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A Case of Missed Diagnosis, Part of the Focused Sight Initiative: Quality Improvement Interventions in Retinal Disease

Announcer:

Welcome to CE on ReachMD. This activity, titled “A Case of Missed Diagnosis, Part of the Focused Sight Initiative: Quality Improvement Interventions in Retinal Disease” is provided by Evolve Medical Education.

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Dr. Kim:

So I will be presenting the case of misdiagnosis. As retina specialists, we work closely with a lot of referring doctors, that includes general ophthalmologists, optometrists, who play a major role in primary care, basically, of the eye. And that involves monitoring and diagnosing retinal diseases. As retina specialists, we get the benefit of having a lot of ancillary testing at our fingertips. And we will be discussing the case of a patient who perhaps could have benefited from an earlier referral on the basis of having access to those ancillary testing here in the retina clinic that may have helped him get diagnosed and then treated more promptly.

So this is a 36-year-old Caucasian male. He's quite young, but he does have a history of type 2 diabetes, hypertension, and kidney disease. Presenting with decreased vision in both eyes, and he reports for about the last 2 to 3 months. So already with this, a couple of red flags. He's very young, but he has kidney disease. And we know that the retinal vasculature mirrors that very much of the kidney vasculatures of the small glomeruli and the capillary. That architecture mirrors that of the retina. So when a patient has kidney disease, I'm already thinking red flags that there will be some manifestation of diabetes in the eyes as well.

The patient had been followed annually by his optometrist, he states, and he had literally never been told about having any diabetes in his eyes. He had been referred to a general ophthalmologist in the setting of these new extensive retinal hemorrhages in both eyes that, per report, had not been seen last year. His latest hemoglobin A1c is 7.6, so he's fairly well controlled now. However, the patient is obese, and he was first diagnosed with diabetes at the age of 24, meaning he's already had type 2 diabetes for 12 years, despite being very young.

I'm looking through his medication list, and the only medication that I see is furosemide 40 mg, and I don't see any diabetes medications listed. So I am a little bit concerned that this patient may not be properly managed, and the blood sugars are running higher than it should be for his current state.

So we typically get a referral form from the referring doctor to indicate what the reason for referral was. And on his form, it just said: “? possible CRVO.” And then we also have boxes on the sheet that indicate the urgency. So there's a category of routine, there's a category of urgent, so usually within 1 to 2 weeks. And then there's a category of emergency, which is pretty much same day or next day. But on the referral form, none of those boxes were checked, sort of implying there is no great sense of urgency.

So at initial presentation, his vision in the right eye was 20/50, pinhole to 20/40. In the left eye, it was 20/40. His pressures were normal. Just looking at the anterior segment, I didn't see any neovascularization of the iris at the slit lamp, which is reassuring, and really minimal

cataracts, which we would expect for somebody his age. But when I did the dilated fundus exam, what stood out already was that he had nearly 360 degrees of neovascularization of the disc. He had these dilated tortuous veins, indications of concomitant hypertensive retinopathy, so AD nicking, silver wiring. And I think, really, the dilated, sort of tortuous veins are what clued the general ophthalmologist to be thinking along the lines of a central retinal vein occlusion.

The macula had multiple scattered intraretinal hemorrhages, he had cotton wool spots, as well as macular edema, and the periphery had scattered hemorrhages in all 4 quadrants, mostly in the mid-periphery as well as NVD. But as we know, a picture is worth 1000 words, so we'll get straight into the imaging.

So the pseudo-color fundus photos are shown at the top left of each of these. On the left is the patient's right eye. The 9 smaller images —and those are fluorescein angiogram images taken over various time points. And then on the right-hand side, we have the patient's left eye. And what stands out here is that there is significant non-perfusion in the periphery. So you can see, particularly in the left eye, that there is complete capillary dropout. We have early and late leakage at the disc as well as in the peripheral retina, especially along the inferotemporal arcades in both eyes. And he has that diffuse leakage in the macula as well, indicating macular edema.

So this is a picture of a very severe proliferative diabetic retinopathy. And then, of course, we have the blockages from all the hemorrhages, and those are most notably seen there on the autofluorescent images, which are the third images from the left-hand side in each side, at the top right.

So the OCT here. Again, right eye is on the left side; left eye is on the right side. You can see that there are diffuse intraretinal fluid, as well as even some subretinal fluid at the fovea in the left eye, as well as a tiny bit in the right-hand side. Also, we can see these hyperreflective foci or hard exudates. All these things are indicating chronicity and severity. So when patients have that subretinal fluid at the fovea, we know, okay, this is a more severe case of DME or diabetic macular edema.

Other biomarkers that I'm looking for in terms of getting a sense of visual prognosis for this patient are DRIL, which are disorganized retinal inner layers, and that has been corroborated in multiple studies to be an indication of poor visual prognosis. So specifically focused on those inner layers from the inner nuclear layer to the ganglion cell layer, I'm looking to see that the lines are nice and consistent and maintained throughout, including through leading up to the fovea. And for the most part, he actually has preservation of those inner retinal layers. So while he has a pretty severe presentation of DME, thankfully, he doesn't have DRIL, so I'm feeling optimistic that we can help this patient by initiating anti-VEGF injections.

So I had originally seen this patient 6 1/2 years ago, at which time I would say standard of care was ranibizumab 0.3 mg for the treatment of DME, as well as for PDR. So he underwent that in both eyes. I also wanted to get panretinal photocoagulation, PRP, on board sooner than later, especially with these diabetics who have been poorly controlled. You're not sure what compliance is going to look like, whether I'll see this patient again, if he's going to get lost to follow-up. He's young; he's working. He literally has to drive over an hour and a half to come in to see me. I think it’s important to get that PRP on board sooner than later. It may also reduce sort of the VEGF production in the eye and overall reduce treatment burden of needing the anti-VEGF injections.

So just with 2 injections of ranibizumab 0.3 mg, the right eye vision improved to 20/25 and the left eye improved to 20/20, which is really fantastic. So we can see the corresponding OCTs here. There is that complete resolution of intraretinal fluid as well as the subretinal fluid. There is some residual hyperreflective foci or hard exudates, which we know takes some time to resolve but were an indication of both severity and potentially chronicity.

So seeing this is very encouraging. We also know that the way patients respond to the first 3 injections in the treatment of their DME is a good prognostic factor for how much treatment burden and how responsive their DME is going to be in the future. So the fact that he responded so well to just 2 injections of anti-VEGF bodes well for him in terms of having a good prognosis and hopefully having more manageable, readily responsive DME.

So I view this as crisis averted. He came very close. It was a very severe presentation of PDR, but he did really well, and we were able to turn the tide. He has been extremely compliant and very good at following up. And I've been seeing him regularly over the last 6 1/2 years and have some future slides to show how he's doing now.

But in reviewing his case, it does raise some questions. First of all, he says that they hadn't noticed anything last year, but they're noticing it this year. Is it really possible to develop PDR so quickly? Hindsight is always 20/20, but the patient was being seen annually. Should he have been seen more regularly? And were there some warning signs or any factors in sort of his baseline demographic and presentation that we should have caught on earlier, either in his clinical presentation or, again, his demographics that have indicated that he should have been seen and referred more urgently?

So to answer that first question, how quickly does PDR develop, I think that sometimes we can almost get lulled into a false sense of

security. Okay, you're a severe NPDR; we're just going to watch it. Why don't you come every 6 months or once a year, especially your A1c is pretty good at 7.6. But we can see here, in a study that was published in *Ophthalmology* in the ETDRS research group, if you look to the way right-hand side, I kind of circled what category, potentially, he was in last year. And that was a severe NPDR category. And this graph demonstrates the likelihood of converting to PDR in 1 year, 3 years, and 5 years. And so if you ask yourself, okay, if you have severe NPDR, what are your chances of getting PDR within 1 year? It's actually 52%, which to me was a very surprising number. That means over half are going to progress to PDR simply within a year. Within 3 years, it's 71%, and within 5 years, it's 80%. So the vast majority of patients have a very high likelihood of progressing to PDR.

And the takeaway from this is that these patients with severe NPDR need to be seen more frequently, and especially depending on compliance, on the status of the fellow eye, in terms of their A1c control, considering treatment even at this stage, be it with PRP or anti-VEGF injections, to reduce the likelihood of progressing to PDR, especially PDR that can be vision threatening.

In terms of other kind of warning signs, right? We talked about were there any indications that perhaps this patient should have been seen more frequently besides annually? The other factor is that he was very young. He was 36, but we know that he was diagnosed at 24, meaning that he had already had diabetes for 12 years. And so when you look at the duration of diabetes, we can see that that makes a huge difference. On the left-hand side is patients who have had diabetes for only 3 to 7 years. And then, the age of years at examination, the younger that they are, there's going to be already a higher risk of progression.

If you look at his category, in my particular patient's category, he had it for 12 years, so he's on the way right-hand side. He was 36 years old, so he's in that 20- to 40-year range. The likelihood of him having diabetes or progressing to PDR is extraordinarily high. It's about 80% in this category.

So again, he was young, but he had had diabetes for a long time. That also, as a general ophthalmologist or an optometrist, I would personally recommend having these patients be seen by a retina specialist probably sooner than later, even just for a comprehensive, thorough dilated exam plus ancillary testing, which involves a fluorescein angiogram, an OCT or an OCTA to sort of risk stratify this patient for developing complications in the near future. So again, young patients with diabetes are at greatest risk and especially when you've had the diabetes for longer.

So was it actually possible to get PDR so quickly? Most definitely, based on that graph. Should he have been seen more regularly? I would say yes, definitely more than once a year, because he's high risk. He's had diabetes for a long time, he has comorbidities like hypertension and obesity, and so the threshold to refer to a retina specialist should be very low, at least to obtain that baseline fluorescein angiogram and further risk stratify him.

So this is what the patient looked like a year and a half later. We can see that he has PRP 360 degrees in both eyes. He almost had some traction or pre-retinal fibrosis sort of forming at the arcades, the supertemporal arcades in both eyes. Again, without treatment, that would have been very, very high risk to progress to a tractional retinal detachment, which could have led to vision loss, and then much more invasive interventions like surgery, silicone oil, cataract surgery, and all the like. But thankfully, he came in before any permanent damages happened, and we worked to avert that. And so there's just residual old fibrosis sitting there, but there's no traction to the underlying retina, and he's doing great.

This is what the corresponding fluorescein angiogram looks like. So we can still see that there's extensive capillary non-perfusion in both eyes. I think sort of the old-school PRP would be to do heavy PRP all the way up to the arcades. I think that nowadays we have anti-VEGF. Especially if patients are having to get treated anyway for DME, I do try to spare some of that mid-periphery in order to preserve their night vision. Like, even now with the degree of PRP that he has, he does feel like he has lost some of the night vision and peripheral vision. So I want to minimize that as much as possible. But we can see that he doesn't have any more NV, like the neovascular degeneration of the disc and of the elsewhere is all gone.

And then finally, this is his OCT 6.5 years after initial referral. His latest OCT taken like a month ago. And he is looking phenomenal. You can see the nice preservation of all the layers of the retina. His vision is 20/20 in both eyes. Thankfully, he's very faithful and coming for his injections, and so he's had a really, really great outcome. With good days and all of those changes, insurance, I did have to switch him to bevacizumab after 3.5 years of treatment due to costs. He has been on an 8-week interval. Every time we go like a week or 2 beyond that, he gets recurrence involving intraretinal fluid. And this is where other more durable treatment options, I think, will come into play in terms of his next steps, in terms of changing his future treatment modalities. Hopefully, at least when insurance allows, we can switch to a second-generation anti-VEGF agent to get him that durability in the meantime.

But right now, he's 43 years old. He's extraordinarily diligent to attend his appointments. He recognizes the importance of these injections in terms of maintaining his vision. And he's done really, really great. But just a reminder, when we see these risk factors—young age, long-standing diabetes, comorbidities, and then that kidney disease—those are red flags that this patient should be referred

earlier to a retina specialist for further ancillary testing and treatment as needed.

And that concludes the presentation. Thanks so much for your time.

Announcer:

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