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Case Report

Maculopathy and Interstitial Cystitis: An Underappreciated Association of Pentosan Polysulfate Sodium

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A B S T R A C T

A 50-year-old female was referred to the emergency eye clinic with a 2-day history of blurred vision in the left eye. A thorough history and examination revealed she was diagnosed with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) for which she had started Pentosan Polysulfate Sodium (PPS) 300mg once daily 6 weeks earlier. Examination and investigations revealed a bilateral toxic circumferential para-foveal maculopathy. The patient was advised to discontinue PPS and was referred for monitoring in the medical retina clinic. Her Urologist was also made aware.

Keywords: Maculopathy; Interstitial cystitis; Bladder pain syndrome

1. Introduction

1.1 Background

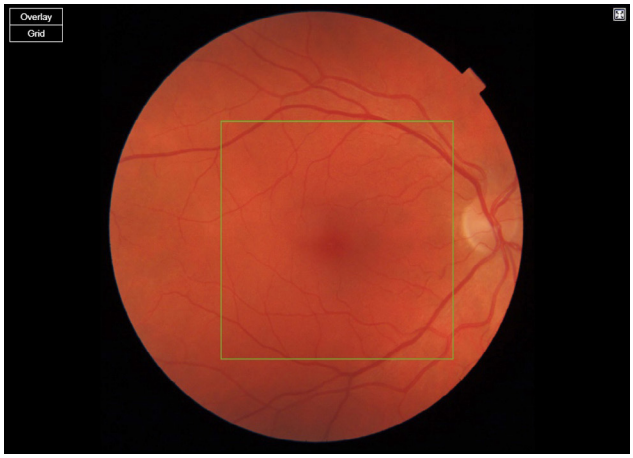
Interstitial Cystitis is common[1,2], affecting up to 6.5% of women in the United States (US).Curhan et al[3] demonstrated that up to 70 cases per 100,000 women in the US have IC. In Europe and Japan, the numbers are approximately 18 and 4 cases per 100,000 women respectively. This is likely due to differences in diagnostic criteria. In the UK, as many as 400,000 people are affected, with 90% being women[4].

PPS is an established treatment for IC, especially in the US. It is often used after the failure of conservative management, antispasmodic/antimuscarincs, non-narcotic analgesics, tricyclic anti-depressants and H2 antagonists[2]. PPS is the only medication specific to IC and is a last line of treatment. PPS related maculopathy is a significant and irreversible Ophthalmicmorbidity. The chances of developing it are cumulatively dose dependent. This means thatpatients on a standard dose will eventually reach at leasta 41.7% risk of having maculopathy[5-7].

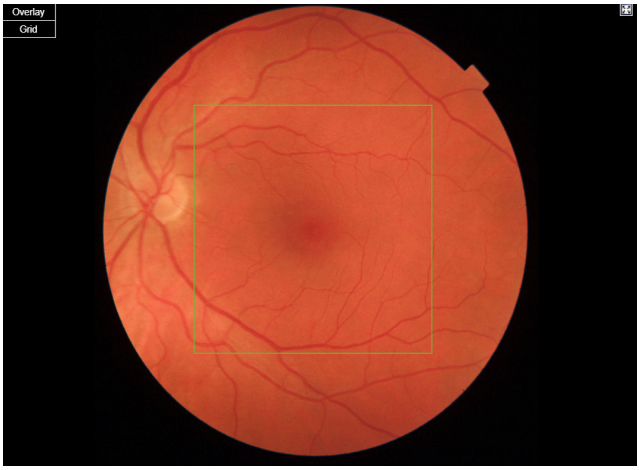
We report a case of maculopathy occurring within 6 weeks of PPS initiation. This case demonstrates that whilst evidence suggests maculopathy is generally cumulative dose dependent, maculopathy can still occur early.

2. Case Presentation

A fit and well 50-year-old Caucasian female Presented to the eye clinic with a 2-day history of blurred vision. She has no previous attendances at the hospital and a past medical history of interstitial cystitis. Her vision was 6/6 in both eyes. Anterior segment examination was entirely normal. After pupillary dilatation, examination of the macula with a 78D lens revealed patchy bilateral circumferential para-foveal retinal pigment epithelial (RPE) changes/ yellowish sub-retinal deposits left more so than right. Both eyes had a small degree of RPE hypertrophy and pigmentation mixed with the RPE changes, also left more so than right. Colour fundus photography and examination showed RPE bunching, pigmentation and hypertrophy as well as yellow subretinal deposits (**Figures 1a,1b**). Magnified fundus photos showed patchy bilateral circumferential para-foveal retinal pigment epithelial (RPE) changes/ yellowish sub-retinal deposits left more so than right (**Figures 2a,2b**). Both eyes had a small degree of RPE hypertrophy and pigmentation mixed with the RPE changes, also left more so than right. These findings are known associations of PPS maculopathy[8].

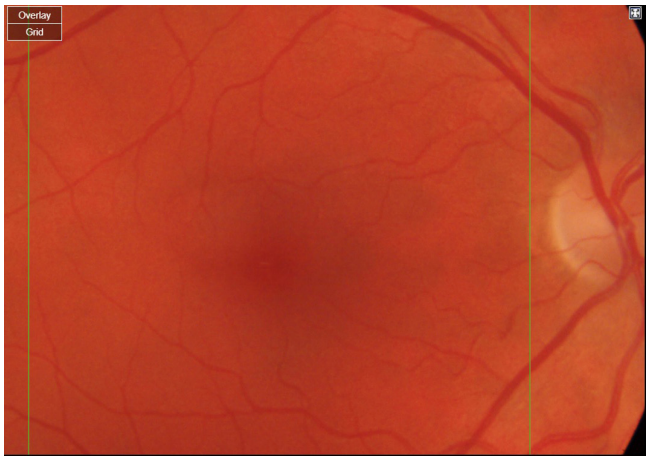


(a) Right Eye

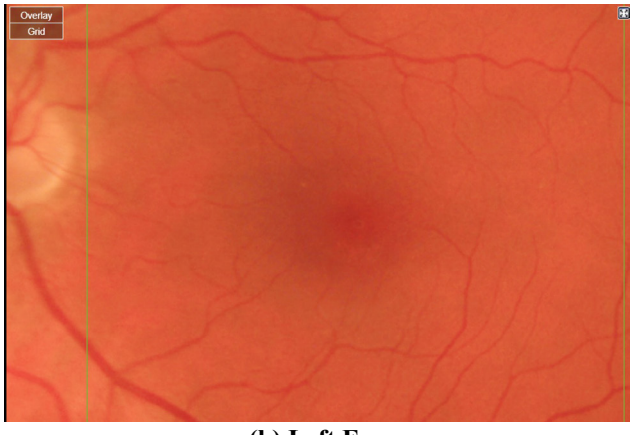


(b) Left Eye

Figure 1: Standard fundus photos.



(a) Right Eye

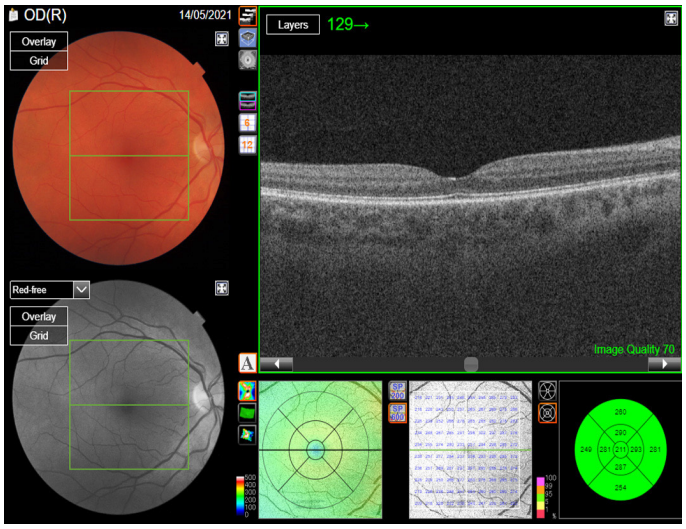


(b) Left Eye

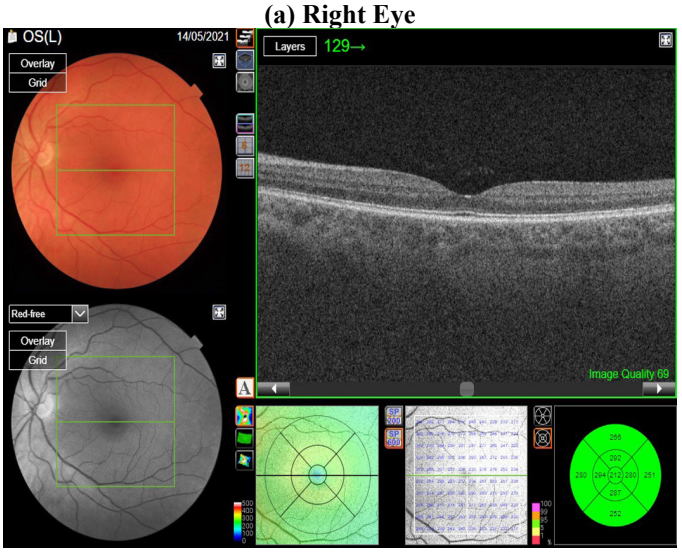
Figure 2: Magnified standard fundus photos.

2.1 Investigations If relevant

Optical Coherence Tomography (OCT) is a non-invasive imaging modality that uses low-coherence light to capture micrometer resolution images of the retina. Using the information obtained, two and three dimensional images of the retina are formed which the clinician can use to give an indication of retinal/ RPE health. The case study patient's macula OCT scans were normal (**Figures 3a,3b**).



(a) Right Eye



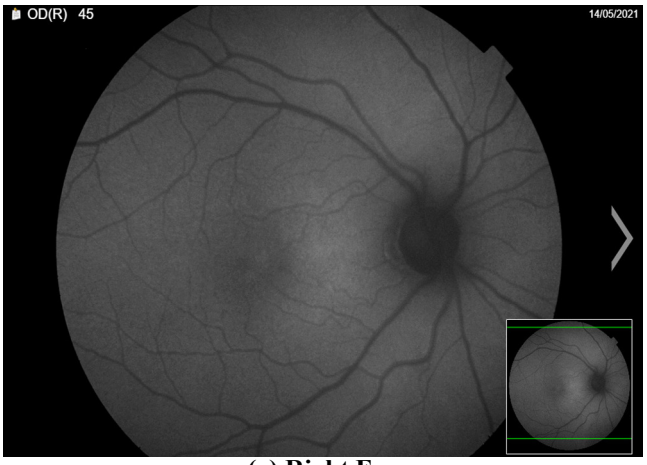
(b) Left Eye

Figure 3: Optical Coherence Tomography (OCT).

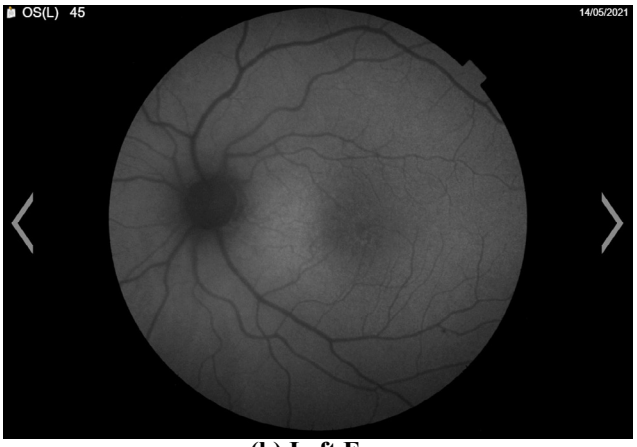
Fundus Autofluorescence (FAF) is a non-invasive imaging modality that captures an image from ocular endogenous fluorophores found within the retinal pigment epithelium and the choroid. These are composed mainly of lipofuscin and melanin. By capturing an image composed of the distribution of lipofuscin and melanin, the clinician can formulate an impression of the health of the retina/RPE.

The patient's FAF was abnormal. We could see from the images that there were areas of hyper and hypo-autofluorescent spots circumferentially, with the left more defined than right (**Figures 4a,4b**). Magnified images showing defects more clearly (**Figures 5a,5b**).

Visual field testing was obtained to assess the sensitivity of the macula area. They demonstrated very mild central field loss (**Figures 6a,6b**).

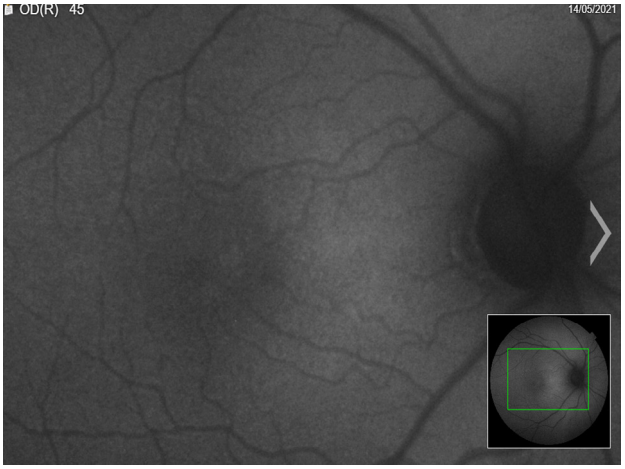


(a) Right Eye

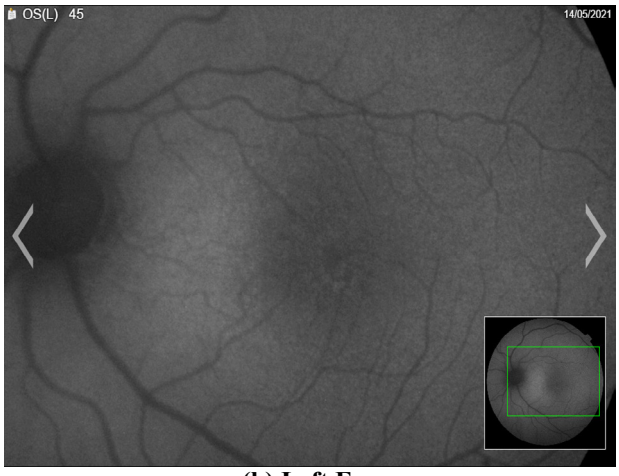


(b) Left Eye

Figure 4: Fundus Autofluorescence (FAF).

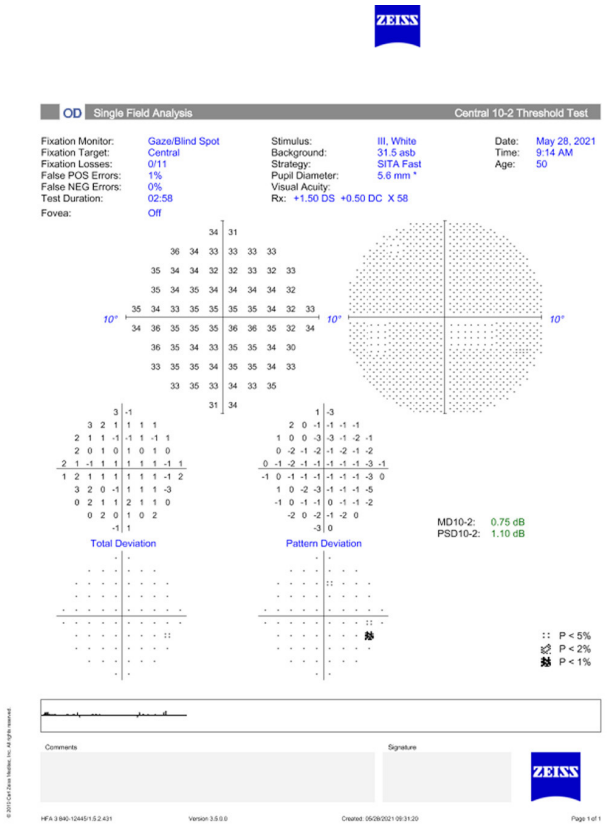


(a) Right Eye

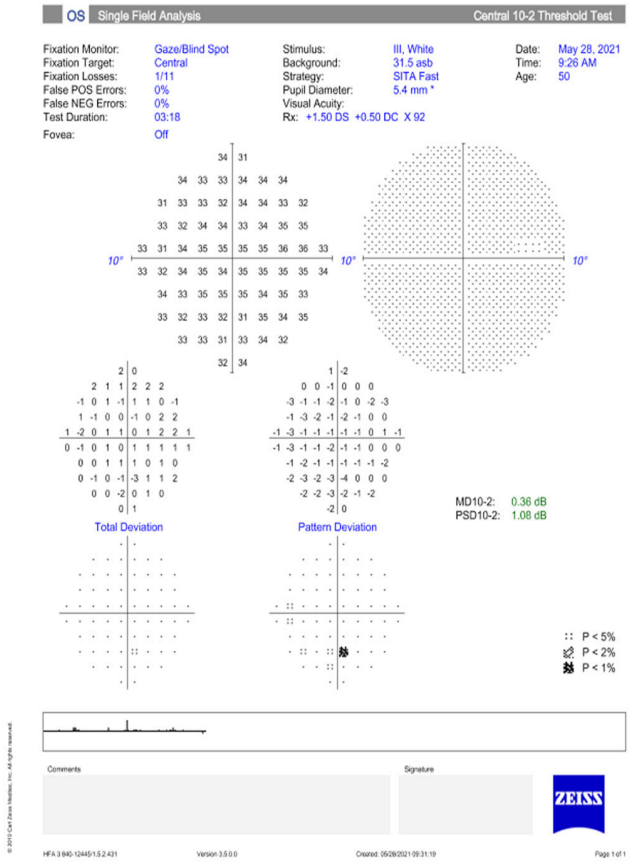


(b) Left Eye

Figure 5: Fundus Autofluorescence (FAF) (magnified**).**



(a) Right Eye



(b) Right Eye

Figure 6: Visual Field Testing VF 10-2.

3. Differential Diagnosis If Relevant

PPS maculopathy has a few differential diagnoses that we considered. These are Macular Dystrophies, Age Related Macular Degeneration (ARMD), Pachychoroid Pigment Epitheliopathy and Maternally Inherited Diabetes and Deafness Syndrome (MIDD)[18].

It is quite simple in this case to exclude ARMD. The patient does not fit the general age criteria for development, there was no family history of ARMD and the FAF pattern suggested a toxic maculopathy rather than ARMD[9]. Additionally, the hyper-autofluorescent lesions observed in this patient were distinct from the expected retinal oedema, drusen and subretinal drusenoid deposits normally seen in ARMD. The patient's lesions wereat the level of the RPE and they caused no interference when visualising the choroid.

Inherited macular and pattern dystrophies often present with less densely packed FAF lesions than PPS maculopathy[10].The patient's lesions were not typical of a diagnosis of inherited dystrophy and there was no family history of this.

MIDD was ruled out because unlike PPS, the pigmentary maculopathy characteristics of MIDD do not involve the fovea until late stage disease. Also MIDD with macular changes most often presents with additional systemic manifestations such as diabetes and deafness[11].The patient did not have any associated systemic manifestations.

Pachychoroid diseases can present with similar macular changes to PPS maculopathy. However, the clinician would expect additional findings such as dilated choroidal vessels, RPE and neurosensory retinal detachments and streaks representing previous exudation on FAF[12].

Given that the patient has no prior history or signs of the above discussed differential diagnosis, as well as recent initiation of PPS therapy and a symptomatic scotoma despite normal BCVA, we can confidently assume a diagnosis of PPS maculopathy.

4. Treatment If Relevant

Currently there is no treatment for PPS Maculopathy. Prescribing clinicians are advised to avoid or minimize cumulative exposure to PPS as primary prevention. When prescribing PPS, clinicians should discuss the risks of vision loss associated with PPS and its dose dependant nature with the patient. This will then lead to an informed decision as to whether the benefits outweigh the risk. Should PPS be recommended and agreed with the patient, the clinician should prescribe the minimum dose and length of time for IC management.

Additional to PPS maculopathy, PPS can also cause Cystoid Macular Oedema (CMO) and Macular Neovascularisation (MNV). CMO can be treated with topical therapy (carbonic anhydrase inhibitors, corticosteroids or NSAIDs), oral therapy (diamox) or intravitreal therapy. Both CMO and MNV can be treated with anti-Vascular Endothelial Growth Factor (anti-VEGF).

In the event of PPS maculopathy, CMO or MNV, the diagnosing clinician should make the prescribing clinician aware. The prescribing clinician should cease PPS then transition to other therapies. Patients with PPS maculopathy should ideally be monitored annually with multimodal imaging (colour fundus photography, FAF and OCT) in the event that treatable ophthalmic sequelae of PPS occur. Cessation of PPS may not prevent progression of maculopathy[13,14].

5. Outcome And Follow-Up

This patient was advised to stop PPS and referred back to her prescribing clinician for alternative management of IC. A medical retina appointment was requested for 6 weeks with multimodal imaging to assess for progression of her maculopathy due to the rapidity of onset of her condition.

6. Discussion

As mentioned before, PPS maculopathy has no established risk beyond cumulative PPS drug exposure. Patients may have normal Best Corrected Visual Acuity (BCVA) with symptomatic scotoma.

What can be observed is a disruption to the RPE/ photoreceptor interface. As seen in our case, early disease is defined by para-fovealmultifocal atrophy. In time this may coalesce and involve the centre[15]. RPE atrophy is a sequelae of advanced disease[11,15].

There are no established guidelines for the treatment and monitoring of PPS maculopathy as this is still a novel area.

CMO can be treated with both topical and intravitreal therapies[11,16]. MNV can be treated with anti-VEGF[17].

In terms of prognosis, longer terms studies and more data is needed to predict this novel condition. However, there is no evidence to suggest PPS maculopathy is reversible. The fact that it can also progress after drug cessation is a point of concern and any suspected case should be taken seriously[13,14].

Early detection is important to prevent permanent and progressive sequelae of PPS maculopathy.

Wang et al[15] recommend an initial exam within 6 months of PPS initiation and then annual exams as the patient approaches 500g of cumulative exposure. Based on our case, we would recommend a baseline examination within 1 month of starting PPS treatment followed by annual review depending on initial observations.

7. Learning Points/Take Home Messages

- Please take into consideration alternative and safer therapies for IC. We would recommend only using PPS as a last line of treatment in otherwise refractory cases.
- Use the minimum dose and length of time of treatment to achieve therapeutic value
- To be extremely sensitive to new onset scotoma despite normal BCVA
- Have a low threshold for referral to Ophthalmology after commencement of PPS

8. Patients Perspective

Shortly after starting PPS I became aware of some disturbance of my central vision, especially in the left eye. The eye care professionals confirmed a connection between my medicine and my symptoms. After stopping the treatment my vision did not worsen.

I am glad I was able to avoid losing any more vision. I hope that my case raises awareness of this condition for other patients and professionals.

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