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# Case of the Month – August 2020

**Presented by Stavros N. Moysidis, MD**

A 76-year-old white female was referred for evaluation of dry age-related macular degeneration with complaints of slowly worsening blurry vision in both eyes. She was being monitored every 6 months for her disease, was taking AREDS2 vitamins, and was referred for a second opinion. The patient had a history of smoking, but quit 30 years previously. Her past medical history was significant for interstitial cystitis, ulcerative colitis, hyperlipidemia, and hypertension. Her medications included: Pentosan polysulfate sodium 300 mg PO daily, Mesalamine 1200 mg PO ER QAM, Amlodipine 2.5 mg PO BID, and Atorvastatin 40 mg PO Daily.

Visual acuity was 20/30 in the right eye (OD) and 20/25 in the left eye (OS). Intraocular pressures were 13 OD and 14 OS. Slit lamp exam OD revealed a well-centered 1-piece intraocular lens (IOL) in the capsular bag in each eye with 1+ posterior capsular opacification. Dilated fundus exam revealed a cup/disc of 0.2, without disc pallor or edema, a posterior vitreous detachment, normal caliber vessels, and an attached retina without holes or tears in each eye. Careful examination of the macula in the OD revealed a trace epiretinal membrane, small drusen, moderate mottling of the retinal pigment epithelium (RPE), and no pigmented deposits, subretinal hemorrhage, nor subretinal fluid. The macular exam OS was similar, with small drusen, more RPE mottling compared to the OD, and no pigmented deposits, subretinal hemorrhage, nor subretinal fluid.

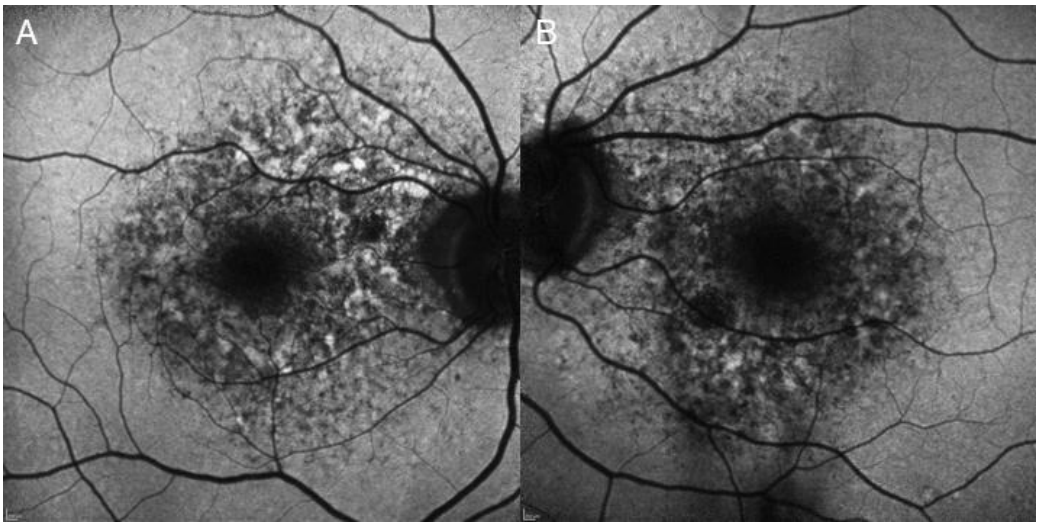
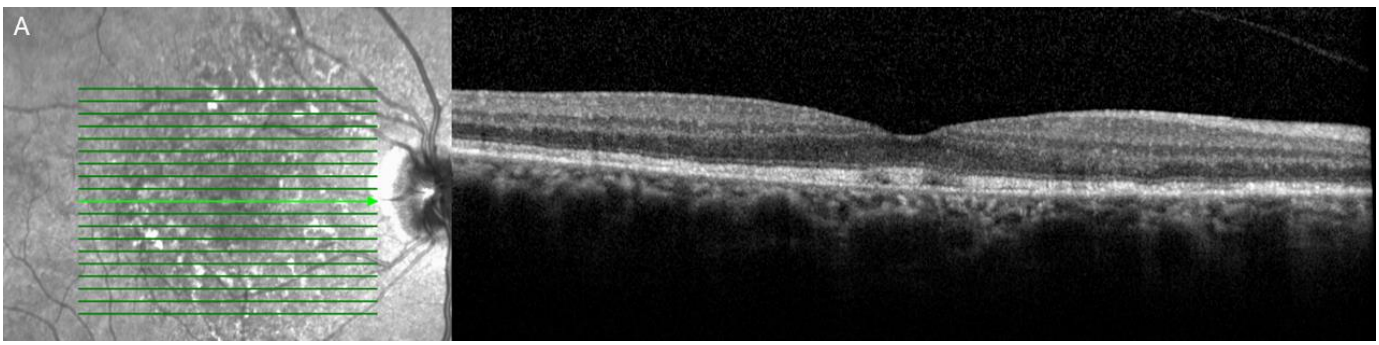



*Figure 1: (A) Fundus Autofluorescence of the right eye shows significant, patchy, hypoautofluorescence and hyperautofluorescence throughout the macula. (B) Autofluorescence of the left eye shows significant, patchy, hypoautofluorescence and hyperautofluorescence throughout the macula. The abnormal autofluorescence pattern in both eyes was confined to the posterior pole.*

Autofluorescence showed patchy hypoautofluorescence and hyperautofluorescence throughout the macula in each eye, with normal autofluorescence elsewhere. Optical coherence tomography showed numerous small, fine drusen, as well as areas of ellipsoid zone (EZ) band dropout with outer nuclear loss and downward deflection of the outer plexiform layer. There was a trace epiretinal membrane without distortion of the foveal contour.



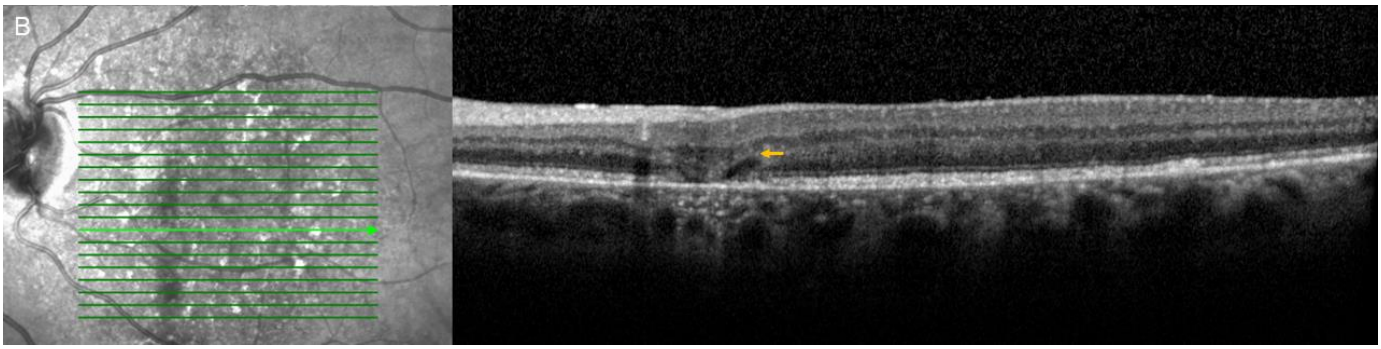



*Figure 2: (A) Optical coherence tomography (OCT) through the fovea of the right eye shows small, fine drusen and a normal foveal contour. (B) OCT in the left eye shows focal ellipsoid band disruption, loss of outer nuclear layer and a downward deflection of the outer plexiform layer (hyperreflective line deflecting downward from the yellow arrow). There was a trace epiretinal membrane without distortion of the foveal contour (not shown).*

**Clinical Course:**

The clinical findings and results from ancillary testing were discussed with the patient. Her findings were consistent with a diagnosis of intermediate stage dry or non-neovascular age-related macular degeneration in both eyes. The patient also had a history of interstitial cystitis and was taking Pentosan polysulfate sodium 300 mg PO daily. Recent reports of a maculopathy secondary to Pentosan toxicity have pointed out similarities in the early appearance of this drug toxicity and dry age-related macular degeneration. The patient had fine parafoveal drusen, but not the characteristic darkly pigmented deposits noted in recently published cases of Pentosan maculopathy. Nor did she have the characteristic hyperautofluorescent spots corresponding to these deposits, as hers were consistent with drusen. Nevertheless, recent reports regarding a maculopathy secondary to chronic Pentosan toxicity were reviewed with the patient. She was advised to continue eating green leafy vegetables, continue taking AREDS2 vitamins, reduce UV exposure by wearing sun glasses, and to avoid tobacco products. The need to monitor closely for Pentosan maculopathy was discussed with the patient. Given her history of intractable pelvic pain when off the drug, the decision was made for close monitoring.

**Discussion:**

Pentosan polysulfate sodium (PPS; trade name Elmiron) is an FDA approved drug for the management of discomfort or pain of the bladder due to interstitial cystitis. It is a semisynthetic compound with a glycosaminoglycan structure. Its mechanism of action is to adhere to bladder mucosal cells, buffer cellular permeability and protect the epithelium. While a discussion of interstitial cystitis is beyond the scope of this writing, in brief, it is a syndrome in which there is chronic pain of the bladder, more commonly affecting women, with symptoms of pelvic pain, urinary urgency and frequency, and nocturia. PPS was first used as a treatment of varicose veins in the 1950s, with more widespread use in the last 2 decades for the treatment of interstitial cystitis, after receiving FDA approval for interstitial cystitis in 1996. In 2018, the first report of a series of patients with a toxic maculopathy secondary to PPS was published. Since then, additional reports have been published.

In the initial publication reporting pentosan maculopathy in 6 patients, all patients were female, median age was 60 years old, and the median age at symptom onset was 55 years. The median PPS dose was 400 mg PO Daily, which was a median daily dose by body weight of 5.9 mg/kg. Two of 6 patients were active smokers. Genetic testing for inherited retinal dystrophies was performed on 4 of the patients, and all were negative for common pathogenic variants, such as PRPH2, ABCA4, and BEST1. Most of the patients presented with excellent visual acuity of 20/25 or better, but complained of difficulty with reading or with adaptation to dim light settings. All patients had pigmented vitelliform-like deposits on fundoscopic exam with corresponding hyperautofluorescence spots on imaging, while 4 patients also had patchy hypoautofluorescence. On OCT, there were nodular excrescences at the level of the RPE, not unlike drusen. Importantly, a larger follow-up series of 35 patients found that the median duration of exposure to PPS was 15 years (range, 3 – 22 years), with a median cumulative exposure of 1.61 kilograms (range, 0.44 - 4.31 kg).

Numerous publications now suggest that pentosan maculopathy manifests with parafoveal pigmentary deposits in the early stages that ultimately lead to atrophy. Visual acuity in most patients is 20/30 or better, however, their symptoms can be severely pronounced with significant limitation in their quality of vision and function. Reading, contrast sensitivity, and dark adaptation can be very challenging for these patients. Snellen visual acuity alone can be a misleading assessment of visual function. As pigmentary deposits progress to atrophy of the RPE and ellipsoid zone band (photoreceptors), visual function deteriorates.

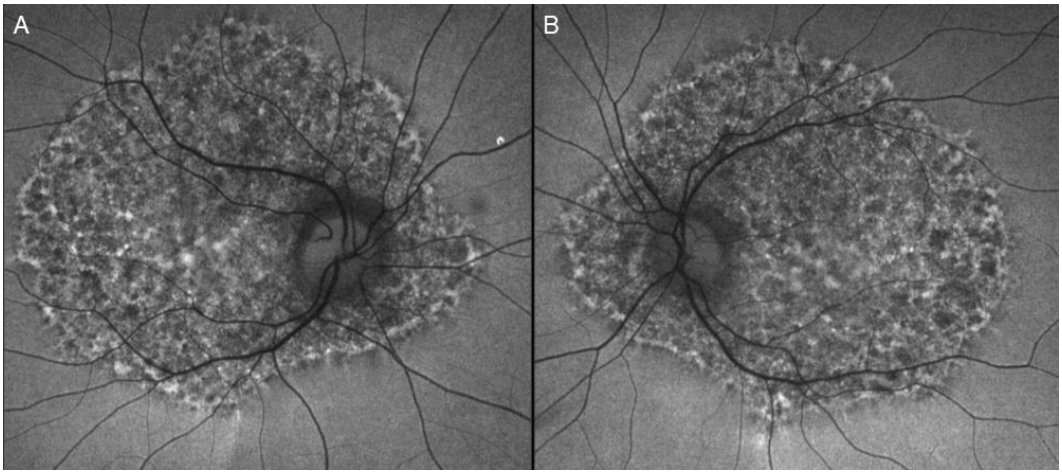



*Figure 3: Fundus autofluorescence of Pentosan maculopathy showing speckled hyperautofluorescence in the posterior pole with peripapillary extension. Hyperautofluorescent spots correspond to pigmented deposits or vitelliform-like lesions noted on clinical exam in patients with Pentosan Maculopathy. This image was published in the Retina Image Bank® website. John S. King, MD, Kent Zocchi, MD. Photographer Karin. Pentosan Maculopathy. Retina Image Bank. 2018; Image Number 28442. © the American Society of Retina Specialists.*

Authors have postulated that the deposits in Pentosan maculopathy may represent diseased RPE cells accumulating byproducts of the visual cycle on their way to cell death. Alternatively, they may represent RPE cells accumulating PPS or one of its metabolic breakdown products, which has been noted on histopathology of the uroepithelium. Studies with radiolabeled PPS have shown that the drug and its metabolites distribute mainly in the uroepithelium and to a significantly lesser degree in the other visceral organs. A 3-month placebo-controlled study of PPS for 258 patients with interstitial cystitis reported no vision-related complications. The longest clinical trial assessing PPS was conducted for 90 months. Pentosan maculopathy appears to be a disease of chronic use of the drug. There is no known treatment for this maculopathy, but once identified, consideration should be given for stopping the drug. It is unclear at this time to what degree the maculopathy progresses or halts after cessation of PPS, but there are reports of progression of Pentosan maculopathy even 10 years after cessation of the drug. The patient's case should be discussed in collaboration with the Urologist or Primary Care Physician in order to assess the risk of stopping the drug on the patient's interstitial cystitis and pelvic pain. We recommend that patients taking Pentosan who have changes in the macula be referred to a retina specialist for further evaluation for possible Pentosan Maculopathy. A baseline screening exam, autofluorescence, and OCT at the onset of treatment should also be considered.

**References:**

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**Take Home Points: Pentosan Maculopathy**

- Pentosan maculopathy is a disease of chronic use of the drug Pentosan polysulfate sodium (PPS; Elmiron), which manifests with early pigmentary deposits, complicated by late outer retinal atrophy.
- Visual acuity may remain excellent in late stages of the disease, but contrast sensitivity, reading, and dark adaptation may be severely compromised. Additional metrics should be monitored.
- In a large series of Pentosan Maculopathy, the median duration of exposure to PPS was 15 years (range, 3 – 22 years), with a median cumulative exposure of 1.61 kilograms (range, 0.44 - 4.31 kg).

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