

Pentosan Polysulfate Maculopathy: An Elusive Masquerader

At first blush, pentosan polysulfate maculopathy may look like a pattern dystrophy or age-related macular degeneration (AMD). Dig deeper, however, and something unique emerges.

“The discovery of pentosan toxicity was a very astute observation by one of our former fellows, Nieraj Jain,” said Mark E. Pennesi, MD, PhD, at the Casey Eye Institute in Portland, Oregon. “Dr. Jain noticed a cluster of patients with a curious pattern dystrophy who also happened be on pentosan polysulfate.” Dr. Jain investigated other patients who had been on the drug and found more cases,¹ and he reached out to a number of colleagues who found similar cases.

Then began the process of working to confirm causality, as well as the presentation, scope, and mechanism of action of this specific condition.

Piecing Together the Puzzle

Used to prevent irritation of the bladder wall, pentosan polysulfate sodium (PPS; Elmiron) is the only FDA-approved oral prescription medication for interstitial cystitis. The drug has been on the market for more than 20 years, and doctors have prescribed it for hundreds of thousands of patients, said Nieraj Jain, MD, at Emory Eye Center in Atlanta.

Typical presentation. Patients with PPS maculopathy can have fairly normal visual acuity—even 20/20, said Dr.

Jain. “But patients tend to suffer from significant subjective visual problems, such as trouble reading or adjusting to dim lighting, glare, and blind spots. In advanced stages, the condition can lead to profound disability, with some patients meeting the criteria for legal blindness.”

On imaging, you see an expanding maculopathy that involves the optic disc as well as the entire posterior pole, said Stephen T. Armenti, MD, PhD, at the Kellogg Eye Center in Ann Arbor, Michigan. As the condition advances, added Dr. Pennesi, you start seeing severe loss of the retinal pigment epithelium (RPE) with photoreceptor loss. “It can be widespread, extending beyond the macula to the far periphery,” he said.

Risk factors. “Long-term exposure seems to have the strongest correlation so far,” said Dr. Pennesi. “This makes sense since most toxicities are related to dosage or duration.” Interestingly, a recent retrospective study of medical claims data found no significant association between PPS use and a diagnosis of macular disease at five years.² Although this appears to contradict earlier reports, it is still consistent, said Dr. Jain. He noted that very few patients in this cohort used the drug for as long as five years; in fact, the mean duration of use was less than one year.

By contrast, in another recent study of claims data, Dr. Jain and colleagues



COLOR FUNDUS PHOTOGRAPHY. Para-central pigment clumps amid a background of yellow subretinal deposits.

identified a significant association between PPS use and macular disease at seven years.³

Dr. Jain and his team have looked at average daily dose by body mass and ideal body weight; and they have explored other possible risk factors, including race, a history of smoking or other medications, and problems with the kidney, liver, or spleen—due to the way the drug is metabolized. Yet, they have not identified an association.

Other factors at play? There is variability in patients’ responses to the drug. “In a fairly small cohort of 35 patients,⁴ we saw a patient who had been on a relatively low cumulative dose in the past who subsequently had a phenotype of maculopathy after being off the medication for several years,” said Dr. Armenti. Other patients have taken a higher dose for a longer time but have relatively mild disease, he said. “It is

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING STEPHEN T. ARMENTI, MD, PHD, NIERAJ JAIN, MD, AND MARK E. PENNESI, MD, PHD.

likely other factors are playing a role that we're not yet aware of."

Progression after cessation. In an unpublished retrospective study of 12 patients followed for a median of one year after drug cessation, Dr. Jain and colleagues did not see any reversal of the disease. "In fact, the majority of patients reported that their visual symptoms continued to worsen." Dr. Pennesi offers two possible explanations for this: The drug may get sequestered in the RPE or may bind to something, creating a reservoir effect. Alternatively, irreversible cell damage may begin, but it may take a long time to fully materialize.

Mechanism of action. Several groups, including Dr. Jain's, are conducting animal studies to determine the underlying mechanism of action. "We know this drug is a macromolecule similar to glycosaminoglycans," said Dr. Jain. "It is a highly negatively-charged compound, which causes it to bind to positively-charged molecules, and this could play a role. From the clinical imaging studies we've done, we think the primary site of damage is at the level of the RPE or possibly at the interphotoreceptor matrix."

Regardless, the condition fills in a missing piece of the pattern dystrophy puzzle, said Dr. Pennesi. "For the many patients with inconclusive genetic test results, we have long suspected that there were either more genes that we hadn't yet discovered or there was some other acquired cause."

What You Will—and Won't—See

This condition can easily be missed, not only because visual acuity is often fairly good but also because fundus findings tend to be subtle, said Dr. Jain.

Fundus photography. "With fundus photography, you can see some very subtle pale-yellow or even orangish deposits deep in the macula," said Dr. Jain. "Hyperpigmented spots may be present around the fovea, but they don't stand out as being very prominent."

Optical coherence tomography (OCT). "In combination with fundus autofluorescence, macula OCT is helpful in finding the outer retinal and RPE

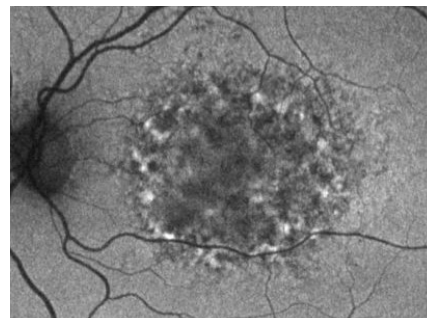
changes that you see with this disease and in differentiating from the typical findings seen in macular degeneration," said Dr. Armenti.

Near-infrared fundus reflectance (NIR). With NIR, you can see a pattern of hypo- and hyperreflective abnormalities in the posterior pole, said Dr. Jain. "However, this imaging modality often reveals nonspecific changes that may make it difficult to distinguish between different conditions."

Fundus autofluorescence (AF). With fundus AF, said Dr. Armenti, PPS maculopathy produces a pattern of hypo- and hyperautofluorescent spots throughout the macula, which extends throughout the posterior pole and can expand over time—a sign of RPE dysfunction.

Fundus AF imaging best captures the subtle manifestation of this condition and the extent of the diseased tissue, added Dr. Jain, describing a "wow" effect from viewing fundus AF images after observing relatively subtle findings in the clinic. "In cases where the disease involves the peripapillary retina," he said, "we identified a unique, fairly consistent feature—a hypoautofluorescent ring around the optic disc. This helps distinguish the condition from common hereditary maculopathies."

Multimodal imaging. Dr. Jain noted



FUNDUS AUTOFLUORESCENCE IMAGING. A dense pattern of hyper- and hypoautofluorescent spots that involves the fovea.

that integrating information from multiple imaging modalities may be necessary, especially since PPS maculopathy can mimic both hereditary maculopathies and AMD. It can be particularly hard to distinguish it from AMD, he said, because the two conditions share similar demographics—usually middle-aged or older white women.

Multimodal imaging is very helpful, agreed Dr. Pennesi. "Near-infrared reflectance is useful for seeing the characteristic bright deposits. Short wavelength autofluorescence is useful for seeing a pattern of changes in deposits and RPE dropout. Combined with a history of medication use, these two modalities can allow you to make a fairly confident diagnosis."

Watch for PPS Maculopathy

Here are some tips for spotting pentosan toxicity.

Scan medication lists. Look for PPS and add it to your list of the drugs you ask about whenever a patient has macular pathology, said Dr. Pennesi.

Beware the mimics. "If a patient has an atypical form of AMD or a pattern dystrophy, or if the 'AMD patient' is young, put this condition on your differential," said Dr. Jain.

Cast a broad net. Consider asking all patients with atypical maculopathy whether they are on this drug, said Dr. Armenti. "Otherwise, the topic may not come up unless the patient has a history of interstitial cystitis, the drug appears on a medication list, or specific signs show up on a fundus exam or retinal imaging."

Know that effects can continue after the drug is stopped. Dr. Armenti pointed to an example of a patient with concerning features on the fundus exam and OCT. "I had to dig way back in the history to help her remember that she was on this medication for a short time more than 15 years ago."

Consider referring PPS suspects to retina experts. They may have greater access to the advanced fundus imaging technology needed to confirm a diagnosis, said Dr. Jain.



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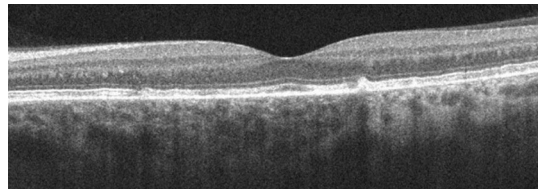
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OPTICAL COHERENCE TOMOGRAPHY. Irregularity to the outer retinal bands with a focal thickening of the retinal pigment epithelium temporal to the fovea.

Minimizing the Risks

Hydroxychloroquine maculopathy has robust screening guidelines promoted by the Academy, said Dr. Jain. Although there isn't yet enough data to formalize similar PPS screening guidelines, he does offer some recommendations.

Informal screening guidelines. "We recommend that all patients initiated on a long-term treatment course undergo a baseline screening exam, which includes a dilated fundus exam, color fundus photography, fundus AF imaging, and OCT imaging of the macula," said Dr. Jain.

In addition, patients with underlying macular disease should use caution in starting on this drug, he said. Patients who do proceed with a long-term course should have repeat screening with the same fundus imaging within five years of being on the drug, and annually thereafter. He added that these guidelines are likely to evolve as we learn more about the condition.

Case-by-case assessments. "Given that data regarding risk are continuing to emerge, it's hard to make a specific recommendation about screening and stopping the drug," said Dr. Armenti. He manages patients on a case-by-case basis, in part, by assessing how the patient weighs the risk of worsening cystitis against the possible risk of maculopathy.

"Without more information, I can't yet really make a clear recommendation for those taking the drug that have no signs of toxicity," said Dr. Pennesi. It's also not possible to tell patients that stopping the drug will prevent pentosan toxicity, added Dr. Armenti.

A placebo effect? Although some patients swear by the drug, there is some controversy about its efficacy. Based on a randomized controlled trial that

found PPS no more effective than placebo,⁵ the Royal College of Obstetricians and Gynaecologists no longer recommends its use. As Dr. Pennesi noted, a placebo effect often can be seen with the different therapies used to treat chronic conditions such as interstitial cystitis.

While this is often harmless,

"if something can cause toxicity, you have to rethink how you manage the disease," he said.

When signs of toxicity appear.

"If a patient on this medication has any signs of toxicity, we disclose that the drug is a suspected cause of maculopathy," said Dr. Armenti. "We also encourage the patient to speak with the urologist about whether to continue or stop the medication, or whether to try a different treatment."

When Dr. Pennesi sees evidence of toxicity, he also asks patients whether the drug is making a difference and whether they really need to take it. "We also explain that the longer they stay on it, the worse things may get, so they really need to weigh the risks versus the benefits."

So far, there is no known treatment, said Dr. Jain.

1 Pearce WA et al. *Ophthalmology*. 2018;125(11):1793-1802.

2 Ludwig CA et al. *Ophthalmology*. Published online Nov. 4, 2019.

3 Jain N et al. *Br J Ophthalmol*. Published online Nov. 6, 2019.

4 Hanif AM et al. *JAMA Ophthalmol*. Published online Sept. 5, 2019.

5 Nickel JC et al. *J Urol*. 2015;193(3):857-862.

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