

A PRIMER ON PENTOSAN POLYSULFATE SODIUM MACULOPATHY



Evidence of a new maculopathy is emerging in the clinic.

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Mounting evidence links chronic exposure to pentosan polysulfate sodium (PPS; Elmiron, Janssen Pharmaceuticals) with the development of a novel pigmentary maculopathy. PPS is a semi-synthetic heparin-like macromolecule used to treat interstitial cystitis (IC), a chronic, incurable bladder pain syndrome manifesting as relentless bladder or pelvic pain, incontinence, and dyspareunia. It is estimated that IC affects more than 1 million individuals in the United States, predominantly women.^{1,2} PPS is the only oral option of the two US FDA-approved therapies for IC. Since compassionate use in 1986 and regulatory approval in 1996, PPS has been prescribed by urologists and gynecologists to hundreds of thousands of patients with IC.^{3,4}

The association of PPS with maculopathy was first reported in 2018 by Pearce et al in a single-center case series of six patients (six white women, median age 60 years, age range 37-62 years) reporting difficulty reading, paracentral scotomas, and prolonged dark adaptation despite relatively preserved visual acuity.⁵ Examination revealed paracentral retinal pigment epithelium (RPE) hyperpigmentation surrounded by subtle vitelliform-like deposits with highly irregular appearances on fundus autofluorescence (FAF)

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and near-infrared reflectance (NIR) imaging. These patients underwent genetic screening and evaluation for hereditary retinal dystrophies and mitochondrial cytopathies, all of which were negative. Diagnosis of IC and exposure to PPS was the common denominator in all patients.

Subsequent case series and cohort studies demonstrated a pattern of PPS exposure characteristics and clinical features.⁶⁻⁸ In these studies, affected patients tended to be white women of median age 60 years (range 37-79 years). Symptoms most commonly reported were blurred

AT A GLANCE

- Patients exposed to pentosan polysulfate sodium (PPS) have increased risk of developing maculopathy.
- PPS is used to treat interstitial cystitis and has been used by patients since 1986.
- Annual exams with imaging are recommended for patients who have had chronic PPS exposure.

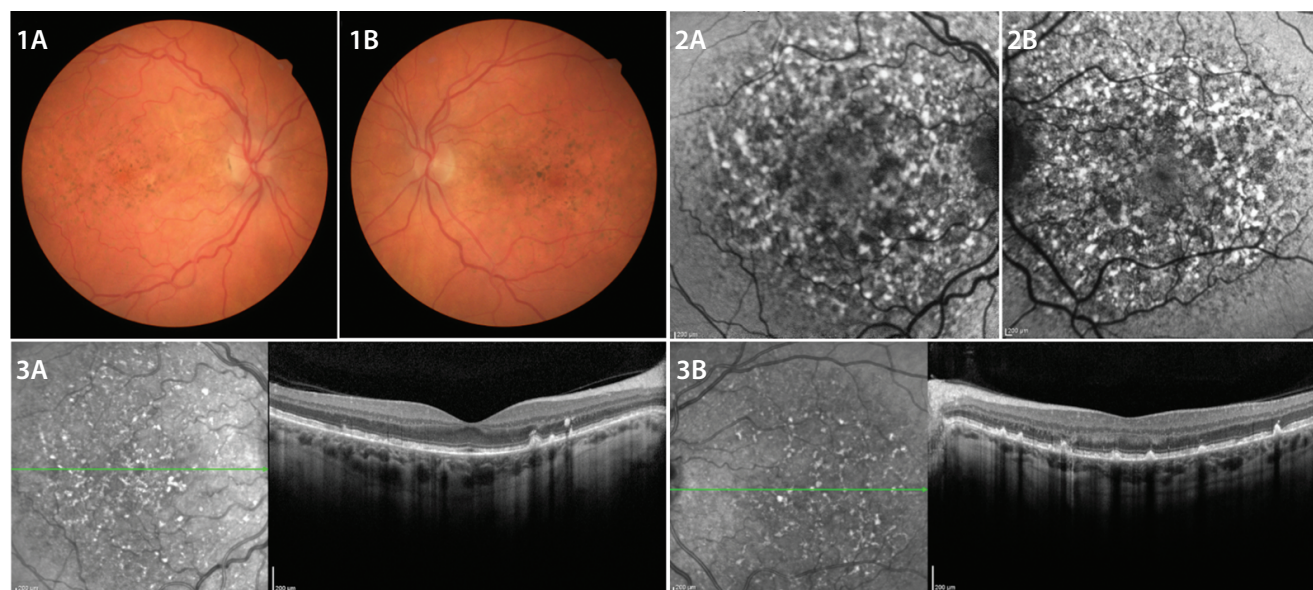


Figure. Clinical characteristics of PPS maculopathy are demonstrated here, with bilateral symmetric pathology centered on the fovea. Hyperpigmented spots, pale yellow-orange deposits, and/or patchy RPE atrophy are observed on color fundus photography (1 A, B). FAF imaging reveals a dense array of hyper- and hypoautofluorescent spots in the posterior pole that tend to be much more striking than relatively subtle fundus examination findings (2 A, B). OCT imaging demonstrates focal thickening or elevation of the RPE layer with associated hyperreflectance on NIR imaging (3 A, B).

vision, prolonged dark adaptation, and metamorphopsia. The most common presenting diagnoses for these cases were macular or pattern dystrophy and age-related macular degeneration (Figure).

Longitudinal follow-up suggests a progressive maculopathy that spreads centrifugally. Macular pigment clumps appear to be a sign of early disease and may ultimately progress to RPE atrophy in later stages. Visual acuity tends to be preserved, except in cases of center-involving RPE atrophy and cystoid macular edema.^{6,8} To date, there is also a single case report of choroidal neovascularization associated with PPS maculopathy that resulted in vision loss.⁹ Full-field electroretinography demonstrates variable mild attenuation of response amplitudes that is consistent with macular disease, and multifocal electroretinography reveals mild to severe attenuation.

RELATIONSHIP TO PPS EXPOSURE

In a cohort of 219 patients with IC and PPS exposure, the odds ratio for developing an unspecified pigmented maculopathy was 11.25, and all

14 patients with definite clinical characteristics of PPS maculopathy had exposure to PPS.⁷ No other IC therapy demonstrated a significant association with maculopathy. Patients with maculopathy reported duration of PPS intake ranging 3 to 22 years (median 16-17 years).⁵⁻⁹ A retrospective cohort study by Jain et al involving a large US claims database found that, by 7 years, PPS users had significantly increased odds (odds ratio = 1.41) of developing maculopathy compared with matched controls.¹⁰

In a large cohort of patients, Vora et al reported definite signs of PPS maculopathy in 11% of patients taking 500 to 999 g PPS daily, and in 42% of those taking more than 1,500 g PPS daily.⁸ Patients with maculopathy had ingested an average of 14,067 capsules compared with 10,561 capsules in those without maculopathy.⁸

IMPLICATIONS

It is unusual for a potential drug toxicity to manifest decades after initial FDA approval. PPS safety was not a major issue in clinical trials, and no ocular adverse events were identi-

fied.¹¹⁻¹³ Pathogenesis remains unclear. Based on the prolonged exposure time and cumulative dose, the mechanism is potentially related to toxic PPS metabolites accumulating in the RPE, thereby disrupting processing of photoreceptor outer segments or the interphotoreceptor matrix.⁶

These findings represent a major patient safety issue. Many patients with PPS exposure may have been misdiagnosed with age-related macular degeneration or retinal dystrophies, which may have led to preventable, irreversible vision loss or unwarranted genetic counseling. It remains unclear whether discontinuing PPS will halt or alter the course of maculopathy. For now, evidence suggests that the smallest effective dose should be used for the least amount of time.

It may be advisable to perform annual exams with imaging (ie, fundus photography, FAF, NIR, and OCT) of patients with chronic PPS exposure. Discussion with urology and gynecology colleagues is ongoing to raise awareness of PPS toxicity; at the time of publication, the FDA has not

issued any warnings.¹⁴⁻¹⁷ Further investigation is warranted to explore pathogenesis and to inform screening guidelines for this sight-threatening condition. ■

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