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An unusual case of rapid resolution of bilateral vitelliform deposits after discontinuation of pentosan polysulfate sodium

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ABSTRACT

Purpose: To report the structural and functional changes in a 67-year-old male with pentosan polysulfate sodium (PPS) maculopathy with a progressive resolution of bilateral vitelliform lesions after PPS cessation.
Observations: The patient was initially seen after taking daily PPS for over 26 years. Three months after discontinuing PPS, the bilateral vitelliform lesions identified on spectral-domain optical coherence tomography (SD-OCT) at initial consultation had completely resolved. Bilateral resolution of vitelliform lesions was associated with a decline in best-corrected visual acuity, and ellipsoid zone disruption on SD-OCT.
Conclusions and importance: Several PPS maculopathy phenotypes have been previously described including vitelliform lesions. Our case highlights that discontinuing PPS may lead to rapid resolution of vitelliform lesions in PPS maculopathy and may be associated with a rapid reduction in vision.

1. Introduction

Pentosan polysulfate sodium (PPS) is an oral medication used to treat bladder pain or discomfort associated with interstitial cystitis (IC).[1] It has been United States Food and Drug Administration (FDA)-approved since 1996 and has remained the only approved drug for treating IC. In 2018, maculopathy associated with PPS was first reported by Pearce and colleagues.[2] PPS maculopathy has been phenotypically described using multimodal imaging as causing a highly irregular autofluorescence pattern centrally surrounded by normal fluorescence and nodular excrescences at the level of the retinal pigment epithelium (RPE).[2,3] PPS maculopathy has been further classified by different researchers into three categories of severity, mainly focusing on the extent of the lesion and the presence and location of outer retinal atrophy.[3–5] A recent collaborative study identified different PPS maculopathy phenotypes.[6] However, consensus guidelines have yet to be established to accurately diagnose PPS maculopathy.

This report describes a patient with chronic PPS exposure who had an atypical presentation of PPS maculopathy. Of interest was the documented regression of the vitelliform lesion after cessation of PPS. It is known that atrophy in PPS maculopathy continues to progress even after years of drug cessation.[7] This report may provide insight into the natural history of the progression and functional consequences of the vitelliform PPS maculopathy phenotype following drug cessation.

2. Case report

A 67-year-old Hispanic man was initially referred by his optometrist for evaluation of bilateral RPE detachments. The patient's medical history was remarkable for diabetes mellitus managed with insulin, metformin, and dulaglutide. He was known to have chronic interstitial cystitis (IC), symptoms of which were treated with 100–200 mg PPS daily for 26 years leading to an estimated cumulative dose of 1338 g. The patient had no known history of ocular disease.

A comprehensive ophthalmologic evaluation revealed a best-corrected visual acuity (BCVA) of 20/32 in both eyes, intraocular pressures of 18 and 20 mmHg in the right and left eyes, respectively, and a relatively unremarkable anterior segment examination with nuclear sclerosis (NC2NO1 based on the Lens Opacities Classification System [LOCS] III[8]) of both lenses. Dilated fundus examination revealed yellow deposits and retinal pigment epithelium (RPE) mottling of the macula in both eyes. Fundus pseudocolor imaging highlighted yellow deposits in

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the central macula bilaterally. Fundus autofluorescence (FAF) identified central macula hyper-autofluorescence with surrounding spots of hypo-autofluorescence. Near-infrared reflectivity imaging demonstrated heterogenous reflectance. Macular SD-OCT identified subretinal vitelliform lesions bilaterally, with overlying intact external limiting membrane (ELM) and ellipsoid zone (EZ). Additionally, multiple hyperreflective elevations were noted at the level of the RPE in the parafoveal region. Bruch's membrane and RPE reflectivity were not clear in the sub-foveal region, however parafoveal areas appear to have RPE thickening with hyperreflective nodular elevations (Fig. 1A). In view of the ocular findings suggesting PPS maculopathy, the patient was advised to discontinue taking PPS. In order to exclude other diseases with similar phenotypes, including diseases result in inherited vitelliform disease, the patient was referred to the Inherited Retinal Disease (IRD) clinic for further work-up to rule out the possibility of a genetic disease.

The patient was initially seen in the IRD clinic one month after discontinuation of PPS. A repeat comprehensive ophthalmologic examination found a reduced BCVA of 20/50 in both eyes. SD-OCT at this visit revealed a small decrease in the peak height of the subfoveal deposits (Fig. 1B) by 38 μm (right eye) and 28 μm (left eye).

Multifocal electroretinogram (mfERG), full-field electroretinogram (ffERG), microperimetry, and exome IRD testing were performed as part of the work-up after the IRD clinic. Retinal electrophysiological testing was performed weeks after cessation of PPS. MfERG found ring responses slightly reduced in ring 1, including the fovea on the right eye, and within normal limits although with poor waveform morphology in ring 1 on the left eye (Figure S1). FfERG showed responses within normal limits for both general cone-dominated and rod-dominated responses (Figure S2).

Genetic testing included sequence analysis and deletion/duplication testing of 330 genes from the IRD panel (Invitae; Invitae Corporation, San Francisco, CA) and did not identify any variants associated with a genetic disorder. This test was Clinical Laboratory Improvement Act (CLIA)-certified.

At 12-week follow-up in the IRD clinic, the patient's BCVA had reduced further to 20/60 in the right eye and 20/125 in the left eye. Microperimetry was performed and showed reduced sensitivity at the fovea in both eyes with eccentric fixation (Fig. 2). FAF was noted to have a more mottled appearance with areas of hyper- and hypo-autofluorescence at the fovea. SD-OCT revealed a resolution of the vitelliform deposits bilaterally. The nodular excrescences remained in the right eye at the level of the RPE in the parafovea. Similarly, plaque-like lesion extending from the Bruch's membrane-RPE complex remained in the left eye. Although the ELM was observed to be intact bilaterally, the ellipsoid zone appeared to be disrupted in the left eye but appeared intact on the right subfoveally.

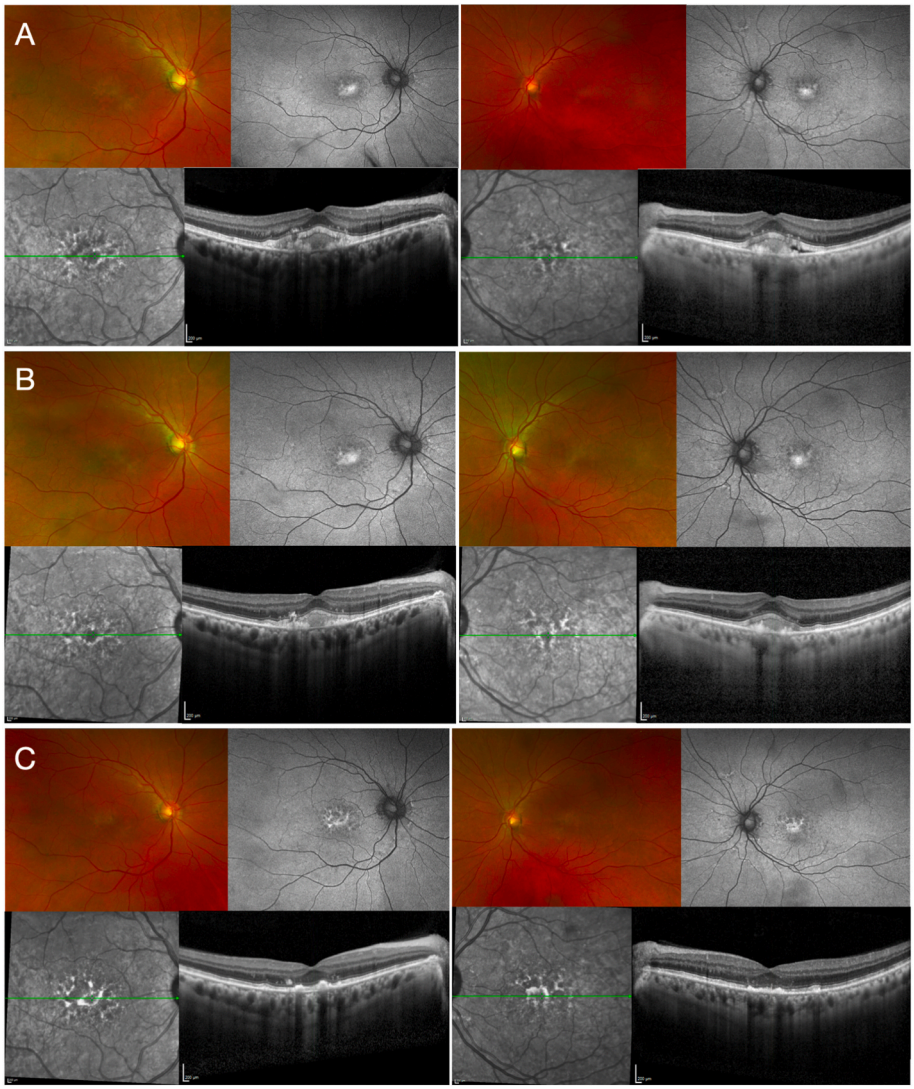

Fig. 1. Multimodal imaging of both eyes during the initial visit (A), one month (B), and three months (C) after discontinuation of pentosan polysulfate sodium.

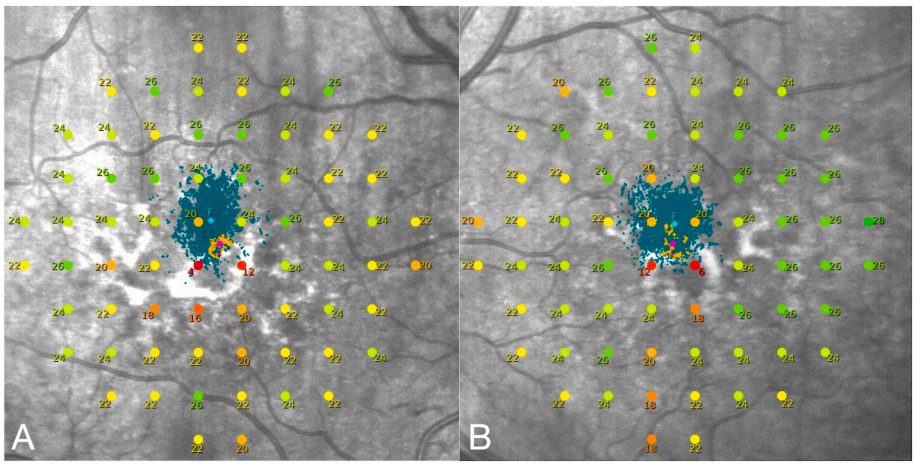

Fig. 2. Microperimetry sensitivity map showing reduced sensitivity in the right (A) and left (B) central fields with eccentric fixation.

3. Discussion

We present a case of PPS maculopathy with rapidly resolving vitelliform lesions post-PPS cessation. There have been multiple published articles characterizing and categorizing[4,5] the phenotype of PPS maculopathy along with a number of reports describing vitelliform deposits in PPS maculopathy.[4,6,9,10] However, the novel finding in our case was the rapid bilateral resolution of vitelliform lesions after PPS cessation, which has not been reported previously in cases of PPS maculopathy. This finding warrants discussion to help better understand how dosing regimens, effects of cessation, and patient characteristics affect PPS maculopathy. Vitelliform lesions in PPS appear similar to those seen in other vitelliform diseases, which is why the patient was initially tested to exclude inherited retinal disease from *BEST1*, *PRPH2*, *IMPG1*, *IMPG2*-associated retinopathy. In these inherited vitelliform diseases and other vitelliform diseases, RPE dysfunction is thought to lead to the accumulation of subretinal material.[11,12] As yet, there have been no histopathology reports of PPS maculopathy. However, histopathology and ultrastructural studies of other vitelliform diseases have yielded some clues as to the constituents of the vitelliform lesion, including lipid droplets, lipofuscin, photoreceptor outer segments, and RPE organelles.[13,14]

Freund et al.[15] postulated that vitelliform lesions spontaneously resolved when there was enough loss of overlying ONL and that RPE could again clear material generated by photoreceptors. In addition, recent findings by Battaglia Parodi et al.[16] identified the factors most strongly associated with retinal sensitivity in Best vitelliform macular dystrophy which included lesion type on SD-OCT and outer nuclear layer (ONL) thickness. The authors found that reabsorption of the vitelliform material was associated with a reduction of retinal sensitivity, similar to the findings in the present case. Additionally, the thickness of the ONL above the vitelliform lesions was correlated to retinal sensitivity. A similar study by Bianco et al.[17] hypothesized that vitelliform lesions in Best vitelliform macular dystrophy resulted from lack of apposition of photoreceptors and RPE. This led to subretinal accumulation of shed photoreceptor outer segments, photoreceptor degeneration, and subsequent loss of retinal sensitivity. The eventual collapse of the vitelliform lesion was attributed to the lack of new photoreceptor outer segments, with resorption of the remaining subretinal material. This sequence is similar to our case, with a drop in BCVA and microperimetric sensitivity prior to the resolution of the vitelliform lesions. We also hypothesize that there was an imbalance between the production of subretinal material from the neural retina and the clearance by RPE.

In our case, we hypothesize that PPS caused RPE dysfunction, especially at the apical surface of RPE, and so reducing clearance of materials from the subretinal area and resulting in vitelliform lesion formation. It could be that cessation of PPS rapidly restored the equilibrium between production and clearance of subretinal material and allowed RPE to clear the subretinal material.[11] This supports a role for apical RPE dysfunction in vitelliform lesions in PPS maculopathy and potentially the disruption of normal RPE-photoreceptor homeostasis. This may occur as PPS is a heparan sulfate glycosaminoglycans-like molecule.[18] The RPE has heparan sulfate binding sites as well as binding to melanin,[19] and so PPS binding to RPE may induce RPE dysfunction.

4. Conclusion

There are a number of different phenotypes related to PPS maculopathy. Large studies are required to identify toxicity susceptibilities based on patient characteristics, dose regimens, and concomitant disease. In patients with vitelliform lesions, close monitoring upon cessation of the medication is warranted to observe for the progression of outer retinal atrophy. This report highlights the importance of counseling patients about visual outcomes in the setting of vitelliform lesions in PPS maculopathy.

Patient consent

A written informed consent was obtained from the patient.

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Authorship

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

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.

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None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajoc.2023.101875.

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