JAMA Ophthalmology | Original Investigation

Phenotypic Spectrum of Pentosan Polysulfate Sodium–Associated Maculopathy
A Multicenter Study

Adam M. Hanif, MD; Stephen T. Armenti, MD, PhD; Stanford C. Taylor, MD; Rachel A. Shah, MD; Austin D. Igelman, BS; K. Thiran Jayasundera, MD; Mark E. Pennesi, MD, PhD; Rahul N. Khurana, MD; Jenelle E. Foote, MD; Ghazala A. O'Keefe, MD; Paul Yang, MD, PhD; G. Baker Hubbard III, MD; Thomas S. Hwang, MD; Christina J. Flaxel, MD; Joshua D. Stein, MD; Jiong Yan, MD; Nieraj Jain, MD

IMPORTANCE A unique pigmentary maculopathy was recently described in 6 patients with long-term exposure to pentosan polysulfate sodium (PPS), a long-standing oral therapy for interstitial cystitis.

OBJECTIVE To characterize the exposure characteristics and clinical manifestations of PPS–associated maculopathy.

DESIGN, SETTING, AND PARTICIPANTS In this multi-institutional case series, medical records of patients who exhibited the characteristic maculopathy in the setting of prior PPS exposure were retrospectively reviewed. Data were collected from August 1, 2012, to October 1, 2018, and data were analyzed from October 2018 to January 2019.

MAIN OUTCOMES AND MEASURES Drug exposure, visual acuity, and retinal imaging characteristics.

RESULTS Of the 35 included patients (70 eyes), 34 (97%) were female, and the median (range) age was 60 (37-79) years. The median (range) duration of PPS intake was 15 (3-22) years, and the median (range) cumulative exposure was 1.61 (0.44-4.31) kg. The leading visual symptoms were metamorphopsia, blurred vision, and prolonged dark adaptation. Median (range) logMAR visual acuity of all eyes was 0.10 (−0.12 to 1.18). Fundus examination often revealed hyperpigmented macular spots (34 of 64 eyes [53%]) with interspersed pale-yellow deposits, although less commonly in eyes that exhibited retinal pigment epithelial atrophy (6 of 26 eyes [23%]; $P < .001$). Optical coherence tomography showed foci of retinal pigment epithelium elevation or thickening associated with hyperreflectance on near-infrared reflectance imaging. Fundus autofluorescence imaging typically revealed a symmetric, confluent pattern of hyperautofluorescent and hypoautofluorescent spots that involved the fovea in all eyes and extended to the retinal periphery in 24 eyes (36%). Longitudinal evaluation demonstrated dynamic changes in pigmentary abnormalities.

CONCLUSIONS AND RELEVANCE These findings suggest that PPS–associated maculopathy is a vision-threatening condition that can manifest in the setting of long-term exposure to the drug. Multimodal imaging posits a distinctive clinical phenotype, characterized in this cohort by dynamic alterations within the retinal pigment epithelium and at the retinal pigment epithelium–photoreceptor interface. Ongoing work might explore causality and direct screening guidelines.

JAMA Ophthalmol. 2019;137(11):1275-1282. doi:10.1001/jamaophthalmol.2019.3392
Published online September 5, 2019.

Supplemental content

Author Affiliations: Emory University School of Medicine, Atlanta, Georgia (Hanif); Department of Ophthalmology and Visual Sciences, University of Michigan Kellogg Eye Center, Ann Arbor (Armenti, Jayasundera, Stein); Casey Eye Institute, Department of Ophthalmology, Oregon Health and Science University, Portland (Taylor, Igelman, Pennesi, Yang, Hwang, Flaxel); Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia (Shah, O'Keefe, Hubbard, Yan, Jain); Northern California Retina Vitreous Associates, Mountain View (Khurana); Midtown Urology, Atlanta, Georgia (Foote).

Corresponding Author: Nieraj Jain, MD, Department of Ophthalmology, Emory University School of Medicine, 1365B Clifton Rd NE, Ste 2400, Atlanta, GA 30322 (nieraj.jain@emory.edu).

Pentosan polysulfate sodium (PPS) is the only oral therapy approved by the US Food and Drug Administration for interstitial cystitis (IC), a chronic pain syndrome of the bladder that has been estimated to affect more than 1 million people in the United States.[1-5] An analogue of biologic glycosaminoglycans, PPS purportedly binds to the bladder epithelium and serves as a barrier to potential irritants.[6,7] In 2018, we described a unique pigmentary maculopathy observed by a single clinician in 6 patients undergoing long-term PPS therapy for IC.[8] Despite relatively preserved visual acuity, patients endorsed difficulty reading and prolonged dark adaptation. On examination, patients exhibited subtle macular pigmentary changes, yet manifested striking alterations on fundus autofluorescence (AF) and near-infrared reflectance (NIR) imaging.

Although present in a small group of patients, these findings were suggestive of a vision-threatening medication toxicity. Because PPS has been widely prescribed for IC since its approval by the Food and Drug Administration in 1996, many more patients may be at risk for this condition. Here, we present a retrospective case series of patients with retinal abnormalities who had PPS exposure treated across 4 institutions to further characterize the risk factors and clinical manifestations of this potentially unique maculopathy.

Key Points

Question What are the exposure characteristics and clinical manifestations of pentosan polysulfate sodium–associated maculopathy?

Findings In this case series, 35 affected patients reporting long-term pentosan polysulfate sodium exposure were identified. Fundus examination revealed macular pigment clumps amidst yellow subretinal deposits in mild disease with atrophy in more extensive disease, and fundus autofluorescence imaging demonstrated a pattern of abnormality centered on and involving the fovea, occasionally extending to the retinal periphery.

Meaning These findings suggest pentosan polysulfate sodium–associated maculopathy is a vision-threatening condition that can manifest in the setting of long-term exposure to the drug, and multimodal imaging posits a distinctive clinical phenotype.

Methods

This retrospective case series was approved by each participating institution's institutional review board and conducted at Emory University. Information was gathered and secured in compliance with the Health Insurance Portability and Accountability Act. All data were deidentified and shared securely with the Emory University study center. As this study involved retrospective medical record review, it met all requirements for a waiver of informed consent per institutional policy.

Case Identification

Electronic health records were searched for patients with PPS exposure at the Emory Eye Center, Emory University School of Medicine, Atlanta, Georgia (n = 16); Casey Eye Institute, Oregon Health and Science University, Portland (n = 6); University of Michigan Kellogg Eye Center, Ann Arbor (n = 11); and Northern California Retina Vitreous Associates, Mountain View (n = 2). Of these, a subset of the patients identified with PPS exposure came from the Sight Outcomes Research Collaborative Ophthalmology Data Repository. This repository captures the electronic health record data of all patients receiving eye care at academic centers participating in this research collaborative. All contributing sites used the Epic electronic health record system (Epic Systems Corporation). The repository captured patient demographic characteristics as well as structured and unstructured (free text) data for all clinical encounters from August 1, 2012, to October 1, 2018.

Expert reviewers at each institution (K.T.J., M.E.P., R.N.K., and N.J.) assessed the available retinal imaging for each patient exposed to PPS and identified affected patients according to the presence of characteristic features noted in our initial report,[8] including (1) fundus photography revealing macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium (RPE) atrophy; (2) AF imaging revealing a densely packed array of hyperautofluorescent and hypoautofluorescent spots involving the posterior pole; and (3) optical coherence tomography (OCT) imaging demonstrating focal thickening or elevation of the RPE with associated hyperreflectance on NIR imaging. A broad case definition was used to ensure inclusion of the full spectrum of clinical phenotypes.

For all cases of the characteristic maculopathy, medical records were reviewed for demographic and clinical characteristics, including patient age, sex, race, height, and weight. Duration of IC symptoms and PPS exposure history were recorded. Presence of potential risk factors was assessed. Finally, best-corrected visual acuity (BCVA) in logMAR at the initial visit was recorded.

Image Analysis

Expert graders (R.A.S. and N.J.) masked to exposure histories reviewed images of each case to confirm inclusion in the series.[8] The image graders assessed all available retinal imaging, including color fundus photography (TRC-50DX [Topcon Medical Systems]; California rg/af [Optos]), spectral-domain OCT (Spectralis [Heidelberg Engineering]; Cirrus 5000 [Carl Zeiss Meditec]), NIR imaging (Spectralis), and AF imaging (California rg/af; Spectralis).

Images were evaluated for features, including macular pigment clumps, RPE atrophy, yellow or orange deposits, and subretinal hemorrhage on color fundus photography; disease extent, foveal involvement, atrophy exceeding one-third of a disc diameter, and peripapillary signal abnormality on AF imaging; hyperreflectant spots, foveal involvement, and atrophy on NIR imaging; and cystoid macular edema, fibrovascular pigment epithelium detachment, subretinal fluid, focal RPE thickening or elevation, and atrophy on OCT imaging. Presence of atrophy with diameter exceeding one-third of a disc diameter was identified primarily with AF imaging according to a previously described approach.[9] Areas of well-demarcated decreased AF were identified using the hypoautofluorescence associated with blood vessels as a reference. Other imaging modalities were referenced to confirm cases of questionable atrophy. Foveal center

involvement was assessed with OCT. Regions of peripapillary atrophy were excluded from this analysis.

A disease staging system assessed severity based on the extent of fundus involvement and presence of macular RPE atrophy exceeding one-third of a disc diameter. Cases were classified into 1 of 3 grades: (1) contained within the vascular arcades without atrophy; (2) extending to the temporal vascular arcades but not spanning 2 disc diameters beyond the arcades and/or presence of noncentral atrophy; and (3) extending at least 2 disc diameters beyond the temporal vascular arcades and/or presence of atrophy involving the foveal center.

Statistical Analysis

Descriptive statistics were used to summarize demographic characteristics, exposure histories, and imaging findings. A Kruskal-Wallis test was performed to compare the average cumulative exposures per unit of body mass between the 3 grading groups. The associations between categorical variables were assessed with χ^2 tests. Statistical significance was set at a *P* value less than .05, and all *P* values were 2-tailed.

Results

A total of 70 eyes of 35 patients with PPS-associated maculopathy were identified (**Table**). These patients were retrospectively identified from a larger pool of 404 patients who reported active PPS use at the 4 centers during the study period, although many of the other patients did not have a comprehensive evaluation to adequately assess macular status. A total of 34 patients (97%) were female, and the median (range) age at the time of diagnosis was 60 (37-79) years. Most patients identified as white (33 [94%]). The most common presenting diagnoses were macular or pattern dystrophy (n = 15) and age-related macular degeneration (n = 10).

Patients reported a median (range) IC symptom duration of 19 (6-44) years. Median (range) PPS intake duration was 15 (3-22) years, with a median (range) cumulative dose of 1.61 (0.44-4.31) kg. Median (range) daily dose of PPS prescribed was 300 (150-592) mg. Median (range) cumulative exposure per unit of body mass was 24.7 (9.83-61.9) mg/kg. The median (range) height was 160 (142-175) cm, and median (range) body mass index (calculated as weight in kilograms divided by height in meters squared) was 25.5 (18.1-36.3).

The most commonly reported symptoms were blurred vision (n = 17), subjectively prolonged dark adaptation (n = 17), and metamorphopsia (n = 4). Median (range) logMAR BCVAs were 0.10 (0-1.18) OD (Snellen equivalent, 20/25 OD) and 0.10 (−0.12 to 1.30) OS (Snellen equivalent, 20/25 OS) (*P* = .93). Most eyes (60 of 70 [86%]) had a logMAR BCVA of 0.30 (Snellen equivalent, 20/40) or better. Two eyes (3%) had a BCVA of 1.0 (Snellen equivalent, 20/200) or worse. One of these eyes had RPE atrophy involving the foveal center, and the other had a hyperpigmented subfoveal RPE elevation with associated photoreceptor atrophy. Of the 6 eyes with center-involving atrophy, the median (range) logMAR BCVA was 0.54 (0-1.30) (Snellen equivalent, 20/70).

Visual field testing demonstrated fairly normal responses except in the presence of RPE atrophy (eTable 1 in the Supplement). Full-field electroretinography demonstrated variable mild attenuation of response amplitudes that was consistent with macular disease. Multifocal electroretinography demonstrated a range of abnormality from mild to severe attenuation of response amplitudes.

Imaging Findings

In all patients, pathology manifested bilaterally, centered on and involving the fovea. Color fundus photography revealed paracentral hyperpigmented spots in 34 of 64 eyes (53%), often with interspersed pale-yellow or orange deposits (**Figure 1**). There were no cases with typical macular drusen or subretinal or intraretinal hemorrhage.

Autofluorescence imaging permitted clearer visualization of disease extent and typically revealed a confluent, densely packed pattern of hyperautofluorescent and hypoautofluorescent spots and reticular changes, occasionally extending into the periphery (**Figure 2**). Hyperautofluorescent lesions colocalized with both the hyperpigmented macular spots and yellow deposits noted on fundus photography. No hyperautofluorescent spot was larger than 2 venule widths in any eye. In most eyes (37 of 66 [56%]), there was a well-circumscribed region of diseased tissue in the posterior pole, whereas some eyes exhibited ill-defined margins of disease (29 of 66 [44%]). In most cases that involved the peripapillary retina, there was a homogenous halo of peripapillary hypoautofluorescence (Figure 2).

Atrophy of the RPE exceeding one-third of a disc diameter in size was noted in 26 of 66 eyes (39%), involving the central fovea in 6 of them (eFigure 1 in the Supplement). Eyes with atrophy were less likely to have hyperpigmented macular clumps (6 of 26 eyes [23%]) compared with those without atrophy (28 of 38 eyes [74%]) (*P* < .001). Pigment clumps were also more frequently present in cases of pathology confined within the temporal arcades (20 of 26 eyes [77%]) than those that traversed the arcades (14 of 38 eyes [36.8%]) (*P* = .002).

Optical coherence tomography demonstrated that pigmented macular spots consisted of focal elevation or thickening of the RPE (**Figure 3**). These lesions cast a prominent shadow onto the underlying choroid, often appeared to be intraepithelial, and were associated with prominent signals on AF and NIR imaging. In some cases, RPE lesions were associated with hyperreflective foci within the overlying retina. There was not a clear OCT-based correlate for the yellow and orange deposits noted on color fundus photography. However, in all eyes, there was either a loss of definition of the interdigitation zone or a merging of interdigitation zone and ellipsoid zone bands in diseased areas. Cystoid macular edema was observed in 9 eyes of 6 patients. Fluorescein angiography performed on 1 of these patients demonstrated leakage associated with the cystoid macular edema. Two patients had prior diagnoses of choroidal neovascularization (CNV) in 1 eye. On review of available imaging, one such case was deemed to be highly suspicious of having a prior CNV (patient 15), whereas the other (patient 1) was thought to have cystoid macular edema.

Table. Demographic Information, Medical History, and Clinical Features of Identified Cases of Pentosan Polysulfate Sodium (PPS)–Associated Maculopathy

Patient No.	Sex/Race/Age, y	Referral Diagnosis	BMI[a]	IC Symptom Duration, y	Duration of PPS Intake, y	Mean Daily Dose, mg	Cumulative Exposure, kg	Visual Symptoms	Visual Symptom Duration, y	LogMAR VA		Grade
										OD	OS	
1	F/white/late 40s	AMD	23.5	14	13	231	1.10	Blurred vision	9	0	0.1	2
2	F/white/late 60s	AMD	25.5	13	13	323	1.55	Blurred vision	7	0	0.2	3
3	F/white/early 70s	Cone dystrophy vs AMD	26.1	15	15	300	1.64	Transient vision loss in the left eye and flashes, ringed scotomas, prolonged dark adaptation, impaired color vision, and light sensitivity in both eyes	8	0.6	0.9	3
4	F/American Indian/early 50s	Drusen vs AZOOR	24.9	16	12	450	2.04	Decreased near and peripheral vision and prolonged dark adaptation	2	0	0	2
5	F/white/mid-50s	Self-referral	24.7	8	7	400	1.02	Blurred vision and floaters	1	0	0	2
6	F/white/mid-50s	Metamorphopsia	30.2	6	Unknown	300	Unknown	Blurred vision, flashes, floaters, and decreased near vision	4	0.1	0	1
7	F/white/early 60s	Macular dystrophy	20.7	18	17	218	1.35	Prolonged dark adaptation and light sensitivity	6	0.1	0.1	2
8	F/white/early 50s	AMD	26.9	9	6	400	0.88	Metamorphopsia and light sensitivity	8	0	0	1
9	F/white/late 70s	Type 2 diabetes	29.3	6	6	300	0.68	Blurred vision	6	0.1	0.3	1
10	F/white/mid-50s	Type 2 diabetes	28.3	20	20	300	2.19	Blurred vision	Unknown	0	0	2
11	F/white/early 40s	Macular dystrophy	22.3	20	6	300	0.68	Metamorphopsia	1	0	−0.1	1
12	F/white/late 40s	Macular dystrophy	24.2	9	7	300	0.77	Blurred vision	1	0	0.2	2
13	F/white/early 60s	AMD	28.3	20	15	300	1.64	Blurred vision	2	0.2	0.3	NA
14	F/white/early 60s	Vitamin A deficiency	21.0	9	9	400	1.29	Prolonged dark adaptation	3	0	0.2	3
15	F/white/early 60s	AMD	18.1	10	10	300	1.10	Transient vision loss in the right eye	5	0.6	0.1	1
16	F/white/late 70s	AMD	26.7	35	15	150	0.82	Prolonged dark adaptation	Unknown	0.1	0.3	2
17	F/white/mid-40s	Metamorphopsia	25.4	43	3	400	0.44	None reported	NA	0	0	1
18	F/white/late 50s	AMD	26.0	18	18	457	2.98	Prolonged dark adaptation	5	0.3	0.3	3
19	F/white/early 60s	Macular dystrophy	26.1	18	18	389	2.56	Generalized dimming of vision, blurred vision, and prolonged dark adaptation	5	0.1	0.1	2
20	F/white/mid-60s	Pattern dystrophy	22.9	28	22	200	1.57	Blurred vision, spots in vision, and central scotomas	5	0.5	1.3	3
21	F/white/early 60s	Macular dystrophy	18.7	20	20	380	2.77	Paracentral scotoma and prolonged dark adaptation	4	0	0	1
22	F/white/early 60s	Pattern dystrophy	27.8	29	19	400	2.74	Prolonged dark adaptation, intermittent metamorphopsia, and spots in vision	6	0	0.1	3
23	F/white/early 60s	Macular dystrophy	19.7	39	12	300	1.31	Generalized dimming of vision, blurred vision, and prolonged dark adaptation	4	0.6	0.4	3
24	F/white/mid-40s	Macular dystrophy	35.4	14	14	400	2.04	Decreased near vision, blurred vision, and prolonged dark adaptation	4	0	0	2
25	F/white/late 30s	Macular dystrophy	36.3	13	14	400	2.04	Decreased near vision, blurred vision, and prolonged dark adaptation	7	0	0	3
26	F/white/mid-70s	AMD	18.8	22	22	300	2.40	None reported	NA	0.1	0.1	1
27	F/African American/late 30s	Macular dystrophy	21.5	25	9	300	0.99	Paracentral scotomas and blurred vision	1	0.2	0.4	3

(continued)

Table. Demographic Information, Medical History, and Clinical Features of Identified Cases of Pentosan Polysulfate Sodium (PPS)–Associated Maculopathy (continued)

Patient No.	Sex/Race/Age, y	Referral Diagnosis	BMI[a]	IC Symptom Duration, y	Duration of PPS Intake, y	Mean Daily Dose, mg	Cumulative Exposure, kg	Visual Symptoms	Visual Symptom Duration, y	LogMAR VA		Grade
										OD	OS	
28	F/white/late 60s	Urologist referral	28.7	30	20	300	2.18	Prolonged dark adaptation and impaired color vision	1	0.1	0	3
29	F/white/early 60s	Macular dystrophy	27.2	20	17	400	2.48	Metamorphopsia and prolonged dark adaptation	2	0	0	1
30	F/white/early 60s	Pattern dystrophy	23.0	20	20	400	2.92	Blurred vision	3	0.1	0.1	1 OD; 2 OS
31	M/white/late 70s	Pattern dystrophy	28.1	44	20	592	4.31	Blurred vision, prolonged dark adaptation, and spots in vision	5	1.2	0.5	1
32	F/white/early 70s	Macular dystrophy	21.0	20	20	400	2.92	Prolonged dark adaptation	Unknown	0.1	0.1	2
33	F/white/mid-50s	Pigment dispersion	36.3	20	Unknown	Unknown	Unknown	None reported	NA	0.1	0.1	NA
34	F/white/early 60s	Uveitis	21.6	Unknown	Unknown	200	Unknown	Blurred vision	Unknown	0.7	0	3
35	F/white/mid-60s	AMD	27.1	8	7	300	0.81	Prolonged dark adaptation and generalized dimming of vision	Unknown	0.1	0.1	3
Median	60.0	NA	25.5	19.0	14.5	300	1.61	NA	4.0	0.1	0.1	NA
Mean (SD)	59.1 (10.9)	NA	25.5 (4.6)	19.4 (10.0)	13.9 (5.5)	338 (87)	1.76 (0.90)	NA	4.2 (2.4)	0.2 (0.3)	0.2 (0.3)	NA

Abbreviations: AMD, age-related macular degeneration; AZOOR, acute zonal occult outer retinopathy; BMI, body mass index; F, female; IC, interstitial cystitis; M, male; NA, not applicable; VA, visual acuity.

[a] Calculated as weight in kilograms divided by height in meters squared.

Longitudinal Follow-up

Longitudinal data exceeding 3 years were available in 8 patients. As the study was conducted retrospectively, follow-up intervals were not uniform across all cases. Visual acuity was the primary measure of visual function available across multiple visits and remained fairly stable over time, except in the case of center-involving RPE atrophy. Hyperpigmented parafoveal spots, when present, appeared to spread within the macula over time (eFigure 2 in the Supplement), with an expanding area of macular involvement noted on AF imaging (**Figure 4**). In 1 eye with 6 years of follow-up, hyperpigmented spots resolved with onset of paracentral RPE atrophy (eFigure 2 in the Supplement). Regions of RPE atrophy were noted to enlarge in area with time (eFigure 4 in the Supplement). In 1 patient, serial OCT imaging at the same retinal location demonstrated changes in RPE nodule shape and size over 1 year (eFigure 3 in the Supplement).

Polypharmacy and Risk Factors

Patients reported off-label use of other medications for IC, including tricyclic antidepressants (n = 11); gabapentin and its analogues (n = 11); cyclobenzaprine (n = 8), bladder relaxants (n = 7), and pyridium (n = 5); and hyoscyamine or hyoscyamine-containing compounds (n = 3) (eTable 2 in the Supplement). One patient reported 6 months of hydroxychloroquine intake. Smoking history was reported in 8 patients. Three patients reported chronic kidney disease, and 1 patient had a prior splenectomy. Molecular testing performed in 17 patients returned a single pathogenic *ABCA4* variant (patient 12), a variant of unknown significance in *ABCA4* in 2 different individuals (patients 4 and 11), and 1 variant of unknown significance each of *ADAM9* and *IMPG2* (patient 3), *MPZ* (patient 23), and *TIMP3* (patient 29). Patient 20 harbored a nonsense *IMPG2* variant, although fundus findings did not resemble those typically associated with *IMPG2*-associated disease.

Severity Grading

A total of 21, 21, and 24 eyes received severity grades of 1, 2, and 3, respectively (Table). Only 1 patient had eyes with differing grades, which was due to a small patch of atrophy in 1 eye. The mean (SD) cumulative PPS doses for patients within groups 1, 2 and 3 were 1.81 (1.26) kg, 1.74 (0.78) kg, and 1.74 (0.67) kg, respectively (P = .85). The mean (SD) cumulative dose per unit of body mass for each group was 30.5 (19.7) mg/kg, 28.7 (15.1) mg/kg, and 25.9 (9.1) mg/kg, respectively (P = .89). There was no significant association between cumulative dose per unit of body mass and severity grading (r^2 = 0.016). Further, there was no association between cumulative dose per unit body mass and visual acuity (r^2 = 0.014). Finally, there was no significant association between PPS exposure and disease extent or atrophy.

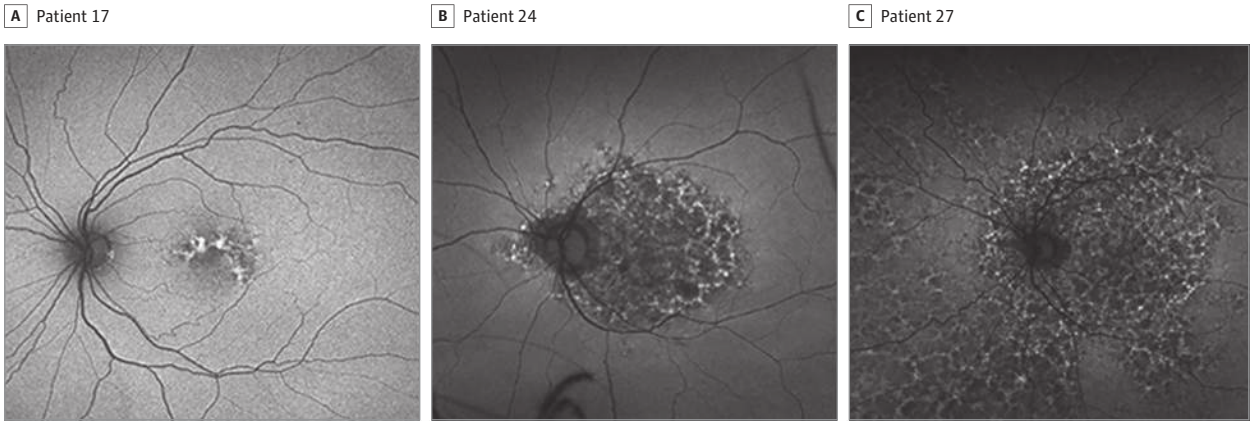
Discussion

This broad case series provides a comprehensive assessment of the phenotypic range of what appears to be a unique maculopathy among patients exposed to PPS. Imaging findings in

Figure 1. Representative Color Fundus Photography

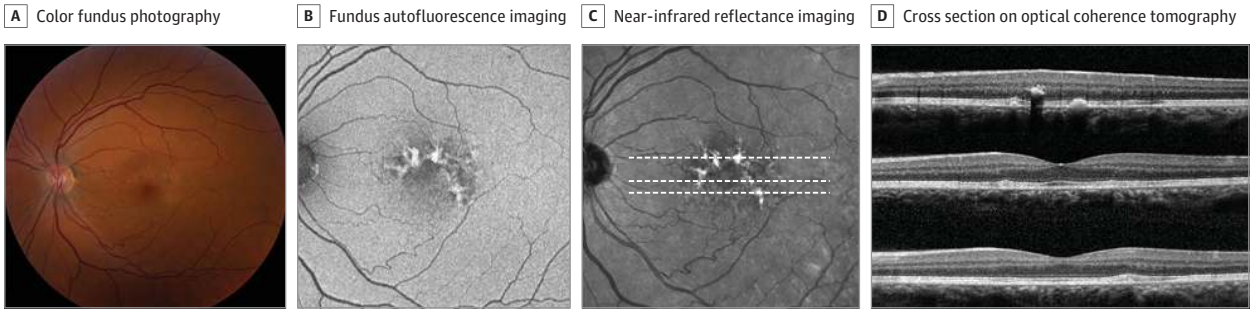
Representative color fundus photography demonstrating a variety of disease presentations, depicting pigment clumps and pale-yellow or orange deposits.

Figure 2. Representative Fundus Autofluorescence Imaging



Representative fundus autofluorescence imaging demonstrating a variety of disease presentations. Retinal pathology was subjectively more apparent on fundus autofluorescence imaging.

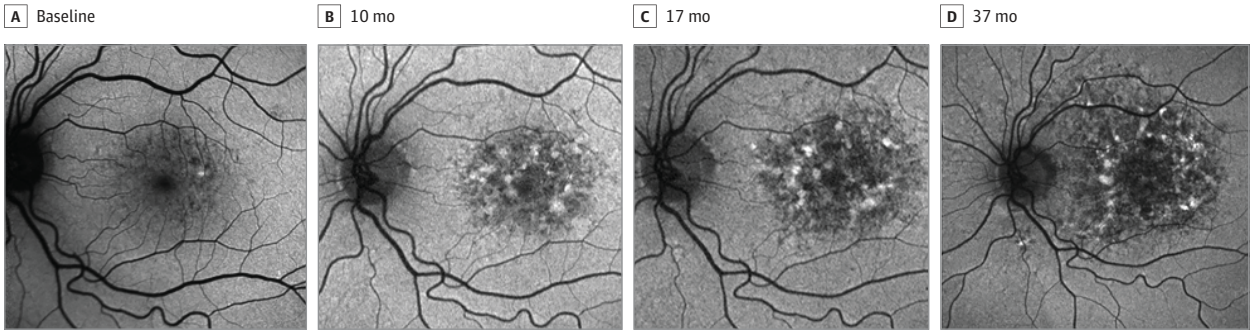
Figure 3. Multimodal Imaging of Macular Pigment Alterations



Representative images from patient 17. Some macular pigment clumps on color fundus photography (A) colocalize with increased signal on fundus autofluorescence imaging (B) and near-infrared reflectance imaging (C) and often appear to reside at the level of the retinal pigment epithelium on optical coherence tomography (D). The dotted lines in panel C correspond to the cross sections in panel D in descending order.

this series suggest that PPS-associated maculopathy is a dynamic condition that is characterized primarily by RPE and photoreceptor-RPE interface alterations in patients reporting long-term exposure to PPS. Given that this medication has been widely prescribed since its 1996 approval by the Food and Drug Administration and that it is intended to be taken long term for sustained disease control, it is likely that there are many thousands of at-risk individuals in the United States alone.[8,10,11]

Figure 4. Progression of Disease by Fundus Autofluorescence Imaging



Representative images from patient 29. Fundus autofluorescence imaging revealed progression of disease extent across 4 years, with particularly rapid evolution of changes over a 10-month period (panel A to panel B).

All patients reported long-term exposure to PPS, with a median exposure duration of 14.5 years. However, 1 patient had 3 years of exposure and manifested symptoms several years after drug cessation (patient 15). Further investigation is needed to explore the long-term disease course after drug cessation.

All patients reported standard dosing regimens, with body mass indexes ranging from underweight to obese. The mean height in this series of 160 cm is less than the mean height of US women (163 cm).[12] However, there was no correlation between disease severity and cumulative PPS exposure among different individuals, even when normalizing either to unit of body mass or ideal body weight. We did not identify any other predisposing factors for macular disease in this limited sample.

Color fundus photography typically demonstrated macular hyperpigmented spots that often appeared to be within the RPE on coregistered OCT imaging and were associated with blocking of signal to the underlying choroid. These characteristic RPE lesions, also seen in pattern dystrophies, can be readily distinguished from drusen or drusenoid RPE detachments, helping differentiate this condition from age-related macular degeneration. These lesions often appeared amidst a background of poorly defined yellow or orange subretinal deposits that lacked a clear anatomic correlate on OCT imaging, although abnormalities in the outer retinal bands suggest that they may reside in the subretinal space. Some cases were characterized by paracentral RPE atrophy that affected the foveal center only in advanced disease.

A characteristic feature of the maculopathy is that the AF findings are visually more apparent than the relatively subtle fundus examination findings. While AF imaging in most eyes revealed a well-circumscribed area of diseased tissue in the posterior pole, 24 of 66 (36%) exhibited a diffuse distribution. It remains unclear whether the diffuse disease pattern represents a normal late-stage manifestation of disease vs a distinct phenotype in certain individuals.

Many of the features of this condition resemble those seen in pattern dystrophies and other hereditary maculopathies.[13] A unique and clinically important imaging finding that may help differentiate this condition from hereditary maculopathies is the peripapillary AF pattern (Figure 2). In eyes with involvement of peripapillary tissue, there was often a peripapillary hypoautofluorescent halo, which is distinct from the peripapillary sparing that is often seen in conditions such as *ABCA4*-related retinopathies.

Longitudinal observation in a small number of cases suggests that this is a dynamic disease process. Pathology originates centrally and expands centrifugally. Hyperpigmented macular spots appear to be a sign of early disease and may ultimately be replaced by atrophy in later stages. Further longitudinal study in a greater number of cases seems warranted.

Although BCVA is generally well preserved, most patients reported bothersome visual symptoms, ranging from difficulty reading to prolonged dark adaptation. A decline in BCVA was often seen in the presence of cystoid macular edema or atrophy involving the foveal center, as noted in 6 eyes. We also identified a single possible case of vision loss due to exudative CNV (patient 15), diagnosed by an outside retina specialist. Available imaging was suggestive, but not definitive, of CNV.

The pathogenesis of this condition remains unclear. However, our present findings suggest a primary abnormality either within the RPE or at the RPE-photoreceptor interface. One hypothesis is that PPS or one of its many metabolites is directly toxic to the RPE, resulting in impaired RPE processing of photoreceptor outer segments. Another is that PPS somehow interacts with and disrupts the interphotoreceptor matrix, an extracellular matrix that serves numerous functions in mediating the photoreceptor-RPE relationship.[14,15] The interphotoreceptor matrix is comprised primarily of glycosaminoglycans similar in structure to PPS.[16]

Limitations

A primary limitation of this study is that our case definition was based on the initial small series of 6 patients, although we did endeavor to use a broad, inclusive case definition. Additionally, the retrospective nature of this study and relatively small sample size of 35 cases limit our ability to draw definitive conclusions regarding the spectrum of clinical phenotypes and our ability to investigate a dose-response relationship. Finally, there may be a component of selection bias given that most cases were identified at tertiary referral centers.

Conclusions

These findings suggest PPS-associated maculopathy is a vision-threatening condition that can manifest in the setting of long-term exposure to PPS. Multimodal imaging posits a distinctive clinical phenotype. Of the patients evaluated, many experienced prominent visual symptoms of difficulty reading and prolonged dark adaptation despite generally well-preserved visual acuity. In some instances, center-involving atrophy led to substantial visual disability.

Fundus findings in PPS-associated maculopathy may be subtle, yet multimodal posterior segment imaging, particularly AF imaging, suggests a distinctive appearance characterized by bilateral fundus abnormality centered on and involving the fovea. Structural changes suggest primary abnormalities within the RPE and at the photoreceptor-RPE interface. Longitudinal evaluation documents a dynamic disease process characterized by outward extension of pigmentary changes and ultimate development of macular RPE atrophy in many eyes. Further work seems warranted to more firmly establish causality and guide screening programs.

ARTICLE INFORMATION

Accepted for Publication: July 14, 2019.

Published Online: September 5, 2019. doi:10.1001/jamaophthalmol.2019.3392

Author Contributions: Drs Hanif and Jain (principal investigator) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hanif, Jayasundera, Pennesi, Khurana, Jain.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hanif, Jayasundera, Hubbard, Jain.
Critical revision of the manuscript for important intellectual content: Hanif, Armenti, Taylor, Shah, Igelman, Jayasundera, Pennesi, Khurana, Foote, O'Keefe, Yang, Hwang, Flaxel, Stein, Yan, Jain.
Statistical analysis: Hanif, Yang, Jain.
Obtained funding: Hanif, Jain.
Administrative, technical, or material support: Hanif, Khurana, Foote, O'Keefe.
Study supervision: Jayasundera, Khurana, O'Keefe, Flaxel, Jain.

Conflict of Interest Disclosures: Dr Hanif has received grants from the VitreoRetinal Surgery Foundation. Dr Jayasundera has received grant K23 EY026985-01from the National Institutes of Health. Dr Pennesi has consulted for Editas Medicine, ProQR Therapeutics, Nacuity Pharmaceuticals, Astellas Pharma, Gensight Biologics, Horama, Spark Therapeutics, Wave Life Sciences, Eyevensys, Nayan Pharmaceuticals, AGTC, Sanofi, and Nightstar Therapeutics. Dr Khurana has received grants from Clearside Biomedical, Roche, and Santen Pharmaceutical and has consulted for Alkahest, Allergan, Clearside Biomedical, Genentech, and Regeneron Pharmaceuticals. Dr Yang has received grants from the Foundation Fighting Blindness and National Institutes of Health; personal fees for consulting for Astellas Pharma; and clinical trial support from Sanofi, Nightstar Therapeutics, Foundation Fighting Blindness, and AGTC. Dr Hwang has received grants from the National Institutes of Health. Dr Stein has received grants from the National Institutes of Health. Dr Jain has received grants from the Foundation Fighting Blindness. No other disclosures were reported.

Funding /Support: Dr Hanif was supported by a research grant from VitreoRetinal Surgery Foundation. Dr Jain was supported by Career Development Award CD-C-0918-0748-EEC from the Foundation Fighting Blindness; core grants P30 EY006360 and EY010572 from the National Institutes of Health paid to the Emory Eye Center, Emory University School of Medicine, Atlanta, Georgia, and the Casey Eye Institute, Department of Ophthalmology, Oregon Health and Science University, Portland; and unrestricted departmental funding from Research to Prevent Blindness paid to the Casey Eye Institute.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Data contained herein were previously presented at the Association for Research in Vision Science and Ophthalmology 2019 Annual Meeting; April 30, 2019; Vancouver, British Columbia, Canada; and at the American Society of Retina Specialists 2019 Annual Meeting; July 30, 2019; Chicago, IL.

REFERENCES

1. Nickel JC, Moldwin R. FDA BRUDAC 2018 criteria for interstitial cystitis/bladder pain syndrome clinical trials: future direction for research. *J Urol*. 2018;200(1):39-42. doi:10.1016/j.juro.2018.02.011

2. Hanno PM, Erickson D, Moldwin R, Faraday MM; American Urological Association. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. *J Urol*. 2015;193(5):1545-1553. doi:10.1016/j.juro.2015.01.086

3. Giusto LL, Zahner PM, Shoskes DA. An evaluation of the pharmacotherapy for interstitial cystitis. *Expert Opin Pharmacother*. 2018;19(10):1097-1108. doi:10.1080/14656566.2018.1491968

4. Patnaik SS, Laganà AS, Vitale SG, et al. Etiology, pathophysiology and biomarkers of interstitial cystitis/painful bladder syndrome. *Arch Gynecol Obstet*. 2017;295(6):1341-1359. doi:10.1007/s00404-017-4364-2

5. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. *Urology*. 1997;49(5A suppl):2-9. doi:10.1016/S0090-4295(99)80327-6

6. Frileux C. Thrombocid: a new synthetic anticoagulant [article in French]. *Presse Med*. 1951;59(8):159.

7. Elmiron [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2012.

8. Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology*. 2018;125(11):1793-1802. doi:10.1016/j.ophtha.2018.04.026

9. Kuehlewein L, Hariri AH, Ho A, et al. Comparison of manual and semiautomated fundus autofluorescence analysis of macular atrophy in Stargardt disease phenotype. *Retina*. 2016;36(6):1216-1221. doi:10.1097/IAE.0000000000000870

10. Al-Zahrani AA, Gajewski JB. Long-term efficacy and tolerability of pentosan polysulphate sodium in the treatment of bladder pain syndrome. *Can Urol Assoc J*. 2011;5(2):113-118. doi:10.5489/cuaj.10095

11. Hanif AM, Shah R, Yan J, et al. Strength of association between pentosan polysulfate and a novel maculopathy [published online April 18, 2019]. *Ophthalmology*.

12. Institute of Medicine Food and Nutrition Board. *Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients*. Washington, DC: National Academies Press; 1998.

13. Hanif AM, Yan J, Jain N. Pattern dystrophy: an imprecise diagnosis in the age of precision medicine. *Int Ophthalmol Clin*. 2019;59(1):173-194. doi:10.1097/IIO.0000000000000262

14. Brandl C, Schulz HL, Charbel Issa P, et al. Mutations in the genes for interphotoreceptor matrix proteoglycans, *IMPG1* and *IMPG2*, in patients with vitelliform macular lesions. *Genes (Basel)*. 2017;8(7):E170. doi:10.3390/genes8070170

15. Ishikawa M, Sawada Y, Yoshitomi T. Structure and function of the interphotoreceptor matrix surrounding retinal photoreceptor cells. *Exp Eye Res*. 2015;133:3-18. doi:10.1016/j.exer.2015.02.017

16. Clark SJ, Keenan TD, Fielder HL, et al. Mapping the differential distribution of glycosaminoglycans in the adult human retina, choroid, and sclera. *Invest Ophthalmol Vis Sci*. 2011;52(9):6511-6521. doi:10.1167/iovs.11-7909