Pentosan polysulfate and a pigmentary maculopathy: causation versus correlation?

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Introduction: Interstitial cystitis (IC) is a chronic disease with urinary tract symptoms and pain. Pentosan polysulfate (PPS) is the only U.S. Food and Drug Administration approved oral medication for the treatment of IC pain and symptoms. Recently, articles described a pigmentary maculopathy in IC patients on long term PPS therapy. Currently, there is no definitive study directly linking PPS as the cause of the pigmentary maculopathy. The aim of this review is to evaluate if PPS is the causative factor of the pigmentary maculopathy or if PPS use is only associated with the pigmentary maculopathy.

Materials and methods: A comprehensive review of peer reviewed journals using the search terms IC, maculopathy, mast cells, immune inflammatory components, Tamm-Horsfall protein, cations and tight junctions was performed to examine the pathophysiology and role of chronic inflammation in IC and known retinal maculopathies.

Results: Chronic inflammatory cells have been reported in age-related macular degeneration choroid blood vessels and in bladder submucosal and detrusor layers in IC patients. Studies in IC and maculopathies demonstrate a significant milieu of activated chronic inflammatory and immunologic responses that cause a more “leaky” epithelium and a subsequent cascade of inflammatory events that results in the pathological changes seen in these two conditions.

Conclusions: After an analysis of the literature describing a pigmentary maculopathy in IC patients on long term PPS, a causal relationship does not appear to be present. An alternate model is proposed postulating that the causative factor for the pigmentary maculopathy is the underlying inflammatory state associated with IC and not PPS use.

Key Words: cations, interstitial cystitis, pigmentary maculopathy, pentosan polysulfate, retinal pigment epithelium

Introduction

Interstitial cystitis (IC), also known as bladder pain syndrome (BPS), is a complex of urinary symptoms consisting of urinary frequency, urgency and/or pain. Symptoms wax and wane and can progress over time, particularly when untreated. Epidemiologic studies reveal symptoms consistent with IC/BPS affect up to 7.9 million American women and up to 2.1 million American men.1,2 The only U.S. Food and Drug Administration (FDA) approved oral medication for the treatment of IC symptoms and pain is pentosan polysulfate (PPS; Elmiron, Janssen Pharmaceuticals). Several randomized, placebo controlled, and meta-analysis studies have demonstrated that PPS is effective compared to placebo for the treatment of IC pain, urinary frequency and urgency.3-7 PPS is...
also a recommended treatment option listed in the American Urological Association (AUA) guidelines for the treatment of IC.8 Recent studies have suggested a potential PPS related pigmentary maculopathy (PM). The aim of this review is to evaluate if PPS is the causative factor of the PM or if it is simply correlation and the underlying cause is an inflammatory milieu common to both diseases. The pathophysiology and the role of immune inflammation in PM has not been evaluated. Therefore, the pathophysiology and the role of chronic inflammation in known maculopathies and IC will be reviewed and evaluated for similar findings in both conditions. A model will be proposed that postulates that the PM that has been seen in patients with chronic PPS exposure is most likely a result of the heightened immune response that encompasses both IC and PM.

Materials and methods

A comprehensive review of urology, ophthalmology and other peer reviewed journals using the search terms IC, maculopathy, mast cells, immune inflammatory components, Tamm-Horsfall protein (THP), cations and tight junctions was performed to examine the pathophysiology and role of chronic inflammation in IC and known retinal maculopathies. The results were evaluated to compare similar pathophysiological processes in both IC and retinal maculopathies, as well as to review the study data attempting to connect PM with PPS exposure.

Results

Pathophysiology and role of inflammation in IC

During the holding phase of urine, the principal barrier to solute movement across the epithelium is the surface mucus glycosaminoglycans (GAG) layer.9,10 With disruption of the protective urothelial barrier, the epithelium will “leak”.9,10 Parsons et al postulated that abnormalities of the GAG layer might be associated with the urothelial dysfunction of IC.11 Tight junction proteins are downregulated in patients with IC without Hunner’s lesions.12 “Leaky” tight junction proteins create permeability changes allowing urinary solutes/potassium/noxious stimuli to cross the urothelium into the underlying layers of the bladder.12 These molecules then trigger the depolarization of C-fibers which release Substance P, an inflammatory mediator that can activate mast cells (MC).

The immune inflammatory response in the submucosal and detrusor layers of the bladders of patients with IC is characterized by proliferation and activation of MCs, macrophages, and lymphocytes.13,14 Damaged urothelial cells release cytokines that stimulate the production and activation of MCs.15 There are significant increases in MCs, activated MCs and degranulated MCs in the detrusor of patients with IC.15 Activated MCs release histamine, tryptase, and cytokines (including tumor necrosis factor-α (TNFα)). These mediators induce increased permeability, recruit other immune cells, and cause local tissue damage, all contributing to further urothelial dysfunction. Tryptase is released from MCs and increased in the urine of IC patients causing microvascular leakage resulting in inflammation.16,17 Significant upregulation of TNFα in IC patients bladder mucosa could lead to apoptosis of urothelial cells.18 Macrophages and MCs release cytokine interleukin-33 (IL-33) and are significantly elevated in the urine of IC patients.19 IL-33 further activates macrophages and MCs, further perpetuating an inflammatory response.20 These vasoactive, proinflammatory and nociceptive mediators released from activated MCs cause neuronal sensitization and neurotransmitter secretion, which in turn cause additional MC stimulation.15 In addition to being a passive barrier, the urothelium also has a sensory component that is similar to sensory neurons that use diverse signal-transduction mechanisms to detect physiological stimuli.21 A loss of epithelial integrity could result in passage of toxic/irritating urinary constituents through the epithelium, leading to changes in the properties of sensory pathways.21

The composition of urine aids in containing urine solutes to the bladder’s lumen in the holding phase. There are protein and nucleic acid metabolites that are cationic, and these molecules have the potential to bind and injure the bladder mucosa layer.22 Studies demonstrate that total urine cation content and individual toxic cationic metabolites of nucleic acids and tryptophan are significantly increased in IC patients compared to controls, and that they are toxic to cultured urothelial cells.23 Urinary Tamm-Horsfall protein (THP) or uromodulin is synthesized in the kidney, is strongly anionic, and binds to the toxic urine cations to neutralize their effects.24,25 Approximately 35% of IC patients have defective THP.26,27 Defective THP has a significant reduction in its urothelial protective capacity.28 The toxic urinary cations likely represent the primary cause of IC.23 Parsons et al suggested the sequence of events that causes IC is an increase in toxic urine cations along with defective THP that is less protective of the urothelium, which then results in injury to the bladder’s GAG layer by these cations. This leads to a “leaky” GAG layer and diffusion of potassium and toxic factors into the
bladder wall, producing symptoms and tissue injury and leading to the cascade of events that creates the destructive cycle that results in an immune system inflammatory response. This response includes proliferation and activation of MCs, macrophages, and increased release of cytokines and TNF-α. This results in further injury to the urothelium and may lead to sensory afferent nerve upregulation, which can contribute to the chronic and painful symptoms associated with IC.

**Incidence of pigmented maculopathy**

In 2018, Pearce et al identified 6 patients with IC who also developed a PM that the authors postulate had a possible link to PPS exposure. They were a single institution, retrospective case series of patients self-reporting use of PPS that identified 38 patients, but only the 6 patients that had been previously evaluated by the authors for a PM were evaluated in the study. The median age was 60 years, a median cumulative PPS exposure of 2,263 grams (400 mg/day), and a median exposure of 15.5 years. The most common symptoms were difficulty reading and prolonged dark adaptation.

In 2019, at the same institution, Hanif et al reported a retrospective cross-sectional study of 219 IC patients that were evaluated for exposure to nine medications used to treat IC including PPS, and hydroxychloroquine. No other comorbidities were evaluated. Fourteen of 80 IC patients on PPS and 0 of 139 patients not exposed to PPS met the full criteria for a PM as defined by the investigators. They further characterized the features of the maculopathy as: (a) bilateral centered on the fovea, (b) fundus photography findings of paracentral macular hyperpigmented spots, round pale-yellowish deposits and/or patchy retinal pigment epithelium (RPE) atrophy, (c) fundus autofluorescence imaging with reticular hyper-and hypo-autofluorescent spots, and (d) optical coherence tomography with reticular hyper- and hypo-AFM. The authors noted that PPS exposure was the only significant predictor of the unspecified PM. However, they combined cases that met all criteria for a PM and those cases that had nonspecific macular pigment changes that did not closely meet the strict PM definition. The fourteen patients with a PM had a median age of 61.3 years and a median PPS exposure of 2.3 Kg (approximately 344 mg/day) for 18.3 years. Of the 139 IC patients without PPS exposure, 106 (76%) had inadequate imaging modalities for assessing pathology, and 10% (11 of 106) of these patients had descriptions of macular pigmentary changes or drusen. Another problem with the controls is that there was no mention of length of time of being diagnosed with IC. The authors suggested that PPS exposure is directly linked to the PM. However, the authors note that although their previous series of 6 IC patients on PPS with a PM “was suggestive of a drug toxicity, it did not address the possibility of an indication bias with IC or one of its other therapies causing this maculopathy.”

Subsequent studies further characterized the maculopathy and commented that many of the fundoscopic imaging findings in the PM are also found in pattern dystrophies and other hereditary maculopathies. In another retrospective study from this same institution, Barnes et al evaluated 1,394 patients with hereditary and other maculopathies and what the authors term “PPS maculopathy.” Fifteen patients in this study were characterized with a “PPS maculopathy.” Two expert graders, blinded to the clinical and medication history, evaluated the fundal imaging studies. The authors state there is a 100% sensitivity and 99.6% specificity for identification of “PPS maculopathy” by masked review. Out of these 15 PM patients, 10 of 10 patients with PPS exposure were correctly classified with “PPS maculopathy” (10 of 15 overall or 67%) while 5 patients without PPS exposure (33%) were incorrectly classified with “PPS maculopathy.” Other conditions can mimic the imaging findings of the PM to the extent that even expert senior retinal imaging specialists are misled by subtle findings, only to reclassify the diagnosis after further unmasked assessment.

Several other authors have investigated the potential association between PPS and the development of a maculopathy. Jain et al in a retrospective, matched cohort study compared 3,012 PPS users versus 15,060 non-PPS controls. A PPS unexposed cohort (cystitis diagnosis, therefore not IC patients) was matched 5 to 1 for PPS exposed IC patients. At 5 years, there was no significant risk of developing an atypical maculopathy and/or age-related macular degeneration (AMD), with 0.3% in PPS exposed patients and 0.2% in the control patients. At 7 years comparing the PPS users (0.6%) and non-PPS users (0.3%), there was no significant increase in developing an atypical maculopathy. AMD is a separate diagnosis and has distinctive features compared to the PM. The authors note that “it is unusual for a potential drug toxicity to manifest decades after initial FDA approval,” and that “the mechanism of PPS-associated maculopathy remains unclear.”
Ludwig et al reported in a multicenter, retrospective study that identified 227,325 commercially insured patients diagnosed with IC for 5 years, who were divided into those using and not using PPS and were then evaluated for the development of a maculopathy. 2.37% of IC patients on PPS developed a maculopathy, versus 2.77% of IC patients not on PPS who developed a maculopathy. Additionally, there was no evidence of a PPS dose-dependent relationship with the development of a maculopathy. In this study, the most common diagnoses of maculopathy in IC patients were exudative AMD (1.50%), drusen (0.80%), nonexudative AMD (0.30%), toxic maculopathy (0.10%), and hereditary maculopathy (0.04%). Only 0.3% of patients were on PPS for more than 5 years. The authors state that “this study adds to the paucity of literature describing the association between PPS and a novel maculopathy that may represent medication toxicity.” In this study there was no association between PPS exposure and ensuing diagnosis of maculopathy.

Based on current epidemiological evidence as well as retrospective studies and evaluation of all Bradford Hill criteria, a causal relationship cannot be established between PPS and a PM because of the variability in effect size, inconsistent diagnostic methodology, and the inability to prove temporality. The pathogenesis linking PPS to the PM has not been explained. Based on the lack of current evidence of a causal relationship between PPS and the PM, one must examine whether the PM is associated with systemic factors and phenomena related to IC itself or with other factors altogether different from IC and PPS.

**Pathophysiology and role of inflammation in maculopathies**

The retina is a light-sensitive layer that lines the back of the eye. The macula is a pigmented area that is responsible for central vision. The choroid blood vessels are responsible for over 70% of the blood flow to the eye and supply the retinal pigment epithelium (RPE) and photoreceptors. The choroid has three vascular layers, and the inner layer is the choriocapillaris (CC). The CC vessels endothelia have multiple fenestrations on the side facing the retina that allow for directional flow of filtered materials and oxygen from the CC to the RPE. Additionally, the normal choroidal stroma contains mast cells, macrophages, lymphocytes, plasma cells and nerve fibers.

The pathophysiology of the PM has not been identified, and the role of immune inflammation in PM has not been evaluated. Therefore, it is worth reviewing the pathophysiology and the role of immune inflammation in known maculopathies. Most people with AMD have the dry form in which the RPE atrophies in the more advanced stages. In AMD, the CC atrophy is greater than the amount attributable to normal aging. CC atrophy is observed in early AMD. CC vessels that have endothelia loss become “ghost vessels” resulting in decreased CC density that precedes RPE atrophy. MCs in elderly subjects are present in the outer two layers of the choroid. The MCs in the choroid of AMD patients are in the CC, which is the inner layer. Areas with the largest numbers of degranulated MCs showed loss to the CC. There are increased MC numbers and degranulated MC seen in all forms of AMD. MC degranulation and tryptase release are stimulated by the complement system. Accumulated complement complexes have been demonstrated in the CC and drusen of eyes with AMD. They are associated with CC thinning, and degeneration of the RPE. Stressed RPE activates MCs and release tryptase, prompting inflammation and macrophage activation. This leads to the destructive cycle of degeneration of the photoreceptors, RPE, and CC complex seen with AMD.

The RPE is a transporting epithelium that regulates the movement of solutes between the photoreceptors of the retina and the fenestrated CC. The RPE also produces and secretes several growth factors, interleukins, and TNFα that are required to maintain the structural integrity of the retina and CC. However, the RPE is not an absolute barrier and is moderately leaky to support the needs of the photoreceptors. Nevertheless, there are tight junctions that control the transepithelial diffusion of solutes between the cells. RPE tight junctions are slightly cation selective, and potassium is slightly more permeable than sodium. TNFα reduces the RPE tight junction transepithelial electrical resistance (TER) by greater than 80%, altering the RPE morphology, leading to impeded tight junction organization. Thus, increased TNFα secretion makes the RPE “leaky” to solutes. The altered RPE morphology has similarities to changes observed in AMD.

THP (uromodulin) is released into the blood. Defective THP is also seen in retinopathies. A significant inverse association of serum THP and inflammatory markers has been observed. Mutations in the UMOD gene (gene encoding the THP) in families with familial juvenile hyperuricemic nephropathy (FJHN) have less urinary excretion of THP compared to both normal controls and patients with FJHN without UMOD mutation.
proinflammatory activity with increased levels of inflammasomes and interleukin-1 beta (also known as lymphocyte activating factor, a cytokine). These studies also suggest that monosodium urate contributes to the retinal inflammation in diabetic retinopathy initiation and progression. THP gene defects lead to hyperuricemia which has been shown to have increased proinflammatory activity and retinal inflammation and contributes to diabetic retinopathy. Uromodulin like-1 (UMODL1) gene is similar to THP. UMODL1 secreted proteins may be involved in cell-to-cell and cell-to-extracellular matrix adhesion and in cell migration. Therefore, defective THP has been identified in patients with IC and retinal inflammation. Defective THP in IC patients could potentially cause retinal inflammatory changes that have a role in the development of a PM.

Another consideration is the size of the molecules being transported through the choriocapillaris as well as the “leaky” tight junctions. PPS is poorly absorbed with less than 1% bioavailability. The majority of PPS (84%) was excreted unchanged in the feces, and 6% in the urine. Distribution of radiolabeled PPS is to the urine tract with lesser amounts found in the liver, spleen, lung, skin, periosteum and bone marrow. PPS radioactivity in plasma samples were insignificant, and radioactive metabolite fractions were too low for HPLC profiling. PPS is a large molecule with a molecular weight of 4,000 to 6,000 Dalton. Toxic cations, in contrast, are small molecules with a molecular weight ranging from 165 to 311 Daltons. The major toxic cation is L-tryptophan with a molecular weight of 204 Daltons. PPS being a larger molecule will be less likely to be transported across the RPE as compared to the smaller toxic cations, making PPS unlikely to be a causative factor in the PM seen with IC patients who have PPS exposure.

Correlation versus causation of PM and PPS
Based on current epidemiological evidence and evaluation of all Bradford Hill criteria, a causal relationship cannot be established for PPS being the culprit of the pigmentary maculopathy. There are two large epidemiological studies of commercially insured patients that demonstrate no significant increased risk of developing a maculopathy in IC patients treated with PPS at 5 and 7 years. Thus, the association of PPS as the causative factor for PM is tenuous and not likely.

PPS was approved by the FDA in September 1996. Twenty-two years later, in 2018 Pearce first reported a unique PM in IC patients on PPS. Multiple publications have followed, many from the same institution (Emory Eye Center). Currently, there are no long term, multi-site, prospective studies with IC patients of similar disease severity and length of time with IC symptoms that compare rates of developing a PM between patients with measured PPS exposure and those patients without any PPS exposure.

There are many fundamental problems with the studies describing the PM. They are retrospective in nature. In these studies, there are no clear definitions of the control cohorts as well as no descriptions of the control arm’s length of time with symptoms and diagnosis of IC or the severity of the IC symptoms. The length of PPS exposure has been on patients recall and not pharmacy data. Additionally, the definition of the PM has changed over time. Studies have demonstrated that many of the fundoscopic imaging findings in the PPS associated maculopathy are also found in pattern dystrophies and other hereditary maculopathies. For example, Barnes evaluated 1,394 patients with hereditary and other maculopathies and PM. In this analysis fifteen patients were characterized with PM, but five of these patients had no PPS exposure. Therefore, PM was found in patients without PPS exposure and in some patients without a diagnosis of IC.

Proposed mechanism of pathogenesis of PM in patients with IC
The pathogenesis of both IC and known maculopathies is multifactorial and complicated. There are common properties in IC patients and generalized maculopathy patients. Chronic immune inflammatory cells (including MC and macrophages) have been reported in human AMD choroids and in bladder submucosal and detrusor layers in IC patients. Data also suggest an immunologic response including complement activation, recruitment of macrophages, and involvement of systemic inflammatory processes in both AMD and IC. Both diseases demonstrate a chronic immune inflammatory response with increased MC and activated MC, macrophages and activated macrophages, TNFα, cytokines, tryptase, and oxidative stress. IC patients with toxic cations and defective THP will have these molecules circulating in the blood systemically, including the retinal blood supply. Defective or decreased THP has been identified in patients with IC and in retinal inflammation.

A key component of the PM is the loss of the choriocapillaris. This loss occurs due to chronic increases in MC and degranulated MC, inflammation with complement system activation, activated macrophages, and toxic cations. The choriocapillaris
vessels lose endothelia creating ghost vessels and decreased choriocapillaris density. The loss of the choriocapillaris leads to RPE atrophy. The RPE becomes more “leaky” due to increased TNFα expression, which decreases the tight junction resistance. Normally the RPE tight junctions have slight cation selectivity. When the RPE is “leaky” the cations and IC toxic cations are preferentially transported through the tight junctions in increased amounts, leading to RPE atrophy. THP is associated with extracellular matrix proteins involved in cell-to-cell and cell-to-extracellular matrix adhesion and in cell migration. Defective THP is less protective of the RPE, causing more permeability of the RPE to toxic cations. Toxic cations additionally injure the RPE making it more “leaky” and further leads to RPE atrophy. Similar to the “leaky” GAG layer in IC, the “leaky” RPE will lead to the cascade of events that perpetuates a destructive cycle resulting in a chronic immune inflammatory response, which includes proliferation and activation of mast cells, activated macrophages, increased release of TNFα and other cytokines, causing further injury to the RPE resulting in the pathological changes described in the PM.

Conclusions

IC and known retinal maculopathies have a complicated and multifactorial pathogenesis. Studies in both diseases demonstrate a significant milieu of an activated chronic immune inflammatory response that causes a more “leaky” epithelium and a subsequent cascade of events that results in pathological changes. Thus, the PM seen in patients with IC is most likely a direct result of the enhanced overactive immune response seen in these patients, irrespective of PPS exposure.

Certain IC phenotypes may be more susceptible to a PM, depending on the severity of the chronic immune inflammatory response, in combination with the quantity of toxic cations and defective THP. For patients with a bladder centric phenotype of IC, the symptoms localize to the bladder. The systemic phenotype of IC has systemic ramifications and effects, and some patients have chronic severe systemic symptoms. A systemic IC phenotype that causes more symptom severity likely has a systemic immune inflammatory response that could eventually lead to a PM. However, it is most likely the underlying pathophysiology that is part of the IC phenotype causing the PM and not the long term PPS, considering the common inflammatory cells and mediators’ activation in IC and PM.

This proposed theory of an IC related PM can explain some of the inconsistent findings that have been reported with the PM. It is the length of time the patient has the disease of IC that is important, not the length of time that the patient has been diagnosed with IC. An epidemiologic study demonstrated that the average symptom duration was approximately 14 years for both groups of women, those who meet the symptom criteria for a diagnosis of IC and those diagnosed with IC. This also explains why some patients on PPS for a relatively brief period of time may develop the PM. This model of an IC associated PM additionally explains why the PM may be diagnosed years after stopping PPS, and why the PM may progress even after stopping PPS.

There is a minimal number of therapies that treat the GAG layer in IC patients. PPS has helped relieve symptoms in many IC patients. The PM is a prominent issue for patients with IC, however PPS has been unfairly branded as the cause of the PM when the data is insufficient at best. Patients are concerned about taking PPS because of the potential PM that has been attributed to PPS, and many IC patients have stopped taking PPS because of this concern, with an increase in their IC symptoms. Often these patients decide to restart the PPS, prioritizing symptom relief and a more normal life over a potential future PM. Additionally, numerous newly diagnosed IC patients are not starting PPS. Unfortunately, the small amount of contradictory data that has been published is having a meaningful negative impact on patients with IC, and they are not availing themselves of a therapy that could provide real relief.

Further research in urology, ophthalmology and immunology are required to elucidate the etiology of the PM that is observed in an exceedingly small percentage of IC patients. Prospective studies quantitating the immune system inflammatory response and evaluating the retina in IC patients without and with PPS exposure with similar age, symptom severity, and length of time of IC symptoms need to be performed. Studies evaluating IC patients with PMs to determine the amount of urine toxic cations and defective THP, and ophthalmologic genetic testing need to be completed. These studies are warranted to confirm a possible causal relationship of the PM with IC, to identify the pathophysiology, and to manage disease guidelines. Unfortunately, PPS has been presumed ‘guilty’ until proven innocent.
References


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