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Maculopathy after long-term use of fondaparinux, a heparin mimetic and heparanase inhibitor

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ABSTRACT

Purpose: To report maculopathy associated with the long-term use of fondaparinux, a heparin mimetic and inhibitor of the extracellular matrix enzyme, heparanase.

Observations: A 41-year-old woman receiving thrice weekly injections of fondaparinux as prophylaxis against deep vein thrombosis for 9 years noticed gray spots in her vision without metamorphopsias. On exam, there was bilateral altered macular pigmentation with speckled hyperpigmentation. Optical coherence tomography revealed irregular thickening of the retinal pigment epithelium. Blue autofluorescence photography demonstrated symmetric well-defined plaques of hyper-and hypoautofluorescence similar to those described in patients chronically treated with pentosan polysulfate (PPS). Review of 13 years of outside medical records confirmed no prior treatment with PPS. Two years before, optical coherence tomography (OCT) done as part of routine eye examination showed early pigmentary changes which were not felt to be clinically significant. Inherited retinal gene panel testing and mitochondrial DNA testing did not reveal pathogenic variants associated with pattern dystrophies. The maculopathy was attributed to fondaparinux due to a pharmacologic effect shared with PPS of heparanase inhibition. Thirteen months after stopping fondaparinux, there was a significant reduction in macular pigmentary changes and improvement in outer retinal abnormalities on OCT.

Conclusions and importance: Fondaparinux is structurally and functionally related to PPS, which is also a heparin mimetic and heparanase inhibitor. Both drugs are now associated with phenotypically similar disruptions of the macular retinal pigment epitheliopathy. Although used for different clinical indications, both fondaparinux and PPS are sulfated oligosaccharides related to heparin that bind and inhibit heparanase, a critical enzyme in the extracellular matrix. This case is relevant for research into pharmacologic uses of heparanase inhibitors and monitoring for retinal disease in patients treated with them.

1. Introduction

Heparin mimetics are newer synthetic or semi-synthetic functional and structural oligosaccharide analogues of heparin, which is a naturally derived heterogenous mixture of polysaccharide chains. Off-target effects of heparin mimetics, in addition to targeted anticoagulation by potentiation of antithrombin III to inactivate factor Xa, include inhibition of heparanase, an enzyme present in the extracellular matrix and on endothelial cell surfaces. The therapeutic uses of the anti-inflammatory, anti-neoplastic, and anti-viral effects of heparanase inhibition are active areas of investigation.[1]

The FDA approved an oral heparin mimetic, pentosan polysulfate (PPS), in 1996 for treatment of interstitial cystitis. Reports of pigmentary maculopathy resulted in an FDA warning in 2020 that recommended retinal imaging within 6 months of initiation and periodically during use. The maculopathy has characteristic features on optical coherence tomography (OCT) and autofluorescence imaging that are easily recognizable.[2] We report a patient with the pathognomonic features of PPS maculopathy who had no exposure to PPS but did have long-term exposure to another heparin mimetic and heparanase inhibitor - fondaparinux.

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2. Case report

A 41-year-old woman presented with gray spots in her vision without metamorphopsia that began in November 2022. Review of her medical records revealed normal visual acuity and visual field testing in September 2019. Previously, in April 2021 there were asymptomatic focal alterations in the macular RPE noted on routine exam and OCT (Fig. 1A). Although visual acuity remained 20/20 in each eye, OCT now revealed widespread RPE clumping and disruption of the ellipsoid zone with foveal sparing (Fig. 1B). Clinically, there was bilateral speckled hyperpigmentation of the central macula with surrounding discoloration (Fig. 1D). Autofluorescence imaging demonstrated symmetric, well-defined plaques of hyper- and hypoautofluorescence similar to PPS maculopathy[3] (Fig. 1F). *En face* swept-source OCT angiography (OCTA) images derived from an outer retinal slab revealed dentate processes extending from the outer plexiform layer into the outer nuclear layer and en face concentric macular rings creating a fingerprint pattern (Fig. 2). Fluorescein angiography revealed early stippled hyperfluorescence with late staining (Fig. 3). Indocyanine green angiography showed early blocking that faded over the course of the angiogram (Fig. 4).

The patient had a complicated medical history of Crohn's disease, Guillain Barre syndrome, avascular necrosis, seronegative rheumatoid arthritis, pulmonary fibrosis, pulmonary embolism, and nonalcoholic fatty liver disease, none of which explained her rapidly progressive maculopathy. The patient denied prior interstitial cystitis. Genetic testing with the Inherited Retinal Disorders panel offered by Invitae (San Francisco, CA, USA), Clinical Laboratory Testing Amendments (CLIA)-certified laboratory, was negative for disease causing pathogenic variants. There were no pathogenic mutations in genes associated with pattern dystrophies, such as *BEST1, PRPH2, IMPG1, IMPG2, ABCA4*. There were no detectable pathogenic mitochondrial gene variants on Mitochondrial NGS testing performed by CLIA-certified Molecular Vision Laboratory (Hillsboro, OR, USA). Current medications included anakinra for 7 years, methotrexate for 5 years, sildenafil for 9 years, and fondaparinux for 9 years. She had taken hydroxychloroquine for 1 year only 10 years ago. She restarted it 2 months after the visual symptoms began, then discontinued it when the maculopathy was discovered.

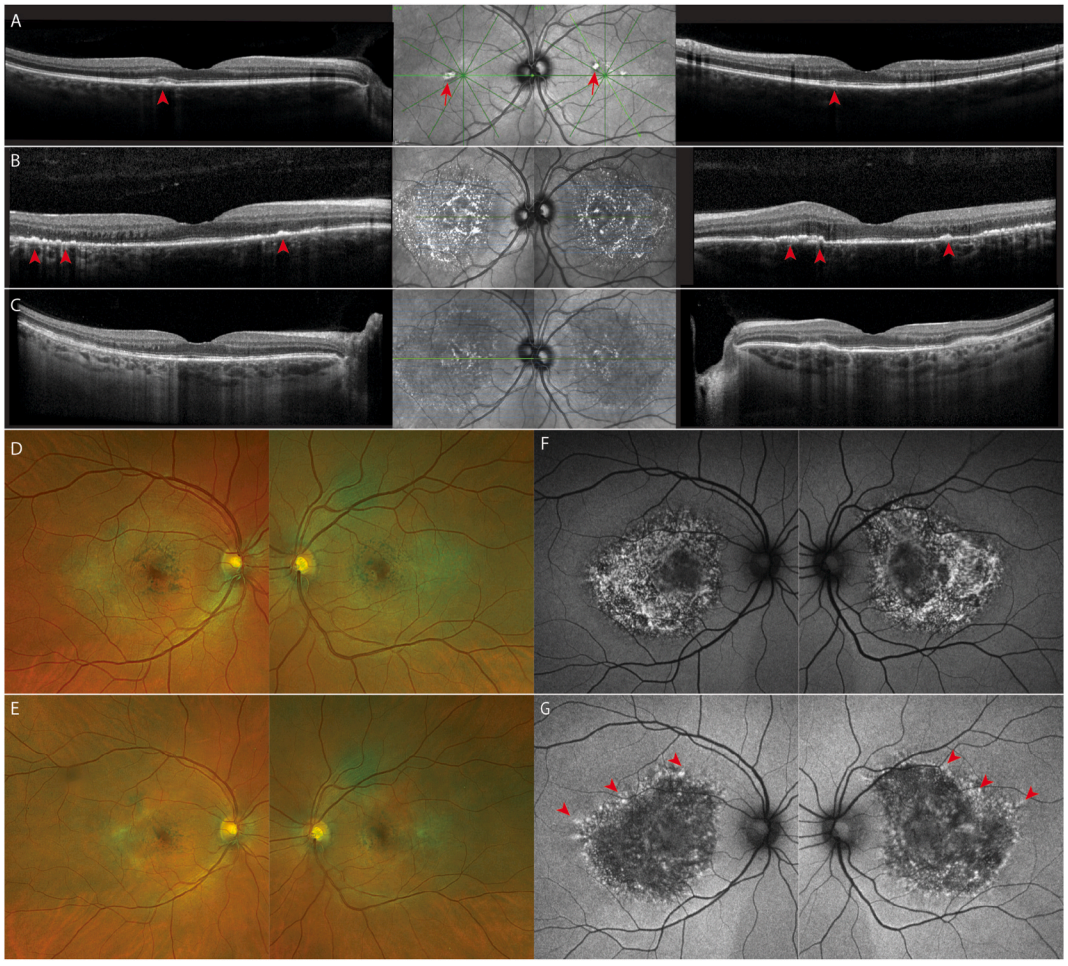

Fig. 1. (A) Spectral-domain OCT (SD-OCT) B-scans from April 2021 showing areas of RPE hyperplasia (arrowheads) corresponding to foci of punctate hyper- and hypo-reflectance changes on near infrared images (arrows). (B) SD-OCT B-scans from January 2023 showing progression of lesions with diffuse disruption of photoreceptors with foveal sparing along with RPE clumping (arrowheads). (C) SD-OCT B-scans 13 months after stopping fondaparinux demonstrate significant reduction and remodeling in the areas of RPE hyperplasia as well as reconstitution of the photoreceptors in both eyes. There is also a reduction in the quantity and size of dentate outer plexiform processes extending into the outer nuclear layer. SD-OCT on this date was taken with an enhanced depth imaging technique and it is difficult to compare transmission defects between different dates. Near-infrared images from both eyes demonstrate improvement in the degree of punctate hyper-reflectance. (D) Color fundus photos from January 2023 demonstrate RPE mottling and surrounding pigmentary changes. (E) Color fundus photos 13 months after stopping fondaparinux demonstrate improvement in pigment mottling. (F) Autofluorescence from January 2023 demonstrates mottled hyper- and hypo-autofluorescence corresponding to macular pigmentary changes. (G) Autofluorescence 13 months after stopping fondaparinux demonstrate a transition from hyperautofluorescence to hypoautofluorescence throughout the majority of the lesion. However, the edges of the lesion remain moderately hyper-autofluorescent (arrowheads).

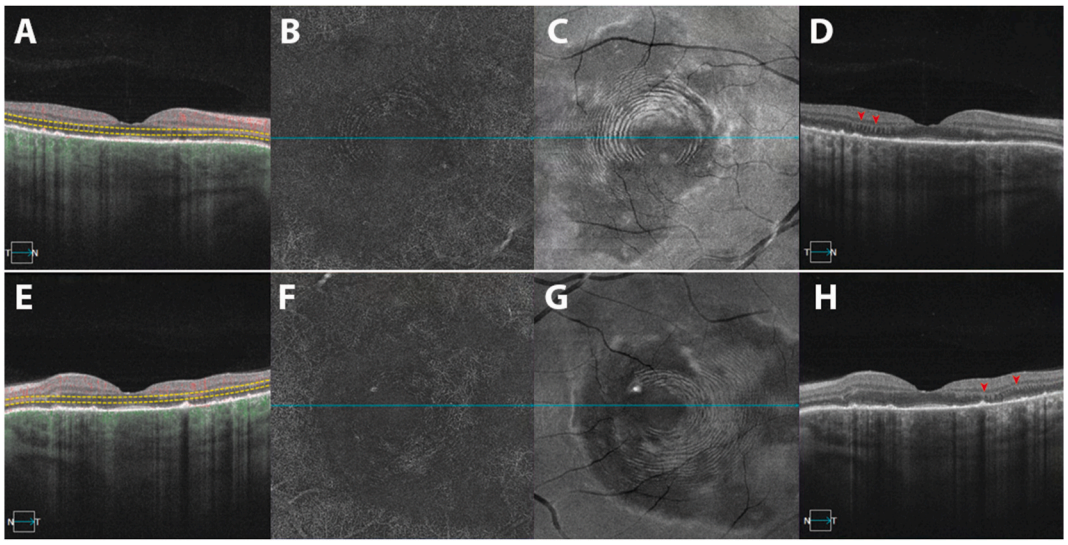

Fig. 2. Images taken in January 2023. Swept-source OCT angiography (SS-OCTA) flow (B,F) and structural (C,G) images from the right (A–D) and left (E–H) eyes with segmentation through the outer plexiform and outer nuclear layers (A and E). *En face* flow (B, F) images show the avascular outer retina. En face structural (C, G) images show prominent concentric macular rings. Dentate hyperreflective processes are appreciated on the structural B-scan images (D, H, arrowheads). The dentate processes are likely hyperreflective extensions of the outer Henle fiber layer in the outer nuclear layer and related to the concentric macular rings.[11].

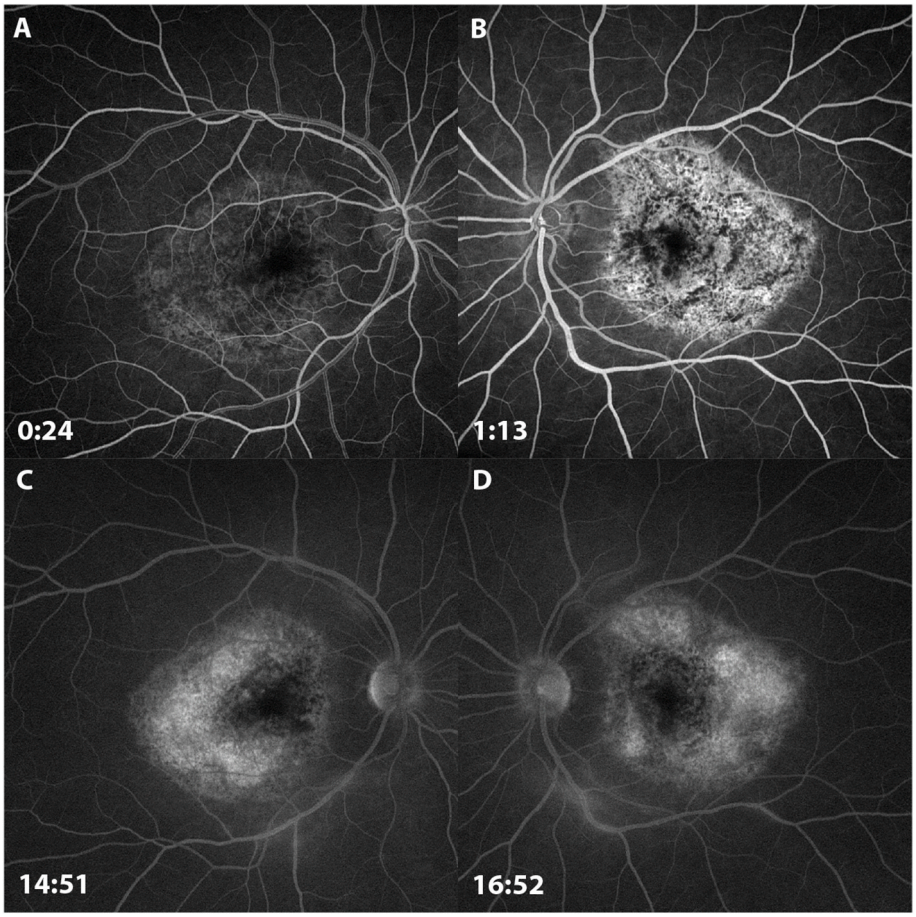

Fig. 3. Fluorescein angiography of both eyes in January 2023 at early (A, B), and later (C, D) time points. Early time points demonstrate stippled hyperfluorescence corresponding to the macular changes with late staining.

None of her long-term medications were known to be associated with maculopathy. Review of 13 years of medical records confirmed no use of PPS. We attributed the maculopathy to her long-term use of fondaparinux, a sulfated oligosaccharide that is structurally and functionally related to PPS, most likely by inhibiting a key enzyme of the extracellular matrix, heparanase. Fondaparinux was stopped. Thirteen

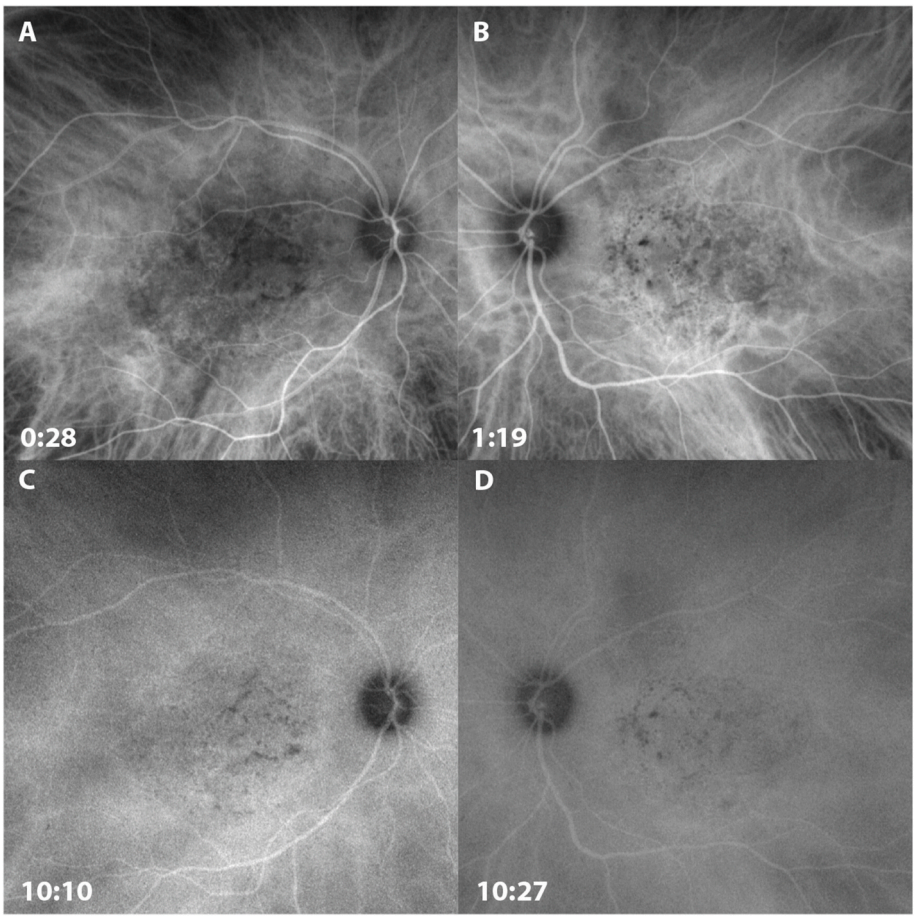

Fig. 4. Indocyanine green angiography of both eyes in January 2023 at early (A,B), and late (C, D) time points. Early time points demonstrate a mild delayed filling in the macula. There is also stippled hypofluorescence secondary to blocking from areas of RPE hyperplasia that remains persistent through the late time points.

months later, the patient's vision remained 20/20 in each eye and she reported improved quality of vision. On exam, the macular hyperpigmentation had decreased and the yellow decolorization had normalized (Fig. 1E). The width of the intact ellipsoid zone on OCT had increased (Fig. 1C). The speckled hyperautofluorescence had mostly subsided except at the lesion edges (Fig. 1G). There was no border progression.

3. Discussion

Fondaparinux is approved for short-term perioperative prophylaxis of deep vein thrombosis or as a heparin replacement during transition to oral anticoagulation,[4] whereas PPS is approved for relief of symptoms of interstitial cystitis. Different indications for use may obscure underlying similarities in these drugs. Fondaparinux and PPS are, respectively, synthetic and semi-synthetic low molecular weight heparinoids.[1,5] Both medications are inhibitors of factor Xa and heparanase.[1] While there is a straightforward link between the labeled use of fondaparinux for anticoagulation based on factor Xa inhibition, the mechanism by which PPS reduces pain from interstitial cystitis is less certain. One possibility is that it shields the bladder wall by binding to heparanase and inhibiting the degradation of heparan sulfate proteoglycans which leads to protection of the extracellular matrix, cell surfaces and basement membranes.

Heparanase degrades extracellular matrix by cleaving the heparan sulfate side chains of heparan sulfate proteoglycans, reducing their levels in tissue.[1] Over-activation of heparanase and loss of heparan sulfate proteoglycans promote cancer progression, inflammation and angiogenesis.[1] Age-related decrease in heparan sulfate in Bruch's membrane is hypothesized to increase the risk of macular neovascularization by providing fewer binding sites for complement factor H and consequently increasing complement activation.[6] In contrast, pharmacologic inhibition of heparanase would lead to an increase in heparan sulfate proteoglycans in the outer retina, which might interfere with physiological tissue remodeling of the extracellular matrix. Imbalance in degradation and renewal may be the common mechanism in the hypertrophic maculopathy in PPS maculopathy and in this single case of long-term fondaparinux use. The biological plausibility of this hypothesis is supported by the similar RPE folds and protrusions that progress over time in genetically engineered knockout mice without heparanase activity.[7] It is also supported by decreased hyperautofluorescence after stopping fondaparinux which suggests modulation of RPE hypertrophy after restoring heparanase activity. Similar reduction in hyperautofluorescence and increase in hypoautofluorescence after cessation of pentosan were interpreted as disease progression but are also consistent with remodeling of the extracellular matrix by heparanase.[8]

There are imaging features in this case that contrast with PPS maculopathy. First, concentric macular rings on en-face OCTA not been reported in PPS maculopathy to our knowledge.[3] There are several hypotheses regarding this pattern, which include mechanical traction or compression of the retina that distorts Henle's layer.[9–12] The dentate pattern largely resolved following cessation of fondaparinux. Second, PPS maculopathy may have progressive outer retinal/RPE atrophy even after cessation of the drug.[13,14] In this patient, the ellipsoid zone partially regenerated following cessation of fondaparinux. It is unclear whether these are specific features related to the causative drug or to individual variability. Based on prior descriptions of pentosan maculopathy, this case would be considered to be relatively mild due to the

absence of complete RPE and outer retinal atrophy (cRORA) or well demarcated hypoautofluorescence.[3]

4. Conclusions

Heparanase inhibitors are a broad class of agents under development for novel indications such as retarding metastatic cancer growth, angiogenesis and inflammation. Saccharide-based heparin mimetics similar to pentosan polysulfate and fondaparinux have been studied in clinical trials as cancer treatments; small-molecules and monoclonal antibodies are other approaches for inhibition.[15] Stereotypical maculopathy associated with two different drugs in the class suggests that retinal monitoring may be needed for other heparanase inhibitors in clinical trials. Like PPS maculopathy and this case associated with fondaparinux, maculopathy may require prolonged exposure. Nonetheless, this case provides additional support for a specific role for heparanase inhibition in PPS-associated maculopathy.[16] The risk of similar maculopathies from other heparin mimetics or heparanase inhibitors should be considered when monitoring individual patients and during development of new agents in this promising pharmacologic class. We propose the term heparanase inhibitor maculopathy to increase awareness of the potential for macular effects by agents other than PPS.

CRediT authorship contribution statement

Benjamin R. Lin: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Erick Rivera-Grana:** Writing – review & editing, Data curation. **Wenting Zhou:** Visualization, Validation, Software, Formal analysis, Data curation. **Mark Barakat:** Investigation, Data curation. **Philip J. Rosenfeld:** Investigation, Formal analysis, Data curation. **Janet L. Davis:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Patient consent

The patient was given the opportunity to read this report and gave her written consent for publication.

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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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