RETINAL Cases & Brief Reports
July 2022, Volume 16 (4), p 482–485
About Journal
CASE REPORT
SUBSCRIBED

PENTOSAN POLYSULFATE SODIUM-INDUCED PIGMENTARY MACULOPATHY WITH NONLEAKING CYSTOID MACULAR EDEMA SUCCESSFULLY TREATED WITH ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

De Larochellière, Elianne MD, MSc, FRCSC[†]; Bourgault, Serge MD, FRCSC[‡] Author Information

Abstract

Purpose:
To report a case of nonleaking cystoid macular edema (CME) associated with pentosan polysulfate sodium (PPS)-induced pigmentary maculopathy.

Methods:
Multimodal imaging, including optical coherence tomography, fundus photography, autofluorescence, and fluorescein angiography, was used to substantiate our diagnosis, further characterize the cystoid macular edema showed by our patient and to monitor the response to treatment.

Results:
A 59-year-old woman was referred for decreased visual acuity and bilateral macular edema. She had been treated for interstitial cystitis with PPS for 10 years. Multimodal imaging showed the characteristic features of PPS-induced pigmentary maculopathy. Moreover, fluorescein angiogram showed nonleaking cystoid macular edema in both eyes. She was treated successfully with intravitreal injections of bevacizumab.

Conclusion:
To our knowledge, this report is the first to demonstrate that PPS-associated cystoid macular edema can be nonleaking on fluorescein angiography and responds well to intravitreal anti-vascular endothelial growth factor injections.

Pentosan polysulfate sodium (PPS) (Elmiron, Janssen Pharmaceuticals) is an oral medication approved for the management of bladder discomfort associated with interstitial cystitis, a chronic disease that predominantly affects women. Pentosan polysulfate sodium is an analogue of biologic glycosaminoglycans that binds to the bladder epithelium and acts as a barrier to potential irritants by altering the mucosal cellular permeability. Pentosan polysulfate sodium-induced maculopathy was first described in 2018, despite the medication being used for over two decades. To our knowledge, there are only two cases of choroidal neovascularization and a few cases of cystoid macular edema (CME) reported as complications of PPS-maculopathy. We present a patient with PPS-induced maculopathy who developed nonleaking CME in both eyes and was successfully treated with anti–vascular endothelial growth factor (VEGF).

Case Report

A nonsmoking 59-year-old Caucasian woman was referred to our clinic by an optometrist for bilateral macular edema and a history of decreased visual acuity (VA) over a period of six months. She had been treated for interstitial cystitis with 300 mg daily of PPS for 10 years, resulting in a cumulative exposure of 1.10 kg and a cumulative exposure per unit of body mass of 23.1 mg/kg. Recent investigation for diabetes was negative. She had no family history of age-related macular degeneration and she did not have any symptoms of mitochondrial diseases. Her initial VA was 20/40 in both eyes. Fundus exam revealed macular pigmentary changes in both eyes (). Optical coherence tomography (OCT) showed CME and absence of subretinal fluid in both eyes (). Autofluorescence imaging (AF) is shown in . Fluorescein angiography showed absence of leakage associated with the CME in both eyes. A small area of hyperfluorescence was found in the left eye and corresponded most likely to pooling of fluorescein in the subretinal space rather than macular neovascularization (). Optical coherence tomography-angiography was not performed. Nepafenac 0.3% (Ilevro, Alcon Canada, Novartis) was initially given in both eyes for a month, but CME increased in both eyes and subretinal fluid developed in the left eye (). VA had dropped at 20/60 in both eyes at this point. Off-label intravitreal bevacizumab 1.25 mg/0.05 mL (Avastin, Roche Canada) was then injected in both eyes and nepafenac was discontinued. Pentosan polysulfate sodium was also stopped because PPS-induced maculopathy was suspected at this point. An OCT performed 2 weeks later showed marked reduction of intraretinal fluid in both eyes and persistence of subretinal fluid in the left eye (). The patient received subsequent bevacizumab injections in both eyes 2 and 6 weeks later. The VA was then 20/25 in both eyes.

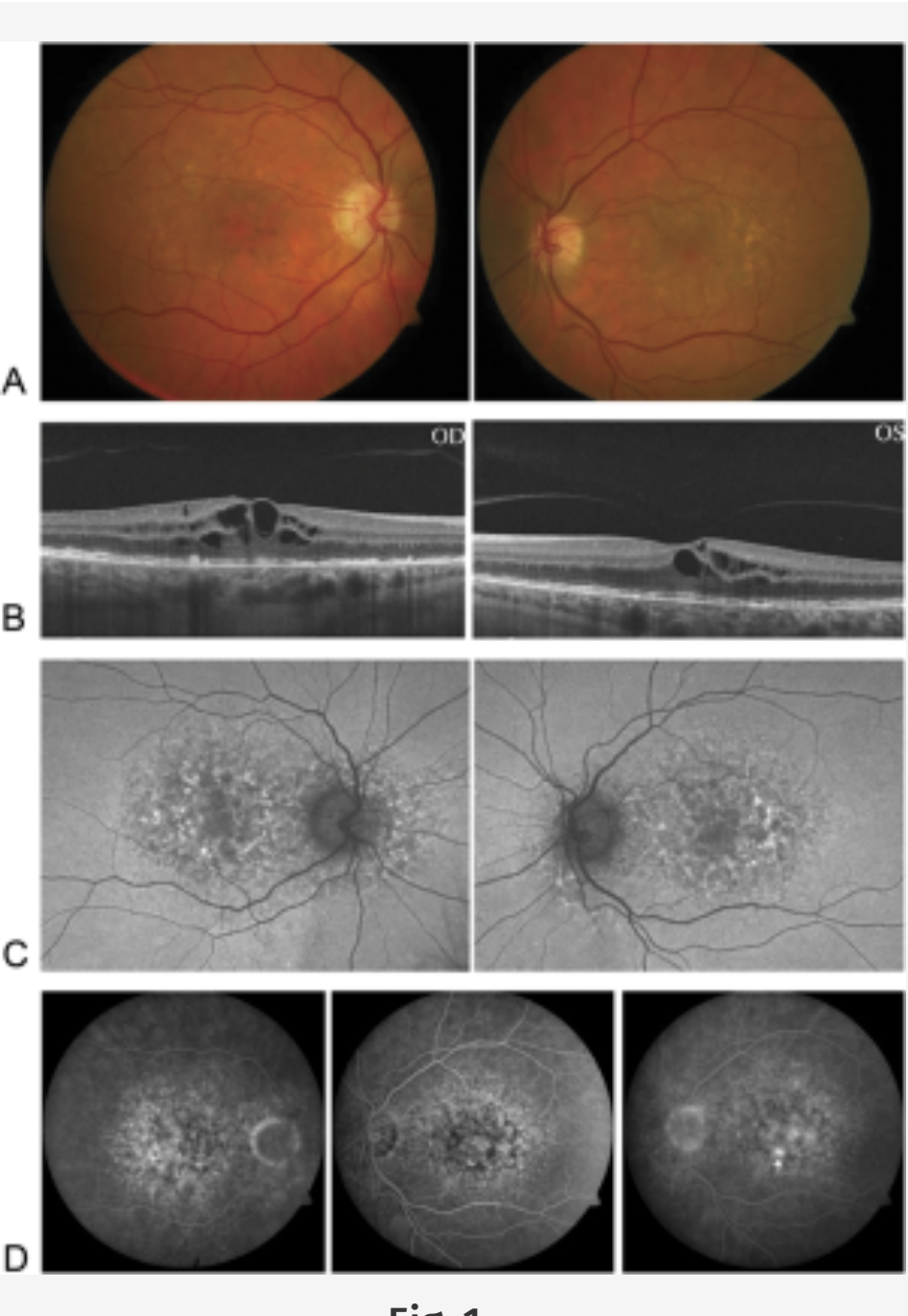

Fig. 1.
Initial multimodal imaging of both eyes. **A.** Color fundus photography showing macular hyperpigmented spots and poorly defined yellow-orange deposits. **B.** Macular OCT revealing focal hyperreflective thickening of the retinal pigment epithelium and CME in both eyes. A grade 2 posterior vitreous detachment is seen in both eyes. **C.** AF imaging demonstrating a peripapillary hypoautofluorescent halo and an extensive densely packed array of hypoautofluorescent and hyperautofluorescent spots involving the posterior pole and the peripapillary area. **D.** Fluorescein angiography of the right eye (late phase) and left eye (early and late phase) showing absence of leakage and pooling of fluorescein (arrow).

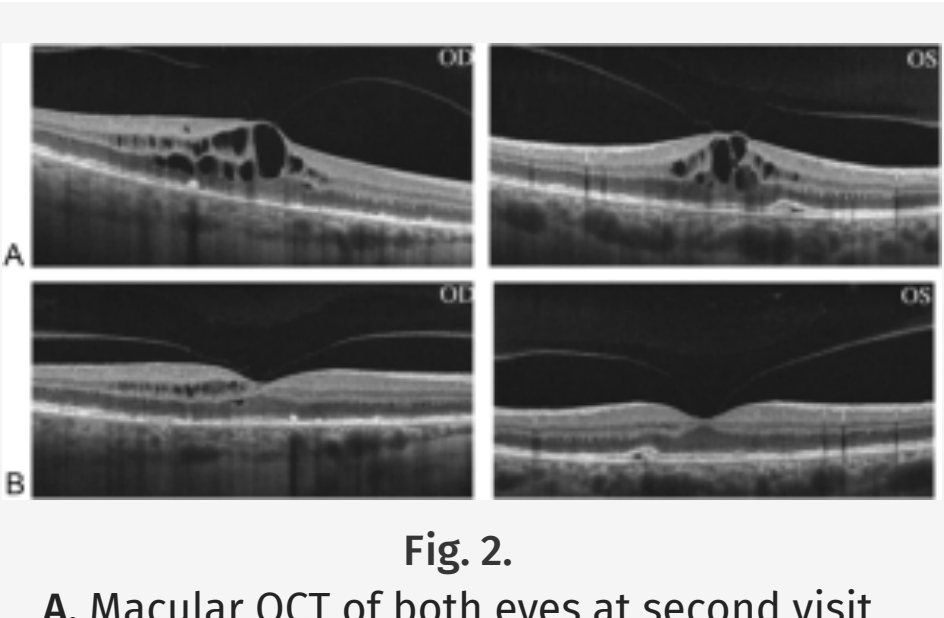

Fig. 2.
A. Macular OCT of both eyes at second visit after a month of treatment with nepafenac. Optical coherence tomography of right eye and of left eye revealing increased CME with a small amount of new subretinal fluid in the left eye. **B.** Macular OCT of both eyes 2 weeks after the first intravitreal injection of bevacizumab. Both right eye and left eye demonstrate marked reduction of CME, but persistence of subretinal fluid in left eye.

Discussion

Pentosan polysulfate sodium-induced maculopathy was first reported in 2018. In 2019, a new retrospective case series of 35 patients, including the patients originally described in 2018, was published. These patients were retrospectively identified from a large pool of 404 patients exposed to PPS. Pentosan polysulfate sodium-induced maculopathy is a bilateral disease, as we would expect from a toxic pathology from a systemic medication. It is believed to affect either the retinal pigment epithelium itself or its interface with the photoreceptors. As well described by Hanif et al, the key findings of this specific maculopathy include 1) macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium atrophy, 2) densely packed macular array of hyperautofluorescent and hypofluorescent spots on AF imaging, and 3) focal thickening of the retinal pigment epithelium with associated hyperreflectance on OCT. Our patient showed identical findings. She also showed the peripapillary hypoautofluorescent halo described by Hanif et al as a distinctive feature to differentiate PPS-induced maculopathy from usually peripapillary-sparing age-related macular degeneration and hereditary retinopathies.

In the larger retrospective series, CME was identified in nine eyes of six patients. Fluorescein angiography was performed in only one patient and demonstrated leakage associated with the CME. Our patient showed non-leaking CME similar to other toxic CME such as the one induced by niacin and taxanes. Treatment of PPS maculopathy-associated CME with topical carbonic anhydrase inhibitors was previously described in one patient. Our patient's CME did not respond to topical nepafenac, but showed nearly complete resolution with intravitreal bevacizumab. Treatment of this condition with intravitreal anti-VEGF has never been described in a peer-reviewed article.

The response of drug-induced CME to intravitreal anti-VEGF is highly variable. This approach has achieved no to questionable results in taxanes-related CME, but had good results with tamoxifen-related CME. We can hypothesize that PPS-induced CME is mediated, at least partly, by VEGF, a potent inducer of vascular permeability. We do not think that stopping PPS played a role in the rapid improvement of our patient's VA and OCT findings. These positive results were most likely attributable to the intravitreal injections of bevacizumab.

Median PPS intake duration and median daily dose in previous reports of PPS-induced maculopathy was 15 (3–22) years and 300 (150–592) mg, respectively. Our patient had similar exposure. Even though it is a possibility that the maculopathy may still progress after stopping the PPS, it is obvious that the medication has to be discontinued when possible.

To conclude, this report demonstrated for the first time that the CME associated with PPS-induced maculopathy can be nonleaking on fluorescein angiography and responds well to intravitreal anti-VEGF injections.

References

1. Hanno PM, Erickson D, Moldwin R, Faraday MM. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol 2015;193:1545–1553. [Context Link]

2. Elmiron (Pentosan Polysulfate Sodium), Jannsen Pharmaceuticals [package insert]. Titusville, New Jersey: Janssen Pharmaceuticals, 2018. [Context Link]

3. Pearce WA, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. Ophthalmology 2018;125:1793–1802. [Context Link]

4. Hanif AM, Armenti ST, Taylor SC, et al. Phenotypic sprectrum of pentosan polysulfate sodium-associated maculopathy—-a multicenter study. JAMA Ophthalmol 2019;137:1275–1282. [Context Link]

5. Mishra K, Patel TP, Singh MS. Choroidal neovascularization associated with pentosan polysulfate toxicity. Ophthalmol Retina 2020;4:111–113. [Context Link]

6. Spirn MJ, Warren FA, Guyer DR, et al. Optical coherence tomography findings in nicotinic acid maculopathy. Am J Ophthalmol 2003;135:913–914. [Context Link]

7. Telander DG, Sarraf D. Cystoid macular edema with docetaxel chemotherapy and the fluid retention syndrome. Semin Ophthalmol 2007;22:151–153. [Context Link]

8. Makri OE, Georgalas I, Georgakopoulos CD. Drug-induced macular edema. Drugs 2013;73:789–802. [Context Link]

9. Rahimy E, Sarraf D. Bevacizumab therapy for tamoxifen-induced crystalline retinopathy and severe cystoid macular edema. Arch Ophthalmol 2012;130:931–932. [Context Link]

10. Huckfeldt RM, Vavvas DG. Progressive maculopathy after discontinuation of pentosan polysulfate sodium. Ophthalmic Surg Lasers Imaging Retina 2019;50:656–659. [Context Link]