American Journal of Ophthalmology Case Reports 36 (2024) 102224

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Advanced pentosan polysulfate sodium maculopathy with low cumulative exposure and hydroxychloroquine use

Elena Flester [a], Shaden H. Yassin [b], Shyamanga Borooah [b,*]

[a] School of Medicine, University of California, San Diego, La Jolla, CA, USA
[b] Shiley Eye Institute, University of California, San Diego, La Jolla, CA, USA

ARTICLE INFO

Keywords:
Pentosan polysulfate sodium maculopathy
Hydroxychloroquine toxicity
Anti-VEGF
Retinal pigment epithelium
Ellipsoid zone
Macular edema

ABSTRACT

Purpose: To report a case of pentosan polysulfate sodium (PPS) maculopathy with cystoid macular edema (CME) with relatively low cumulative PPS exposure and a history of concurrent hydroxychloroquine use.

Observations: A 46-year-old female was treated with PPS daily for 10 years, and hydroxychloroquine intermittently over a span of five years, actively taking hydroxychloroquine for a sum of three years during PPS therapy. Despite a low risk for toxicity based on the cumulative exposure to either medication, fundoscopic examination and multimodal imaging revealed severe PPS maculopathy with CME two and a half years post-PPS cessation. CME was refractory to topical therapy and intravitreal anti-VEGF but improved with intravitreal dexamethasone. Bilateral improved visibility of the ellipsoid zone (EZ) was observed on Spectral Domain Optical Coherence Tomography (SD-OCT) following dexamethasone injection.

Conclusions and importance: Many reports describe an association between cumulative PPS exposure and maculopathy; however, risk factors that may contribute to PPS-associated maculopathy in the setting of low PPS exposure are not well characterized. This case indicates that other risk factors implicated in retinal pigment epithelium dysfunction should be investigated, including concurrent hydroxychloroquine use.

1. Introduction

Pentosan polysulfate sodium (PPS) is a semi-synthetic, sulfated polysaccharide prescribed to treat pain and discomfort associated with the bladder pain syndrome interstitial cystitis (IC).[1] Currently, PPS is the only FDA approved oral medication for IC.[2] Chronic PPS exposure is associated with toxic maculopathy. It was first described in 2018 by Pearce et al.,[3] but there have now been multiple reports globally including a number of large case series.[4–7]

PPS maculopathy is characterized by a wide range of retinal structural changes, as identified by dilated fundus examination (DFE) and various fundus multimodal imaging modalities, with subsequent impact on visual function.[8] DFE characteristically reveals macular pigment clumps in early stages of maculopathy and parafoveal or foveal RPE atrophy in advanced cases.[8] Pseudo-color fundus photography often displays hyper-pigmented macular lesions and yellow subretinal deposits, and in more advanced cases, photos reveal a patchy paracentral atrophy of the RPE.[4,8] Fundus autofluorescence (FAF) imaging in PPS maculopathy illustrates the most striking and unique pattern of abnormalities: a densely packed array of hyper- and hypo-autofluorescent spots centered on and involving the fovea symmetrically between the two eyes.[8] Co-localization with vitelliform lesions displaying focal thickening or elevation of the retinal pigment epithelium (RPE) on SD-OCT has also been described.[9–11] While the mechanism of PPS toxicity is not well-understood, it has been proposed to involve disruption of photoreceptor outer segment processing or RPE growth factors.[8] Distinctive visual symptoms including prolonged dark adaptation, nyctalopia and difficulty reading have been described even in the setting of relatively normal best corrected visual acuity (BCVA).[8] However, the phenotypic spectrum of PPS maculopathy is not yet clear. While several risk factors have been investigated for an association with the development of PPS maculopathy, including genetic associations[12] and kidney and liver problems,[10] high cumulative PPS exposure remains a unifying theme among reports of PPS maculopathy.[5,8] Furthermore, the long-term disease course after drug cessation has been retrospectively investigated. Thus far, no disease reversal has been reported, and most cases exhibit evolution of fundus findings for several years post PPS cessation.[12]

This report describes a patient with PPS-associated maculopathy disproportionate in severity when compared to her cumulative PPS dose.

* Corresponding author.
E-mail address: sborooah@health.ucsd.edu (S. Borooah).

https://doi.org/10.1016/j.ajoc.2024.102224
Received 27 June 2024; Received in revised form 24 October 2024; Accepted 13 November 2024
Available online 22 November 2024

Notably, the patient used hydroxychloroquine, a medication with well-characterized retinal toxicity,[13–15] concurrently with her last three years of PPS therapy. Hydroxychloroquine toxicity classically presents with a fovea-sparing concentric pattern of retinal thinning seen on fundus examination, which in some advanced cases is described as a bull's eye maculopathy.[13–16] The proposed mechanism of this toxicity involves hydroxychloroquine-led disruption of RPE metabolism ultimately leading to photoreceptor degeneration.[13,14] The severity and swiftness of maculopathy after cessation of both medications were unusual, and the pattern of the fundus abnormality noted could not be attributed to hydroxychloroquine toxicity. The reason for this unusual course is unclear but it is possible that the co-treatment of PPS and hydroxychloroquine, both thought to be toxic to the RPE, may have contributed. This report may inform management of similar cases and provide insight into additional risk factors for PPS-associated maculopathy.

2. Case report

A 46-year-old Hispanic female was referred by her ophthalmologist for evaluation for suspected bilateral PPS macular toxicity. The patient's medical history was remarkable for IC, managed for 10 years (2010–2019) with 100 mg PPS three times a day orally. Her medical history was unremarkable for diabetes mellitus, hypertension, kidney disease, and liver disease. The patient's cumulative PPS dose was estimated to be 1095 g. While on PPS, the patient also started taking 200 mg (2.56mg/kg by total body weight) hydroxychloroquine daily, using it intermittently over a span of five years (2016–2021) for management of her systemic lupus erythematosus (SLE). The patient was estimated to have actively taken the medication for a sum of three years. Her cumulative hydroxychloroquine dose was estimated to be 219 g with a cumulative exposure per body mass unit of 2.81 mg/kg by total body weight.

In 2021, the patient presented to her ophthalmologist with increasing blurry vision and metamorphopsia in both eyes. The patient's BCVA was 20/20 OD and 20/20-2 OS. Fundoscopic examination revealed thickening at the level of the retinal pigment epithelial (RPE) in both eyes. The patient was diagnosed with bilateral age-related macular degeneration (AMD); however, PPS retinal toxicity was suspected, and she was advised to follow up with a retinal specialist. In a case series of 35 patients, 29 % were initially diagnosed with AMD prior to the diagnosis of PPS-associated maculopathy.[4] In a retrospective cohort of 1604 PPS users, 5.4 % of patients received a new diagnosis of AMD with atypical maculopathy within 7 years of initiating PPS therapy, compared to 4.1 % of control patients,[17] indicating that PPS users are more likely to carry an AMD diagnosis than controls. Another retrospective series found that of 124 patients who had a cumulative PPS exposure greater than 1031g, 32.3 % had previously received a diagnosis of AMD or pigmentary maculopathy, compared to 15.2 % of control patients.[7] The two conditions can have similar features, and AMD is the more common of the two, which explains the propensity for misdiagnosis.[8,18] However, RPE lesions in PPS-associated maculopathy demonstrate hyperreflectivity on OCT and NIR imaging that distinguish this condition from the sub-RPE drusen associated with AMD.[19] In this patient's case, the medical history prompted further retinal imaging to confirm the diagnosis. Prior to this incident, the patient had discontinued PPS on her own, after learning of its ocular side effects. The patient also discontinued hydroxychloroquine after this initial diagnosis of macular disease.

Fifteen months later, the patient returned to her ophthalmologist with the progression of her blurry vision as well as metamorphopsia. BCVA was 20/20 OD and 20/30 OS. Fundus examination revealed bilateral cystoid macular edema (CME). The patient was started on a regimen of non-steroidal anti-inflammatory (ketorolac) and prednisolone eye drops, each 3 times daily, by her ophthalmologist. However, the edema failed to improve. Subsequently, 125 mg Acetazolamide daily was given orally, which resulted in some initial improvement on OCT, followed by progressive worsening, prompting her ophthalmologist to increase the dose of Acetazolamide to 250 mg twice daily. However, a continued increase of the patient's macular edema was observed with this regimen.

Five months after her CME diagnosis, the patient was referred to our clinic for extensive testing to rule out causes of the maculopathy. The patient described continued deterioration of her vision at her visit. Based on the patient's history, a pharmacologic cause of CME was excluded since she reported no use of nicotinic acid, anticancer agents, prostaglandin eye drops, or epinephrine eye drops, all of which are known to cause CME.[20–23] As the patient was phakic with no history of prior cataract surgery, Irvine-Gass syndrome was also excluded as a cause of CME in this case.[24] Ophthalmological examination was performed which included assessment of best-corrected visual acuity (BCVA) using a Snellen chart, slit lamp biomicroscopy and ophthalmoscopy. The comprehensive examination excluded other known causes of CME, such as retinal vein occlusion,[25] as there was no evidence of retinal hemorrhage, cotton-wool spots, vessel tortuosity, neovascularization, or microaneurysms on dilated fundus exam.[26] An inflammatory etiology of CME such as uveitis[25] was ruled out as there was no anterior chamber cell or vitreous haze on slit lamp examination and no vasculitis on FA.[27] Similarly, chronic central serous chorioretinopathy as an underlying cause of our patient's CME was excluded as there was no evidence of a smokestack pattern of leakage on FA or a serous macular detachment on SD-OCT.[28] Multimodal imaging was also performed, which included Spectral Domain Optical Coherence Tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany)(Fig. 1E and F), ultrawide-field (UWF) pseudo-color photos(Fig. 1A and C), fundus autofluorescence (FAF)(Fig. 1B and D), Fluorescein angiogram (FA)(Fig. 2), and Indocyanine green angiogram (ICG) (Optos, Nikon, UK). Additionally, microperimetry (S-MAIA, Centervue, Italy) was performed and both full-field electroretinograms (ff-ERG)(Fig. S1) and multifocal electroretinogram (mf-ERG)(Table S1) were recorded following pupillary dilation with the Espion system (Diagnosys, Lowell, MA, USA) using Dawson-Trick-Litzkow (DTL) recording electrodes and Ganzfeld stimulation according to standards from the International Society for Clinical Electrophysiology of Vision (ISCEV).[29,30] Genomic DNA extracted from the patient's saliva was enriched for targeted regions using a hybridization-based protocol and sequenced to $\geq$50x depth using standard techniques using Illumina technology in a CLIA-certified laboratory (Invitae, San Francisco, CA, USA).

The patient's BCVA at presentation was 20/40 OD and 20/70 OS. Examination of the anterior segment was unremarkable bilaterally. Fundus examination revealed thickenings at the level of the RPE bilaterally (Fig. 1A and C). FAF imaging demonstrated areas of both hyper- and hypo-autofluorescence (Fig. 1B and D). SD-OCT exhibited bilateral macular RPE abnormalities and CME (Fig. 1E and F) with the right eye also showing subretinal fluid. FA showed a characteristic pattern consistent with CME with macular leakage in both eyes but no retinitis or vasculitis (Fig. 2). ICG angiogram was within normal limits, making occult choroidal neovascularization or polypoidal choroidal vasculopathy unlikely.[31,32] The ff-ERG (Fig. S1) was within normal limits, indicating normal generalized retinal function and making a diagnosis with general rod or cone system dystrophy less likely.[33] The mf-ERG (Table S1) was also within normal limits except for blunting of ring 1 response, suggesting that a generalized macular or cone dysfunction was not present.[33] Electro-oculography (EOG) was within normal limits (Fig. S2), suggesting that there was no generalized RPE dysfunction. Abnormal EOG has been associated with macular dystrophies, such as Best disease,[34] another diagnosis often confused with PPS-associated maculopathy.[3] Next generation sequencing of the patient's buccal swab analyzing 330 IRD genes did not reveal any pathogenic variants. The appearance of this patient's retinal abnormality upon fundus examination and multimodal imaging did not match the major clinical characteristics of hydroxychloroquine retinal toxicity, classically described as a central concentric pattern of fovea-sparing parafoveal

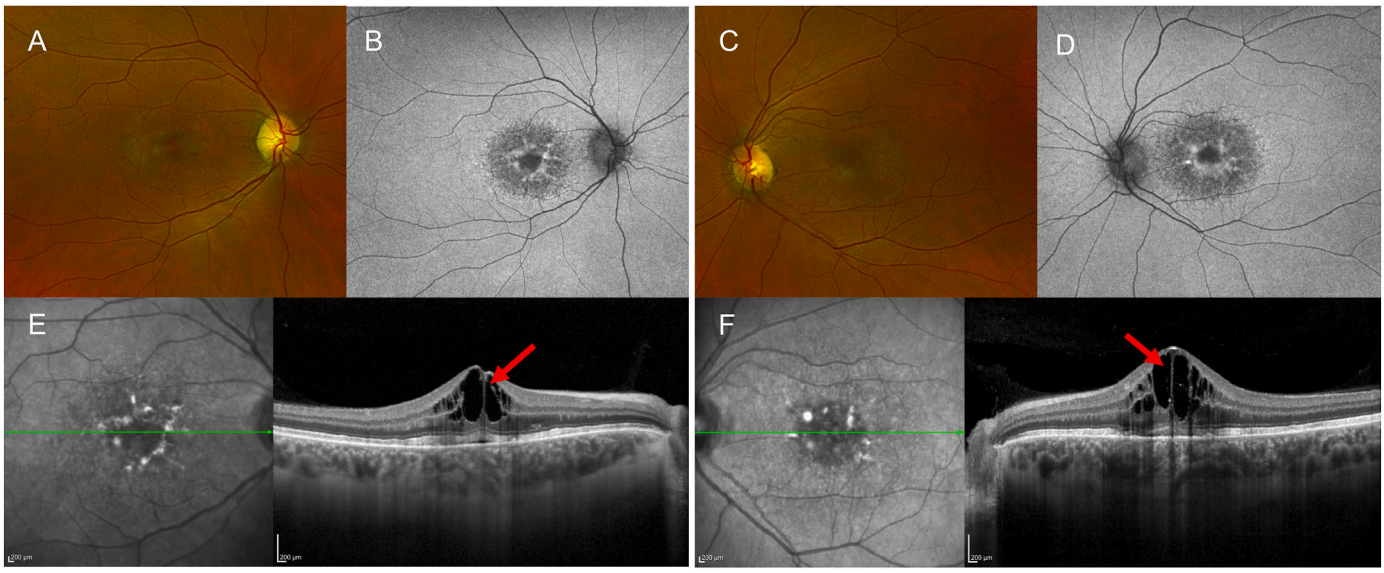

Fig. 1. Baseline multimodal imaging of both eyes. Ultrawide-field (UWF) pseudo-color photos of the right (A) and left (C) eyes showed retinal pigment epithelium (RPE) abnormalities. Fundus autofluorescence (FAF) of the right (B) and left (D) eyes respectively demonstrated a pattern of hyper- and hypo-autofluorescence surrounding the fovea. Spectral domain optical coherence tomography (SD-OCT) of the right (E) and left (F) eyes showed bilateral intraretinal (red arrows) and subretinal fluid, macular edema, and both RPE hypertrophy and irregularity.

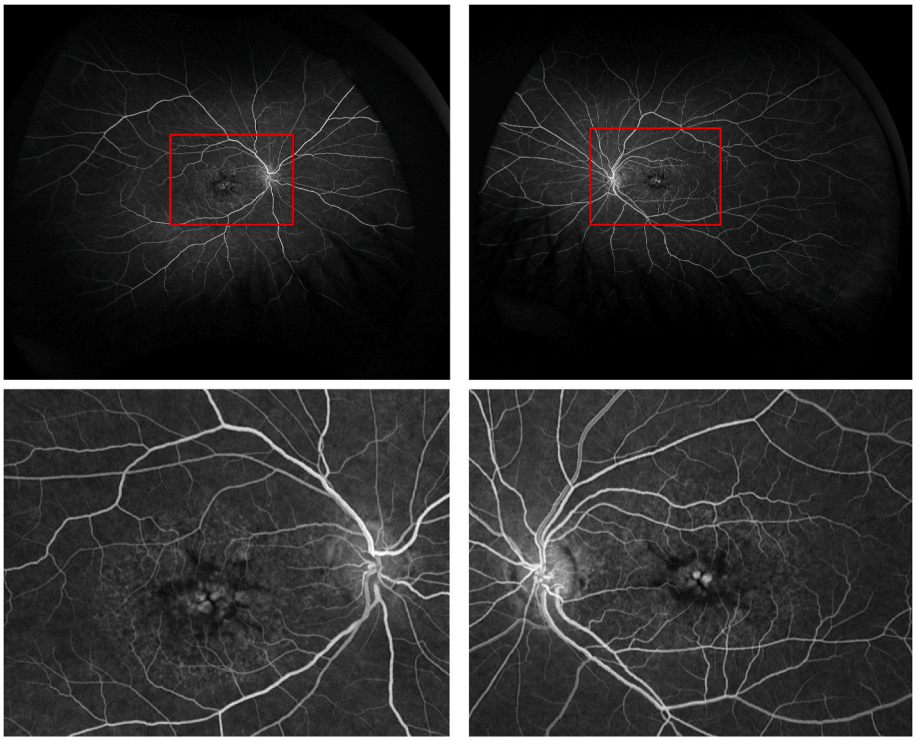

Fig. 2. Fluorescein angiography (FA) of both eyes showed the classic petaloid appearance characteristics of cystoid macular edema (CME) with macular leakage (red box).

thinning or bull's eye maculopathy,[13,14,16] therefore making the diagnosis of PPS maculopathy with CME more likely.

Following the patient's extensive diagnostic workup, her BCVA deteriorated to 20/400 in both eyes, and the decision was made to trial initial anti-VEGF therapy. The patient was given a series of 2 bilateral intravitreal injections of 1.25 mg/0.05 mL bevacizumab (Avastin), four weeks apart, with no change in CME (Fig. 3A) and continued visual decline in the left eye. This was followed by a series of two bilateral sub-Tenons injections of 40 mg/mL triamcinolone acetonide (Kenalog), administered at four-week intervals. This showed subtle improvement and suggested that the use of a stronger steroid may benefit the patient (Fig. 3B). Intravitreal 0.7 mg Dexamethasone (Ozurdex) implants were injected in the left eye at four weeks post-triamcinolone and in the right eye at six weeks post-triamcinolone. One month following Dexamethasone treatment, SD-OCT of both eyes showed marked reduction of CME with visibility of the ellipsoid zone (EZ) of the retina (Fig. 3C). BCVA improved to 20/250 for the right eye and 20/400 for the left eye at this time. 4.5 months after the initial Dexamethasone treatment, the patient

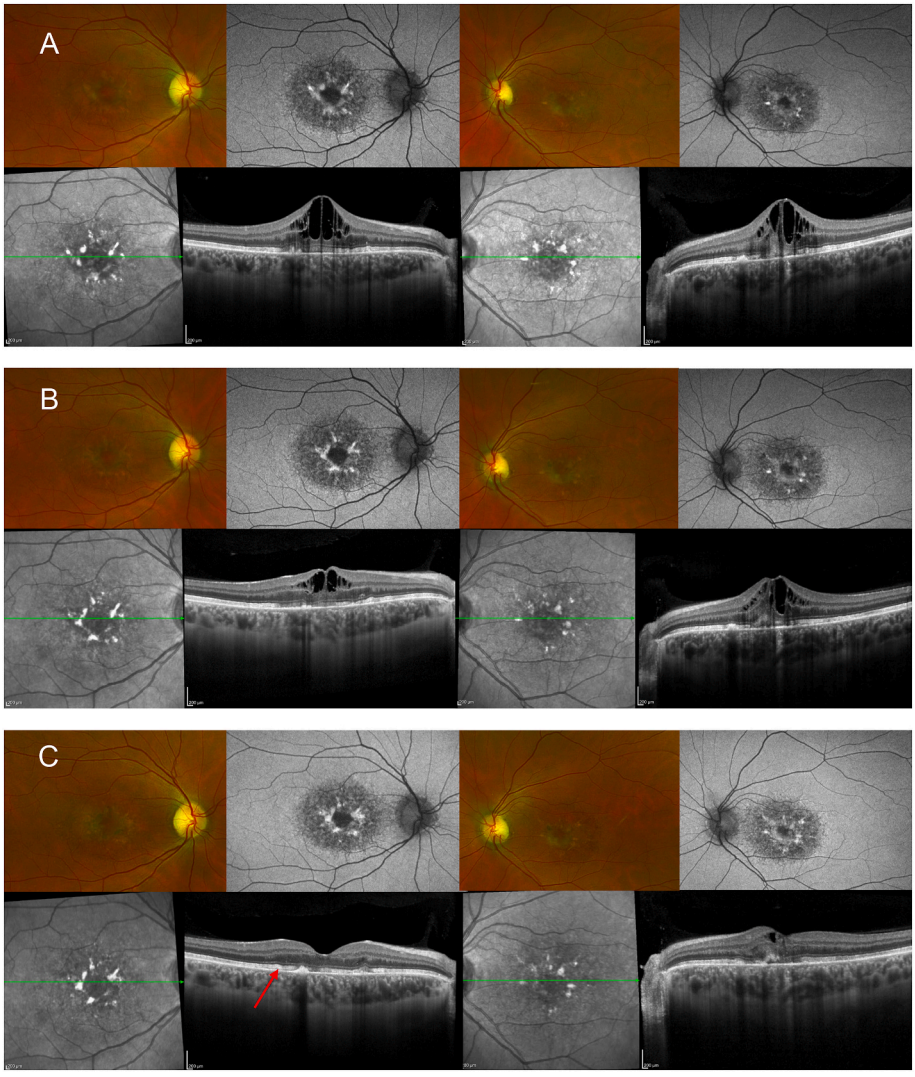

Fig. 3. Persistent cystoid macular edema (CME) after a series of two intravitreal bevacizumab injections (A). Subtle improvement in CME after a series of two sub-Tenon's triamcinolone acetonide injections indicated use of a stronger steroid (B). One month after injection of dexamethosone implants, CME was substantially reduced in both eyes and clearer visibility of parafoveal ellipsoid zone was observed (red arrow) (C).

returned with mildly worsening blurry vision in the right eye and received a second Dexamethasone injection for this eye. One week later, BCVA of the right eye returned to 20/200 and a second Dexamethasone injection was subsequently administered for the left eye, which had BCVA of 20/400 at this time. While the patient's prognosis for visual recovery is poor due to the RPE loss, especially in the left eye, we continue to monitor her condition.

3. Discussion

We report a case of PPS-associated maculopathy with CME arising after PPS cessation, unusual for its severity of pathology and vision loss given the patient's relatively low degree of cumulative exposure to PPS. CME was resistant to treatment with topical therapy, oral acetazolamide, anti-VEGF or sub-Tenon steroid but intravitreal dexamethasone implants effectively reduced CME in both eyes. While the patient had both low cumulative exposure and low cumulative time on dosing to hydroxychloroquine during PPS use, there were no clear signs of maculopathy characteristic of hydroxychloroquine toxicity and no generalized dysfunction of RPE or retina. It is unclear what risk factors may have contributed to the patient's maculopathy with loss of ellipsoid zone but not frank complete retinal pigment epithelium and outer retinal atrophy. There is a possibility that the patient's condition may progress to this stage.

The most well-established risk factor for the development of PPS maculopathy is chronic PPS exposure.[5,8] A survey of existing literature on PPS maculopathy found a median cumulative PPS dose of 1,824g in affected patients.[8] Wang et al. found that cumulative PPS dosage over 1500g was associated with a higher risk for developing maculopathy,[9] but other studies do not yet consistently agree on a threshold for high risk.[8]

The lowest reported cumulative PPS exposure in a patient with PPS-associated maculopathy was 435g.[35] In this case, a 44-year-old female presented with metamorphopsia, prolonged dark adaptation, and characteristics macular changes over thirty months post-PPS cessation. However, the patient did not have CME or ellipsoid zone loss. Cases of CME have previously been reported in PPS maculopathy.[4,36,37] However, it is difficult to rule out neovascularization as a cause. In one case where CME appeared isolated, a female patient in her late 40s was noted to have CME with a cumulative PPS dose of 1100g, but, unlike our patient, vision was not markedly reduced, as demonstrated by her logMAR vision of 0.0 and 0.1.[4] CME has been described before with PPS-associated maculopathy, but the few cases that also include a cumulative dose report a minimum cumulative dose of 1100g.[4,36,38]

The presence of PPS-associated maculopathy and disease progression described in our case appear to be uncommon given the patient's cumulative PPS exposure of 1095g. It is possible that cumulative PPS exposure alone may have contributed to our patient's unusual case of PPS-associated maculopathy. PPS is thought to be RPE toxic from reduced electroculographic data[8] and from a study in mice which showed RPE changes following long-term oral feeding with PPS.[39,40]

We suggest that the patient's concurrent use of hydroxychloroquine and PPS may have contributed to the unusual development of maculopathy. Cumulative hydroxychloroquine exposure greater than 1000g and duration of therapy over five years are major risk factors for hydroxychloroquine toxicity, in addition to liver and renal dysfunction.[13–15,41] However, our patient received a substantially lower cumulative hydroxychloroquine dose (219g) for a shorter period of time and had no systemic comorbidities. Moreover, the pattern of retinal abnormality observed in our patient was not consistent with the established features of hydroxychloroquine toxicity, including a central concentric pattern of parafoveal thinning or loss of photoreceptors, which is often fovea-sparing and may result in the classic bull's eye maculopathy observed in advanced-stage disease.[13,14,16] Additional findings indicative of hydroxychloroquine toxicity include an ovoid appearance of the fovea, or "flying saucer" sign, observed on SD-OCT as a result of perifoveal thinning[42] and a mottled pattern of parafoveal hyper-autofluorescence on FAF imaging.[14] The lack of these features diminished the likelihood of retinal damage due to hydroxychloroquine alone.

We hypothesize that similarities in the mechanisms of toxicity for both hydroxychloroquine and PPS could have contributed to a synergistic effect on RPE damage. The mechanism of toxicity for hydroxychloroquine is proposed to be a result of the drug's melanotropism, which causes it to accumulate in the RPE.[13,14] Reports indicate that once in the RPE, hydroxychloroquine impairs lysosomal function and disrupts RPE metabolism, leading to photoreceptor degeneration and loss.[13–15] The mechanism of toxicity for PPS is less well-understood. It has been suggested that PPS primarily interacts with the RPE and RPE-photoreceptor interface where it may disrupt processing of photoreceptor outer segments or inhibit RPE growth factors, leading to retinal damage.[8] Furthermore, it is possible that the toxic effects of PPS or hydroxychloroquine could have been potentiated by the patient's underlying systemic lupus erythematosus (SLE). An autoimmune condition, SLE has been shown to change enzyme metabolism and membrane transporter activity through increasing levels of pro-inflammatory cytokines.[43] This may both reduce renal clearance and increase the plasma concentration of systemic medications,[44] which could explain side effects disproportional to the dosage. However, as this mechanism has not been demonstrated in PPS or hydroxychloroquine toxicity specifically, further studies would be necessary to understand the potential role of SLE in PPS-associated maculopathy.

It is possible that simultaneous use of both hydroxychloroquine and PPS accelerates RPE damage, leading to a progression of maculopathy that is unexpected based on cumulative exposure to either medication. However, further investigation of the mechanism by which PPS causes maculopathy is necessary in order to understand how PPS and hydroxychloroquine may together contribute to accelerated retinal damage.

In previous cases of PPS-associated maculopathy with CME, macular edema has been successfully treated with a range of therapies, including topical prednisolone, oral acetazolamide, and intravitreal anti-VEGF.[8] Our patient's CME was refractory to each of these medications. Prior reports indicate that intravitreal injection of triamcinolone acetonide has effectively reduced CME associated with central retinal vein occlusion,[45] pseudophakic CME after cataract surgery,[46] and in one case of CME with PPS-associated maculopathy.[47] Subtle improvement of our patient's CME with intravitreal triamcinolone acetonide guided the decision to use dexamethasone intravitreal implants, a more potent steroid which is FDA-approved for treatment of macular edema resulting from retinal vein occlusions and diabetic macular edema.[48] One previous case of CME with PPS-associated maculopathy reports a successful response with intravitreal dexamethasone implants.[47] In our patient, dexamethasone implants effectively reduced CME. EZ disruption has been reported as a clinical characteristic of many degenerative retinal conditions, including cases of hydroxychloroquine toxicity[49,50] and PPS-associated maculopathy.[10,51,52] Several reports describe EZ recovery following intravitreal dexamethasone injection in patients with diabetic macular edema,[53] retinal vascular disease,[54] and hydroxychloroquine toxicity.[55–57]

In our patient's case, we suggest that other factors in addition to cumulative PPS exposure may have contributed to the severity of the patient's PPS-associated maculopathy. We hypothesize that concurrent use of hydroxychloroquine and PPS may have had a synergistic effect on RPE damage and contributed to the accelerated progression of maculopathy. This indicates a need to investigate the toxic mechanism of PPS and any additional risk factors for PPS-associated maculopathy, in order to better assess individual risk for patients using PPS. Our case also suggests that CME with PPS-associated maculopathy may be more responsive to intravitreal steroids, such as dexamethasone, than to intravitreal anti-VEGF.

4. Conclusion

Risk factors for PPS maculopathy other than cumulative PPS exposure are not well-characterized. This report illustrates a need for larger studies to investigate factors that may contribute to the development of PPS-associated maculopathy in addition to cumulative PPS exposure. In the present study, severe PPS maculopathy with EZ loss and CME was associated with the co-treatment with hydroxychloroquine. To our knowledge this is the first report of toxicity following co-prescribing of both PPS and hydroxychloroquine. The insights from the present study may allow prescribers to consider the risks of prescribing two RPE toxic drugs and assess the risk of maculopathy in patients.

CRediT authorship contribution statement

Elena Flester: Writing – original draft, Formal analysis. **Shaden H. Yassin:** Writing – review & editing, Methodology, Formal analysis. **Shyamanga Borooah:** Writing – review & editing, Supervision, Resources, Conceptualization.

Patient consent

A written informed consent was obtained from the patient.

Authorship

All authors attest that they meet the ICMJE criteria for authorship.

Funding

S.B. is funded by a Nixon Visions Foundation Award. The funding organizations had no role in the design or conduct of this research.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the patient for agreeing to publish her data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2024.102224.

References

1. Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs*. 2006;66:821–835. https://doi.org/10.2165/00003495-200666060-00006.
2. U.S. Food and Drug Administration. *Elmiron (Pentosan Polysulfate Sodium) NDA 020193/S015 Approval Letter*. Center for Drug Evaluation and Research; September 26, 1996. https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020193Orig1s000rev.pdf. Accessed May 30, 2024.
3. Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology*. 2018;125(11):1793–1802. https://doi.org/10.1016/j.ophtha.2018.04.026.
4. Hanif AM, Armenti ST, Taylor SC, et al. Phenotypic spectrum of pentosan polysulfate sodium–associated maculopathy: a multicenter study. *JAMA Ophthalmol*. 2019;137(11):1275. https://doi.org/10.1001/jamaophthalmol.2019.3392.
5. Vora RA, Patel AP, Melles R. Prevalence of maculopathy associated with long-term pentosan polysulfate therapy. *Ophthalmology*. 2020;127(6):835–836. https://doi.org/10.1016/j.ophtha.2020.01.017.
6. Foote J, Hanif A, Jain N. MP47-03 Chronic exposure to pentosan polysulfate sodium is associated with retinal pigmentary changes and vision loss. *J Urol*. 2019;201(suppl 4), e688. https://doi.org/10.1097/01.JU.0000556315.46806. ca.
7. Ulner OE, Shah MK, Jain N. Pentosan polysulfate and vision: findings from an international survey of exposed individuals. *Retina*. 2021;41(7):1562–1569. https://doi.org/10.1097/IAE.0000000000003078.
8. Lindeke-Myers A, Hanif AM, Jain N. Pentosan polysulfate maculopathy. *Surv Ophthalmol*. 2022;67(1):83–96. https://doi.org/10.1016/j.survophthal.2021.05.005.
9. Wang D, Velaga SB, Grondin C, et al. Pentosan polysulfate maculopathy: prevalence, spectrum of disease, and choroidal imaging analysis based on prospective screening. *Am J Ophthalmol*. 2021;227:125–138. https://doi.org/10.1016/j.ajo.2021.02.025.
10. Wang D, Au A, Gunnemann F, et al. Pentosan-associated maculopathy: prevalence, screening guidelines, and spectrum of findings based on prospective multimodal analysis. *Can J Ophthalmol*. 2020;55(2):116–125. https://doi.org/10.1016/j.jcjo.2019.12.001.
11. Kalaw FGP, Ignacio JCI, Wu CY, et al. Pentosan polysulfate sodium (Elmiron) maculopathy: a genetic perspective. *Retina*. 2023;43(7):1174–1181. https://doi.org/10.1097/IAE.0000000000003794.
12. Shah R, Simonett JM, Lyons RJ, Rao RC, Pennesi ME, Jain N. Disease course in patients with pentosan polysulfate sodium-associated maculopathy after drug cessation. *JAMA Ophthalmol*. 2020;138(8):894–900. https://doi.org/10.1001/jamaophthalmol.2020.2349.
13. Ding HJ, Denniston AK, Rao VK, Gordon C. Hydroxychloroquine-related retinal toxicity. *Rheumatology*. 2016;55(6):957–967. https://doi.org/10.1093/rheumatology/kev357.
14. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. *Eye*. 2017;31(6):828–845. https://doi.org/10.1038/eye.2016.298.
15. Geamănu Pancă A, Popa-Cherecheanu A, Marinescu B, Geamănu CD, Voinea LM. Retinal toxicity associated with chronic exposure to hydroxychloroquine and its ocular screening. Review. *J Med Life*. 2014;7(3):322–326. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4233433/. Accessed March 11, 2023.
16. Rodriguez-Padilla JA, Hedges III TR, Monson B, et al. High-speed ultra-high-resolution optical coherence tomography findings in hydroxychloroquine retinopathy. *Arch Ophthalmol*. 2007;125(6):775–780. https://doi.org/10.1001/archopht.125.6.775.
17. Jain N, Li AL, Yu Y, VanderBeek BL. Association of macular disease with long-term use of pentosan polysulfate sodium: findings from a US cohort. *Br J Ophthalmol*. 2020;104(8):1093–1097. https://doi.org/10.1136/bjophthalmol-2019-314765.
18. Mukhopadhyay C, Boyce TM, Gehrs KM, et al. Age-related macular degeneration masquerade: a review of pentosan polysulfate maculopathy and implications for clinical practice. *Asia Pac J Ophthalmol (Phila)*. 2022;11(2):100–110. https://doi.org/10.1097/APO.0000000000000504.
19. Christiansen JS, Barnes AC, Berry DE, Jain N. Pentosan polysulfate maculopathy versus age-related macular degeneration: Comparative assessment with multimodal imaging. *Can J Ophthalmol*. 2022;57(1):16–22. https://doi.org/10.1016/j.jcjo.2021.02.007.
20. Spirn MJ, Warren FA, Guyer DR, Klancnik JM, Spaide RF. Optical coherence tomography findings in nicotinic acid maculopathy. *Am J Ophthalmol*. 2003;135(6):913–914. https://doi.org/10.1016/s0002-9394(02)02296-1.
21. Risard SM, Pieramici DJ, Rabena MD. Cystoid macular edema secondary to paclitaxel (abraxane). *Retina Cases Brief Rep*. 2009;3(4):383–385. https://doi.org/10.1097/ICB.0b013e318193492c.
22. Cho H, Madu A. Etiology and treatment of the inflammatory causes of cystoid macular edema. *J Inflamm Res*. 2009;2:37–43. https://doi.org/10.2147/jir.s5706.
23. Miyake K, Ibaraki N. Prostaglandins and cystoid macular edema. *Surv Ophthalmol*. 2022;47(Suppl1):S203–S218. https://doi.org/10.1016/s0039-6257(02)00294-1.
24. Gass JD, Norton EW. Cystoid macular edema and papilledema following cataract extraction. A fluorescein fundoscopic and angiographic study. *Arch Ophthalmol*. 1966;76(5):646–661. https://doi.org/10.1001/archopht.1966.03850010648005.
25. Rotsos TG, Moschos MM. Cystoid macular edema. *Clin Ophthalmol*. 2008;2(4):919–930. https://doi.org/10.2147/opth.s4033.
26. Romano F, Lamana F, Gabrielle PH, et al. Update on retinal vein occlusion. *Asia Pac J Ophthalmol (Phila)*. 2023;12(2):196–210. https://doi.org/10.1097/APO.0000000000000598.
27. Pichi F, Invernizzi A, Tucker WR, Munk MR. Optical coherence tomography diagnostic signs in posterior uveitis. *Prog Retin Eye Res*. 2020;75, 100797. https://doi.org/10.1016/j.preteyeres.2019.100797.
28. Nicholson B, Noble J, Forooghian F, Meyerle C. Central serous chorioretinopathy: update on pathophysiology and treatment. *Surv Ophthalmol*. 2013;58(2):103–126. https://doi.org/10.1016/j.survophthal.2012.07.004.
29. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). *Doc Ophthalmol*. 2015;130(1):1–12. https://doi.org/10.1007/s10633-014-9473-7 [published correction appears in Doc Ophthalmol. 2015 Aug;131(1):81-3].
30. McCulloch DL, Marmor MF, Brigell MG, et al. Erratum to: ISCEV Standard for full-field clinical electroretinography (2015 update). *Doc Ophthalmol*. 2015;131(1):81–83. https://doi.org/10.1007/s10633-015-9504-z.
31. Stanga PE, Lim JI, Hamilton P. Indocyanine green angiography in chorioretinal diseases: Indications and interpretation: an evidence-based update. *Ophthalmology*. 2003;110(1):15–23. https://doi.org/10.1016/s0161-6420(02)01563-4.
32. Koh AH, Expert PCV Panel, Chen LJ, et al. Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. *Retina*. 2013;33(4):686–716. https://doi.org/10.1097/IAE.0b013e3182852446.
33. Robson AG, Nilsson J, Li S, et al. ISCEV guide to visual electrodiagnostic procedures. *Doc Ophthalmol*. 2018;136(1):1–26. https://doi.org/10.1007/s10633-017-9621-y.
34. Constable PA, Bach M, Frishman LJ, Jeffrey BG, Robson AG. ISCEV standard for clinical electro-oculography (2017 update). *Doc Ophthalmol*. 2017;134(2):155. https://doi.org/10.1007/s10633-017-9580-3 [published correction appears in Doc Ophthalmol. 2017;134(2):155.
35. Barnett JM, Jain N. Potential new-onset clinically detectable pentosan polysulfate maculopathy years after drug cessation. *Retin Cases Brief Rep*. 2022;16(6):724–726. https://doi.org/10.1097/ICB.0000000000001090.
36. Abou-Jaoude MM, Davis AM, Fraser CE, et al. New insights into pentosan polysulfate maculopathy. *Ophthalmic Surg Lasers Imaging Retina*. 2021;52(1):13–22. https://doi.org/10.3928/23258160-20201223-04.
37. Jain N, Liao A, Garg SJ, et al. Expanded Clinical Spectrum of pentosan polysulfate maculopathy: a macula society collaborative study. *Ophthalmol Retina*. 2022;6(3):219–227. https://doi.org/10.1016/j.oret.2021.07.004.
38. De Larochellière E, Bourgault S. Pentosan polysulfate sodium-induced pigmentary maculopathy with nonleaking cystoid macular edema successfully treated with anti-vascular endothelial growth factor therapy. *Retin Cases Brief Rep*. 2022;16(4):482–485. https://doi.org/10.1097/ICB.0000000000001013.
39. Girardot PE, Zhang N, et al. Pentosan polysulfate sodium causes diminished function and subtle morphological changes in retina and RPE of mice. *Invest Ophthalmol Vis Sci*. 2024;65(2):28. https://doi.org/10.1167/iovs.65.2.28. published correction appears in Invest Ophthalmol Vis Sci. 2024 Apr 1;65(4):47.
40. Girardot PE, Zhang N, et al. Erratum in: pentosan polysulfate sodium causes diminished function and subtle morphological changes in retina and RPE of mice. *Invest Ophthalmol Vis Sci*. 2024;65(4):47, 10.1167.iovs65.4.47.
41. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res. 1020;62(6):775-784. doi:10.1002/acr.20133.
42. Chen E, Brown DM, Benz MS, et al. Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the "flying saucer" sign). *Clin Ophthalmol*. 2010;4:1151–1158. https://doi.org/10.2147/OPTH.s14257.
43. Cestari RN, de Oliviera RDR, de Souza FFL, et al. Systemic lupus erythematosus activity affects the sinusoidal uptake transporter OATP1B1 evaluated by the pharmacokinetics of atorvastatin. *Clin Transl Sci*. 2020;13(6):1227–1235. https://doi.org/10.1111/cts.12808.
44. Liptrott NJ, Owen A. The role of cytokines in the regulation of drug disposition: extended functional pleiotropism? *Expert Opin Metab Toxicol*. 2011;7(3):341–352. https://doi.org/10.1517/17425255.2011.553600.
45. Park CH, Jaffe GJ, Fekrat S. Intravitreal triamcinolone acetonide in eyes with cystoid macular edema associated with central retinal vein occlusion. *Am J Ophthalmol*. 2003;136(3):419–425. https://doi.org/10.1016/s0002-9394(03)00228-9.
46. Jonas JB, Kreissig I, Degenring RF. Intravitreal triamcinolone acetonide for pseudophakic cystoid macular edema. *Am J Ophthalmol*. 2003;136(2):384–386. https://doi.org/10.1016/s0002-9394(03)00230-7.
47. De Silva SR, De Silva I, Pal B. Treatment of cystoid macular oedema secondary to pentosan polysulfate maculopathy using anti-VEGF and intravitreal steroid injections. *Eur J Ophthalmol*. December 6, 2021. doi:10.1177/11206721211066387.
48. U.S. Food and Drug Aministration. *Ozurdex (Dexamethasone Intravitreal Implant) NDA 022315/S000 Approval Letter*. Center for Drug Evaluation and Research; June 17, 2009. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022315s000_SumR.pdf. Accessed May 30, 2024.
49. Ugwuegbu O, Uchida A, Singh RP, et al. Quantitative assessment of outer retinal layers and ellipsoid zone mapping in hydroxychloroquine retinopathy. *Br J Ophthalmol*. 2019;103(1):3–7. https://doi.org/10.1136/bjophthalmol-2018-312363.
50. De Silva T, Jayakar G, Grisso P, Hotaling N, Chew EY, Cukras CA. Deep learning-based automatic detection of ellipsoid zone loss in spectral-domain OCT for hydroxychloroquine retinal toxicity screening. *Ophthalmol Sci*. 2021;1(4), 100060. https://doi.org/10.1016/j.xops.2021.100060. Published 2021 Sep. 25.

51. Kalaw FGP, Scott NL, Borooah S. An unusual case of rapid resolution of bilateral vitelliform deposits after discontinuation of pentosan polysulfate sodium. *Am J Ophthalmol Case Rep*. 2023;32, 101875. https://doi.org/10.1016/j.ajoc.2023.101875. Published 2023 Jun 20.
52. Blackorby BL, Banda H, Smith BT, Shah GK. Macular findings of patients on pentosan polysulfate sodium. *Mil Med*. 2023;188(3-4):e579–e583. https://doi.org/10.1093/milmed/usab301.
53. Hatz K, Ebneter A, Tuerksever C, Pruente C, Zinkernagel M. Repeated dexamethasone intravitreal implant for the treatment of diabetic macular oedema unresponsive to anti-VEGF therapy: outcome and predictive SD-OCT features. *Ophthalmologica*. 2018;239(4):205–214. https://doi.org/10.1159/000485852.
54. Castro-Navarro V, Monferrer-Adsuara C, Navarro-Palop C, Montero-Hernández J, Cervera-Taulet E. Effect of dexamethasone intravitreal implant on visual acuity and foveal photoreceptor integrity in macular edema secondary to retinal vascular disease. *Ophthalmologica*. 2021;244(1):83–92. https://doi.org/10.1159/000512195.
55. Mititelu M, Wong BJ, Brenner M, Bryar PJ, Jampol LM, Fawzi AA. Progression of hydroxychloroquine toxic effects after drug therapy cessation: new evidence from multimodal imaging. *JAMA Ophthalmol*. 2013;131(9):1187–1197. https://doi.org/10.1011/jamaophthalmol.2013.4244.
56. Allahdina AM, Chen KG, Alvarez JA, Wong WT, Chew EY, Cukras CA. Longitudinal changes in eyes with hydroxychloroquine retinal toxicity. *Retina*. 2019;39(3):473–484. https://doi.org/10.1097/IAE.0000000000002437.
57. De Sisternes L, Pham BH, Durbin M, Marmor MF. Topographic optical coherence tomography segmentation shows limited ellipsoid zone recovery in mild hydroxychloroquine retinopathy. *Retina Cases Brief Rep*. 2022;16(3):263–269. https://doi.org/10.1097/ICB.0000000000000993.