BEWARE OF PIGMENTARY RETINOPATHY WITH PENTOSAN POLYSULFATE SODIUM


One case highlights the possible risks associated with this medication.

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Pentosan polysulfate sodium (PPS; Elmiron, Janssen Pharmaceuticals) is a semisynthetic compound that is derived in part from the bark of the beech tree. It is FDA-approved for the treatment of interstitial cystitis (IC). In 2012, approximately 450,000 prescriptions of PPS were dispensed, with approximately 50,000 patients in the United States being prescribed the medication; however, the number of prescriptions has been declining over the years.[1] In 2018, Pearce et al first reported a potential association between pigmentary retinopathy and PPS.[2]

CASE

A 55-year-old White woman with a history of diabetes, hypertension, Crohn's disease, and IC presented with dry eye symptoms. She had been taking 400 mg PPS daily for 13.5 years, with a total cumulative dose of 1,971 g. On initial examination, her BCVA was 20/30 OD and 20/40 OS. She noted difficulty seeing at night. She was phakic and had bilateral parafoveal hyperpigmentation and subretinal yellow deposits centered on the fovea in each eye. Patchy hyper- and hypoautofluorescence was observed on fundus autofluorescence (FAF), with focal retinal pigment epithelium (RPE) thickening on OCT (Figure 1). She had no family history of macular degeneration. Genetic testing found that she was heterozygous for variants of uncertain significance (VUS) for *CRX* and *USH1*, but she had no known pathogenic variants.

She slowly tapered off PPS. On follow-up examination 6 months later, she had slightly increased hyperautofluorescence with BCVA of 20/40 OU.

DIFFERENTIAL DIAGNOSES

The differential diagnoses for pigmentary maculopathy include medication-related toxicity, inherited retinal dystrophies (IRD), and AMD. Barnes et al defined a six-point grading criteria to help differentiate PPS-associated retinopathy from IRDs:

1. bilateral parafoveal hyperpigmentation and subretinal yellow deposits and/or patchy RPE atrophy on fundus photos;
2. bilateral, densely packed parafoveal hyper- and hypoautofluorescent spots around the fovea on FAF;
3. focal RPE thickening or elevation with hyperreflectance on near infrared images on OCT;
4. peripapillary hypoautofluorescent halo in patients with peripapillary involvement;
5. hyperautofluorescent spots less than two venule widths; and
6. lack of typical drusen.[3]

The fundus findings can be asymmetric.[3]

While IRDs tend to spare the peripapillary region, PPS-associated retinopathy that involves the peripapillary region may exhibit a hypoautofluorescent halo.[4] Genetic testing may be performed to help differentiate the diagnosis. Unlike AMD, which presents with typical drusen and decreased stromal choroidal area (SCA) and choroidal vascular index (CVI) on OCT, eyes with PPS-associated retinopathy tend to not have typical drusen, have more RPE pigment clumping, and may have lower SCA and higher CVI compared with unaffected cohorts.[5,6] Furthermore, IRDs typically affect younger patients, while the prevalence of AMD increases from 0.2% in White individuals 50 to 54 years of age to 16.4% in those older than 80 years of age;[7] the mean age of patients who develop PPS-associated retinopathy is in the 60s.[3]

DISCUSSION

Several studies on PPS have found a statistically significant correlation between pigmentary maculopathy and a longer

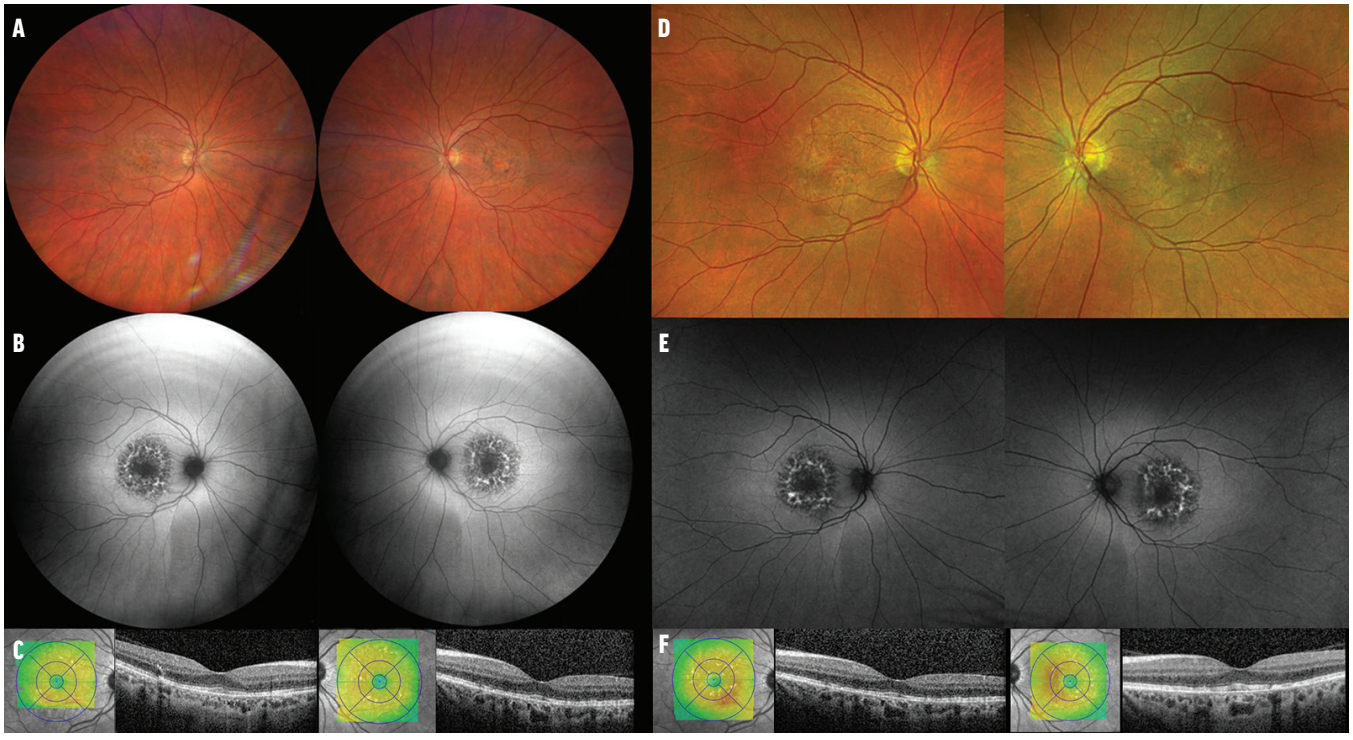

Figure. Multimodal imaging demonstrated hyperpigmentation and yellow spots on fundus photographs (A), patchy hyperautofluorescence on FAF in each eye (B), and RPE elevations on OCT (C). Despite stopping PPS, the patient continued to have hyperpigmentation and yellow lesions in the macula (D), increased hyperautofluorescence (E), and persistent RPE elevations on OCT (F) after 6 months of follow-up.

duration and higher cumulative dosage of PPS.[3,4,8-13] The estimated prevalence of maculopathy in patients taking PPS ranges from 2% to 25%.[5,8,16,17] An insurance database review found an association after 7 years of PPS use.[11] In retrospective studies, the risk increased from approximately 12% to 13% in those with 500 g to 999 g of cumulative exposure to 42% to 50% in those with an exposure of more than 1,500 g, and patients with PPS-associated retinopathy had a mean cumulative dose of approximately 1.5 kg.[8,14] A search of the FDA Adverse Event Reporting System found that there were more reports of maculopathy in patients exposed to PPS compared with other drug groups (3.4% vs .03%).[15]

The exact pathophysiologic mechanism by which PPS may cause pigmentary retinopathy is still unknown. The drug is partially desulfated by the liver and spleen, depolymerized in the kidney, and excreted through the kidneys and gastrointestinal tract, so it is possible that the sulfation pathway can become saturated.[1] PPS may antagonize the fibroblast growth factors that are involved in the development, organization, and maintenance of the retina; PPS may also cause toxicity to the outer retina and RPE because it resembles glycosaminoglycans, which are part of the RPE and photoreceptors. PPS may also inhibit retinal damage repair.[1,3,11,18]

Most patients with PPS-associated retinopathy retain relatively good visual acuity, with an estimated 10% to 20% being asymptomatic;[5] however, difficulty with reading, dark adaptation, and contrast sensitivity may occur, especially in those who develop foveal atrophy.[8,19,20] Furthermore, an estimated 1.4% to 17.6% of patients may develop choroidal neovascular membranes, and 9.5% to 12.4% may develop cystoid macular edema,[3] which may be treated with anti-VEGF therapy, steroid injections, or both.[19,21]

Some patients may experience progression of their retinopathy even after discontinuing PPS.[3,19,22] Due to the risk of pigmentary retinopathy, warning labels have now been added to the medication, and a baseline ocular evaluation

DUE TO THE RISK OF PIGMENTARY RETINOPATHY, WARNING LABELS HAVE NOW BEEN ADDED TO THE MEDICATION, AND A BASELINE OCULAR EVALUATION IS RECOMMENDED WITHIN 6 MONTHS OF COMMENCING PPS.

is recommended within 6 months of commencing PPS.[17] Some have recommended annual screening with OCT, near infrared imaging, and FAF for patients on PPS.[3,5]

CONCLUSION

PPS has been associated with pigmentary retinopathy, especially when taken at higher dosages and for longer durations. PPS-associated pigmentary retinopathy can progress even after discontinuing the medication. Patients should be counseled on the potential side effects of PPS, undergo regular ophthalmic examinations, and consider taking the lowest tolerated dose. ■

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