WENDY SMITH: Hello, I'm Dr. Wendy Smith of the Department of Ophthalmology. I'm happy to be here today to discuss an interesting case involving a patient with panuveitis. He is an 82-year-old white male. He initially presented to the neurology department complaining of several months of recurrent episodes of right-sided weakness involving his right arm, the right side of his face, changes in his voice and his gait, and intermittent blurring of his vision.

He had a history of hypertension, he had been a smoker, he also had atrial fibrillation and mitral valve replacement. He also had hyperthyroidism and a history of gallbladder cancer, which had been treated. Urology planned to obtain an MRI and MRA, and referred to ophthalmology to rule out retinal ischemia. His ophthalmology history, by the time he reached our clinic, was difficult to obtain. He was very tired, and we didn't have any outside records at that time.

Best we could determine, his decreased vision in his left eye had begun in late January, a few months earlier, and he had some testing by his eye doctor closer to home. He was treated with eye drops and oral prednisone. It wasn't clear exactly when the prednisone stopped, maybe three weeks prior to our exam, and he really wasn't sure if his vision had improved on the prednisone.

So this is a color fundus photo of the right eye and his visual acuity with his glasses, and this eye was 20/25, and the other eye a little bit decreased at 20/40. Pressures were normal. In the antechamber, there was no cell or flare. There was a little bit of cataract in each eye. In the vitreous of the right eye, there was no cell. In the left, there was a question of vitreous cell, as well as veils of debris over the macula.

And this is how the retina looked in the posterior pole of the left eye. So we can see that the view is somewhat hazy due to those veils of debris, and there are multiple yellow-white spots that appear deep to the retinal vessels, scattered throughout the macula and along the arcades.

And as we look at a montage view, we can see that these spots extend into the peripheral retina, as well. This is fluorescein on the left side of the screen and ICG angiography on the right. In the early frames, you can already see that these lesions are hypofluorescent on ICG, and as we progress on to the one-minute frame, you can see they're also hypofluorescent on fluorescein on the left side.

Proceeding to the five-minute frames, which are now at the bottom of the screen, later on, these lesions become huperfluorescent on fluorescein and remain hypofluorescent, and we can see that there's quite a lot of them on the ICG on the right side. And then 12 minutes, which is now at the bottom of the screen, if you compare the 12-minute to the 5-minute, which is above, perhaps some of these lesions do look like they're leaking on fluorescein and they remain hypofluorescent on ICG. And the ICG really highlights the number of lesions that are present.

Here's a view looking temporally in the left eye just, again, showing these lesions. Fluorescein on the left and ICG on the right. And this is the right eye, a one-minute and a five-minute frame, which shows that it was essentially normal in each side. That dark spot nasal to the optic nerve was a shadow from a floater.

Here are OCT photographs. This is going through the macula of the right eye, which is essentially normal. This is an enhanced depth imaging photo, which shows the choroid underneath the retina. And here, by comparison, is the enhanced depth imaging of the left eye, which shows that the choroid is less clearly delimited, and you can't see the external border, because it appears to be thickened.

The scan is also going through one of those lesions, which is a little bit nasal to the fovea, and it appears as an area of discontinuity in the RPE and outer retinal structures. And this is another OCT image of the left eye going through an area that appeared clinically elevated in the temporal macula. And you can see on the OCT scan, on the right side of the screen, the area where the retina is kind of pushed upwards, and there's some hyper-reflectivity, suggesting there's a lesion in the choroid there.

So here we are again, looking at our montage color photo of the left eye. 82-year-old man, recent TIAs and unilateral uveitis. He has a mechanical mitral valve, he's a former smoker, he has a history of bladder cancer. So we take these things into account when we think about the differential of what could be causing this presentation. The differential could include sarcoidosis, metastatic cancer, an infection-- or an infection.

And so now we have a little bit more history. It turns out his bladder cancer was diagnosed less than a year prior to presentation. The tumor was excised and he was treated with BCG bladder irrigation weekly times six weeks in July and August. When he had repeat cystoscopy, there was still tumor present. He was then treated with intravesicular chemotherapy, six cycles going through January, which was just about the time when he began to have neurological and visual symptoms. And as I just alluded to, his decrease in his vision in his left eye began at the end of January.

So at this point, we consulted ID. We were concerned about an infectious etiology. We obtained some labs, we obtained aqueous from the anterior chamber. He had a lumbar puncture, a transthoracic echocardiogram, and we also recommended a vitreous biopsy. We had outside labs at this point, which showed that his CD4 count was a little bit below the lowest end of the normal range.

Other testing was normal or negative. And labs that we had obtained locally here at Mayo showed an elevated lysozyme level, elevated CRP, and pertinent negatives included quantiferon, syphilis IgG, and HIV. The aqueous from the anterior chamber had a negative Acid-Fast Bacilii smear, and the mycobacteria culture was also negative.

The cerebral spinal fluid had a negative Acid-Fast Bacilii smear, and the vitreous biopsy also had a negative mycobacterial tuberculosis PCR and a negative culture. And this says 15 days on the slide, but it remained negative even extending out to 45 days. And finally, the blood culture, which was obtained early on, after more than a month had a positive fungal culture for mycobacterium bovis, which is a strain of mycobacterium which differs from tuberculosis.

So again, here is our color montage, to remind us what he looked like. And at this point, we presumed that his diagnosis was BCG panuveitis. This is the brain MRI, which was obtained right around the same time. And we can see in the left hemisphere, which is the right side of the picture in the upper left, that there are some white spots in the brain matter. And here, in another scan we can see additional white spots on these T1 images-- on this T1 image on the left and a T2 image on the right.

And the radiology report-- there's far more words here than one can read, but the important word is miliary. So the radiologist described a miliary pattern of enhancement within the left cerebral hemisphere. And so that certainly caught my attention, because miliary brings to mind tuberculosis for most of us.

So let's talk about intravesicular BCG, or Bacille Calmette-Guerin. This is the installation of live, attenuated mycobacterium bovis into the bladder to treat superficial bladder cancer, or transitional cell cancer. The mycobacteria are lipophilic, so they adhere to the urothelium. They are ingested into the urothelial cells, where they elicit an inflammatory response.

This leads to infiltration of macrophages, T and B cells, and natural killer cells, upregulartion of proinflammatory cytokines, and other inflammatory responses which should cause anti-tumor activity. In addition, the tumor cell mobility is inhibited. This organism is infused into the bladder weekly for 6 to 12 weeks, and then the therapy may continue monthly for several months, up to 9 months.

There are, of course, side effects associated with intravesicular BCG. Those can range from an acute hypersensitivity reaction, which is usually mild and self-limited, to longer-term complications like bladder contracture and other obstructions. In addition, there can be granulomatous involvement of the prostate and other structures, or granulomatous involvement of the organs in a minority, including the liver, lungs, kidney, musculoskeletal system, and the bone marrow.

Severe complications of intravesicular similar BCG can include pericarditis, high fever, sepsis, immune complex glomerulonephritis, some skin changes, and, of course, uveitis or endopthalmitis. In addition, these organisms can cause infections of the large arteries, which can lead to aneurysms and ruptures. It can cause a miliary TB and infection of any implanted things like prostheses or defibrilators.

There are risk factors associated with systemic BCG spread, and that would be traumatic urinary catheterization, if the bladder was inflamed at the time of BCG installation, starting the treatment too soon after transurethral resection of the tumor or prostate biopsy, bladder outlet obstruction, immunodeficiency, and some genetic deletions.

There are some relative or absolute contraindications which, of course, to intravesicular treatment, obviously because they would either increase the risk of complications or cause problems with things like pregnancy or breastfeeding. There is no role for prophylactically treating the patient with isoniazid to prevent spread of BCG, but if there are systemic complications, then it's recommended that BCG treatment is suspended.

And then the patient is treated with systemic medications, isoniazid, rifampin, and ethambutol for 6 to 12 months. All strains of mycobacterium bovis are pyrazinamide-resistant, so this drug is not used. There might be a role for systemic corticosteroids, but of course, only if the triple-drug therapy is used at the same time.

Uveitis associated with intravesicular BCG is rare, but it has been reported anywhere from days to years after BCG treatment. Uppal et al. In 2010 published a case series of 11 cases of uveitis which occurred after BCG treatment. They ranged from mild entrouveitis to endophthalmitis. There was one report of corneal melting.

And the mechanisms for why uveitis occurs range from hypotheses that there's molecular antigenic mimicry versus direct infection of the VCG organism. In some cases, vitreous culture was positive for mycobacterium bovis. On the other hand, we know there are amino acid homologies between BCG proteins and retinal autoantigens. In addition, peripheral T cells show cross-reactivity to PPD and retinal proteins, so perhaps some people have a genetic predisposition which is related to HLA antigens, and therefore are more likely to develop uveitis, either as an immune response or as a direct infection.

This is a photograph from a paper published by Gao et al. of a patient who was treated with intravesicular BCG and also developed pulmonary nodules, as well as liver and bone marrow involvement. Biopsies showed multiple non-caseating granulomas, in this case. The photograph is a partial color montage, which shows some deep choroidal lesions which are similar to those observed in our patient. And these are the histopathologic slides, the top two slides from the liver,

And the bottom two from the bone marrow, which show the non-caseating granulomas. In this case, both culture and PCR were positive for mycobacterium bovis, and this patient was treated with triple-drug therapy for a year, had a repeat biopsy of the liver, which was PCR negative, however, eventually developed GI hemorrhaging due to an abdominal aortic aneurysm and then resumed treatment with triple-drug therapy.

In another case, a patient presented with neurological symptoms three years after having intravesicular BCG. This patient had brain lesions, which showed chronic granulomous inflammation, and PCR was positive for mycobacterium bovis. So this patient had neurological findings which were similar to ours.

So, back to our patient. Unfortunately, he was quite debilitated and so could not have too many further investigative studies, therefore systemic treatment was started with triple-drug therapy, and he was planning to follow up with his local doctor.

And here are the references for the information regarding BCG, as well as the case studies that I discussed in this talk. I'm Dr. Wendy Smith with the Mayo Clinic Department of Opthamology. Thank you for listening to this case and learning about this patient with me today.