patient I first saw in January of 2018. This is a 93-year-old, Caucasian female. She's very active, she's married, she writes and publishes poetry. She's pseudophakic in both eyes. In the right eye, she was 20/100 with inactive wet AMD. And in the left eye, she was 20/30 with dry AMD. And here's what she looked like on presentation in the left eye, which of the eye we'll be talking about here. And we see that she clearly has geographic atrophy and it's kind of multilobar. So, we see kind of three decent-sized areas of atrophy on the fundus autofluorescence, which is on the left. And we see though that the central fovea is still intact, she has RPE present. You can see the hyper-transmission, it's just temporal to the fovea on that slice right through the central macula. I should mention as well on the – it's not pictured well on the OCT, but on the fundus autofluorescence, we see that she has subretinal drusenoid deposits. And again, these are a risk factor for progression of geographic atrophy.

Here's what she looked like in 2019. Now the left eye has declined to 20/50 and we see that the areas of atrophy are clearly expanding. All those lobes are starting to merge together into one larger lesion. Her vision has dropped to 20/50. We see increased hyper-transmission on the OCT.

Then I saw her in 2020. And again, we see now her vision has declined to 20/100. The GA is starting to kind of engulf –typically it encircles and then eventually engulfs the fovea. And that's what we see here in March of 2020.

October of 2021, now, she's 20/150. And we see very diffuse atrophy throughout the central macula. Interestingly, on the fundus autofluorescence, we see hyper-autofluorescence. Again, that's another risk factor for faster progression of geographic atrophy. And that can be helpful as we're thinking about, who do we treat? We want to treat the patients who are at high risk of fast progression. And hyper-autofluorescence is one of those important signs.

Now, in August of 2022, she came to see me, she was 20/150. And I think it's important, if you just look at the central scan which is shown on top here, again, we just see that diffuse atrophy. But it's important to look through the entire volume scan of the OCT, because this patient developed neovascular AMD, exudative AMD at the inferotemporal edge of her geographic atrophy lesion. And you can see that as SHRM, or subretinal hyperreflective material, on the bottom scan. And so, this patient actually had developed exudative AMD, and I treated her with an anti-VEGF agent. And that SHRM thankfully resolved. Here, you can see a month or two later, resolution of the SHRM. Now of course, she still has extensive geographic atrophy, 20/150 vision. This is not a patient I would consider treatment in given the advanced vision loss for her geographic atrophy. But certainly, treating her wet AMD I think is important because that can cause more rapid and extensive vision decline.

At the ASRS Annual Meeting 2023 in Seattle, I actually presented some data, looking at the exudative AMD in the DERBY, OAKS, and GALE open-label extension study. Those were the pivotal trials for pegcetacoplan that led to its approval for the treatment of geographic atrophy. And we know from those studies, as well as pretty much all the studies looking at complement inhibitors as a treatment for geographic atrophy, that one of the side effects is an increased risk of developing exudative AMD. We certainly saw that in DERBY, OAKS, and GALE. Thankfully, we didn't see any increasing rate of exudation over time, it seems to be stable over time, in terms of kind of patient exposure per year to pegcetacoplan. Patients did very well, they were treated both with an anti-VEGF agent and with pegcetacoplan. Those injections were typically spaced out about 30 minutes during the clinical trial. And I'd certainly recommend something similar in clinical practice for patients who need both an anti-VEGF and pegcetacoplan treatment.

One of the things we learned though as we looked at these cases is first of all, the exudation tends to be quite subtle, just like it was in this case. It always developed at the edge of the geographic atrophy. And so, you're again, you really have to kind of be looking with a high index of suspicion and look very carefully through the whole volume scan. Because just like in this case, it can often be quite subtle. Sometimes using the thickness map that comes with the OCT review software can be a helpful way to look for changes from one visit to the next visit.

Thankfully, the patients in DERBY and OAKS did quite well with their anti-VEGF therapy. On average, they developed – they needed an injection of anti-VEGF about once every other month, pretty similar to what we see in the real world. And they had robust anatomic gains. The patients who had developed exudative AMD in DERBY and OAKS needed an anti-VEGF injection about every other month. They showed robust anatomic gains with essential retinal thickness returning to the same level as it was prior to their developing exudative AMD. And the exudation is always at the edge of the geographic atrophy. It can be quite subtle. It's important to look through the entire volume scan, scroll through it. And it can often be helpful to look at the map that comes prepackaged with the OCT review software because that can help show subtle changes in the retinal thickness throughout the central 6 x 6 mm of the macula.

Thank you for joining me for this didactic session and case review for a couple of patients with geographic atrophy.