The Spectrum of Pigment Dispersion: A Case Report and Topic Review

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Abstract

Introduction: The spectrum of disease including pigment dispersion syndrome and pigmentary glaucoma is wide and its potentially rapid progression can affect quality of life if not accurately classified and appropriately managed.

Case Presentation: This case report involves a patient with unilateral pigment dispersion syndrome and contralateral pigmentary glaucoma. Management and Outcome: Vigilant monitoring and longitudinal analysis of this case of secondary open angle glaucoma determined that he was not a rapid progressor and treatment did not need to be intensified.

Discussion: Pigmentary glaucoma is, on average, a more aggressive form of disease and should therefore be managed with the appropriate amount of reverence. The velocity of the disease's progression and risk of functional vision loss will guide the clinician on how intensive the medical or surgical intervention should be.

Keywords: Pigmentary dispersion syndrome (PDS), Pigmentary glaucoma (PG), long anterior lens zonules (LAZ), trait reverse pupillary block, laser peripheral iridotomy (LPI)

Introduction:

Pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) comprise two sides of a spectrum of ocular disease. PDS is characterized by abnormal liberation of posterior iris pigment epithelium with marked accumulation of that pigment throughout the anterior chamber (AC). First described by Sugar and Barbour in 1949 as accumulation of pigment in the AC causing glaucoma, PDS characteristically presents as a triad of vertical pigment deposition on the corneal endothelium (Krukenberg spindle), radial mid-peripheral iris transillumination defects that correspond with underlying zonular fibers, and heavily increased pigmentation of the trabecular meshwork (TM) detected by gonioscopy, all in the presence of a gonioscopically open angle. Secondarily, ocular hypertension (OHT) may result from pigment induced damage to the TM, subsequent reduced aqueous outflow, and resultant pathological increase in intraocular pressure (IOP), potentially causing PG and ultimately loss of functional vision.2–6

PDS is commonly a bilateral condition found between the 3rd and 5th decade of life. It affects men more than women, Caucasians more than any other racial group, and is associated with myopia. Approximately 80% of PDS patients are myopic, and studies show the risk of developing PDS increases as the extent of the myopia increases.7,8

PG is significantly more prevalent in men than women (upwards of 93% of PG patients are male). Siddiqui et al, in a retrospective community-based study involving a 58% male population showed that men had an overall four times greater annual incidence rate of PG when compared to females (2.3%/yr vs 0.6%/yr).9 PG also tends to be more aggressive in males than females and occurs earlier in life. Overall the risk of developing PG from PDS is estimated to be as high as 50% after four years. However, specific longitudinal population data varies with the lowest reported conversion rate reported to be 10% at five years and 15% at 15 years.3,5,9,10

The genetic basis for PDS and PG is poorly understood with some studies reporting a sporadic nature whereas other research has shown a positive family history of glaucoma in as high as 26% of patients having PDS or PG. An autosomal dominant pattern with incomplete penetrance is generally reported and chromosome 7q35-q36 has been isolated and shown to increase the risk of PDS.11

The global prevalence of glaucoma is expected to reach 111.8 million persons by 2040.12 Available data shows that PG accounts for approximately 0.5-5% of all glaucoma cases in the western world.13,14,15 In a U.S study from Olmstead County, Minnesota (95% Caucasian racial makeup) assessing the incidence of PDS and PG over 23 years the incidence of PDS was found to be 4.8 per 100,000 and of PG to be 1.4 per 100,000.9 Although reportedly rare in Asian, African American
and Latino subgroups the incidence may be underreported due to more difficult detection in patients with darker and thicker irides that may mask iris transillumination defects.\textsuperscript{5,16} The presence of long anterior zonules (LAZ) may be helpful as a risk factor in these more heavily pigmented patients where the traditional triad might not apply, as LAZ has been shown to increase glaucoma risk.\textsuperscript{17}

Diagnostic testing such as gonioscopy, ultrasound biomicroscopy (UBM), anterior segment optical coherence tomography (AS-OCT), posterior segment OCT, and visual field (VF) testing, amongst others, can be beneficial in confirming the presence of PDS, as well as its conversion to PG. Gonioscopy can confirm the backward bowing of the iris as well as the heavy deposition of pigment on the TM. UBM and AS-OCT are useful in assessing the AC depth and whether posterior bowing of the iris exists, creating irido-zonular touch which predisposes the release of iris pigment. Circumpapillary retinal nerve fiber layer (cp-RNFL), ganglion cell analysis and VF studies are all well-known diagnostic tools to confirm the presence of glaucoma and track the course of the disease, which can be more aggressive in PG than typical primary open angle glaucoma (POAG).\textsuperscript{1,5,18}

Management of PG can be more challenging than other forms of open angle glaucoma given its potential for both significantly increased and fluctuating IOP.\textsuperscript{15} In a retrospective longitudinal study of PG patients ranging from five to 35 years, 25% of patients had IOP>31mmHg and 12.5% had IOP>39mmHg at the time of diagnosis.\textsuperscript{19} Treatment depends on how extreme the IOP is at diagnosis and the extensiveness of the disease state. Accordingly, treatment can vary and may include medicine, attempting to prevent conversion through the use of laser peripheral iridotomy (LPI), or surgical intervention ranging from less invasive techniques to full thickness ab externo trabeculectomy.\textsuperscript{1,20–23}

**Case History/Details:**

A 71-year-old Caucasian male presented to clinic in January 2019 for a three-month follow-up of mild stage PG OS, and PDS OD. Specifically, he was to return for a glaucoma progression evaluation which included, on this visit; IOP measurement, dilated funduscopic assessment of the optic nerve and surrounding tissue, OCT to assess whether progressive retinal nerve fiber or ganglion cell loss had occurred, and ultimately to assess whether his management was aggressive enough to limit the risk of vision loss in his lifetime. The patient reported good adherence with latanoprost (dosed qam OU secondary to improved schedule adherence) and a review of his refill patterns over the previous five months confirmed that he had been consistently refilling his drops. Review of systems was unchanged at that visit. The patient’s medical history was significant for hyperlipidemia, atrial fibrillation, deep vein thrombosis with pulmonary embolism, adenocarcinoma of the prostate, depression, anxiety, osteoarthritis, vitamin D deficiency, post-traumatic stress disorder, idiopathic peripheral neuropathy, alcohol abuse, and tobacco use. The patient’s active medication list included latanoprost, atorvastatin, dextran/hypromellose, ergocalciferol, metoprolol, tramadol, and warfarin. He was noted to have a penicillin allergy. The surgical history was remarkable for cryoablation of the prostate in 2011, and phacoemulsification with posterior chamber intraocular lens (PCIOL) implants OU (OS 4/29/2014, OD 6/3/3014).

The patient’s BCVA was 20/20 OD, OS with OD: -0.25-0.75x075 and OS: +0.75-1.00x075. His pre-cataract surgery Rx was OD: -3.00-1.25x080 and OS: -6.00-1.25x115. Pupils were equal, round and reactive without an afferent pupillary defect (APD) noted, extraocular motilities (EOMs) were full by versions and confrontational VFs were unremarkable. Anterior segment evaluation by slit lamp biomicroscopy was remarkable for scalloped lid margins, turbid meibum with clumps requiring moderate pressure to express, corneal scars post clear cornea incisions at 7 o’clock OD and 2 o’clock OS and well centered PCIOLs with trace posterior capsular haze OU. Additionally, there was bilateral endothelial pigment in a spindle pattern which extended from the inferior to near central cornea, mid-peripheral iris transillumination defects, and a concave iris contour (Figure 1).

The ACs were deep and devoid of pigment and the angles were graded 4x4 OD, OS by Van Herick. Gonioscopy was

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**Figure 1.** Left image demonstrates a Krukenberg spindle (accumulation of liberated posterior iris pigment on the corneal endothelium driven there by the aqueous convection current). Right image shows radially oriented, mid-peripheral transillumination defects created by chafing of posterior iris epithelium against lenticular suspensory zonules.

**Figure 2.** Anterior segment photograph of a patient with PDS. The yellow arrow highlights the depth and concavity of the peripheral iris root insertion. The blue arrow highlights the uniformly heavy pigmentation of the TM and the red arrow indicates the deposition of pigment on Schwalbe’s line (Sampaolesi line), isolated by use of the corneal wedge technique.
last performed in January 2018. The findings were graded per Spaeth classification as OD D45q with 2+ uniform TM pigmentation 360°and the presence of a Sampolesi line. OS was noted to be D45q with 3+ uniform TM pigmentation 360° (Figure 2). Figure 3 shows a representative UBM demonstrating a concave iris contour, often found in PDS/PG. IOPs measured with Goldmann applanation tonometry (GAT) were 13mmHg OD, OS at 1:45pm. The patient’s historical high in-office IOPs were 20mmHg OD and 22mmHg OS. The most recent corneal hysteresis values were 12.1mmHg OD and 12.4mmHg OS in January 2018.

The patient was dilated with one drop of Paremyd® OU at 1:45pm. The optic nerve head (ONH) vertical heights – assessed with a 66D lens – measured 1.3mm OD and 1.5mm OS. Excessive hyper-reflectance and poor capture of RNFL OU due to the patient’s background fundus pigmentation rendered the funduscopic assessment of RNFL minimally useful. No pathological peripapillary atrophy (PPA) or optic nerve hemorrhages were noted OU. A historical record review showed no documentation of disc hemorrhages throughout the course of his care. Neuro-retinal rim and laminar tissue OD was deemed unremarkable. The superior rim OS appeared eroded with lamina reconfiguration also superiorly, but without substantial posterior excavation. Cup-to-disk (CD) ratios were graded as 0.25H by 0.3V OD and 0.5H by 0.65V OS. Figures 4A and B represent fundus photos taken in 2013. The remaining posterior pole and peripheral retina findings were unremarkable.

Cp-RNFL and ganglion cell layer (GCL) analysis with trend analysis exhibited stable findings (Figures 5 and 6). Of note, although this patient has been followed for over 10 years, the change analysis is based on comparison to the post-phacoemulsification 2015 scans, which highlights the need to obtain new baselines after a major event that could influence IOP and the course of the disease. VF analysis detected no progression OS since the cataract extraction in 2015 and minimal progression since 2010. The OD lacked a cluster of defects to achieve a glaucomatous designation (Figure 7).

Given the stable findings the patient was scheduled for a four-month glaucoma progression evaluation with an additional VF to better utilize guided progression analysis (GPA) in the future. The patient was educated on his disease status, necessity of consistent medication use and adherence to progress examinations.

Discussion:
Pathophysiology

Pigment deposition on the endothelium in the shape of a spindle was first described by Krukenberg in 1899 and considered by him to be a congenital anomaly caused by the proximity of the pupillary membrane to the cornea during development. Multiple experts subsequently proposed that pigment in the TM obstructed aqueous outflow and increased IOP, and that endothelial and trabecular pigment came from the iris, which was reinforced by the later observation that patients with PDS had iris transillumination defects (found in approximately 86% of PDS patients).25,26
Figure 5A: OD cp-RNFL from January 2019. The scan is of good quality, good reflectivity and segmentation of RNFL between ILM and IPL is accurate. There is no focal or diffuse RNFL loss.

Figure 5B. OS cp-RNFL from January 2019. The scan is of good quality, good reflectivity and segmentation of RNFL between ILM and IPL is accurate. Both superior and inferior temporal sectors are thinned in comparison to the reference database.
Figure 5C. Glow scale of isolated GCL posterior pole asymmetry analysis. Although an artifact confounds analysis the OD GCL is more robust than the OS counterpart.

Figure 6A. Trend analysis OD shows no change from the post-phacoemulsification 2015 baseline.
Figure 7A. 2010 VFs. OD is reliable with optimal gaze tracking and 1% false positives (FP). The pattern deviation (PD) shows a slight reverse cataract effect (caused by patient over performance relative to peers, FP of 1% unlikely contributing) without any discernible glaucomatous pattern. OS VF is reliable with excellent gaze tracking and FP of 3%. The PD exhibits a mild inferior arcuate defect.

Figure 6B. Trend analysis OS shows no change from the post-phacoemulsification baseline.
Figure 7B. 2018 OD VFs. Gaze tracking excellent in March, and acceptable in October. Both are reliable and neither shows glaucomatous defects.

Figure 7C. 2018 OS VFs. Both exhibited mild inferior arcuate defects with excellent gaze tracking and FP 0%.
Sugars and Barbour first described myopic patients with endothelial pigment, heavy trabecular pigment, iris transillumination, open angles and increased IOP that would decrease with the use of pilocarpine. They termed this condition PG. This acquired endothelial pigment, known as a Krukenberg spindle, occurs in around 90% of PDS patients and is thought to have the vertical, spindle appearance due to the convection flow of aqueous in the AC that is influenced by blinking. However, the presence of a Krukenberg spindle is benign.29,30

Histological evaluation of Krukenberg spindles has shown granules of melanin both on and within corneal endothelial cells, which has been suggested to indicate that deposited pigment is actually phagocytosed and may account for the uniform appearance of the spindles.4 Interestingly, although studies have shown that endothelial cells in patients with PDS have abnormal shape and size, there is no change to corneal endothelium as the aqueous rises.26,28

The aqueous humor flow and AC convection current is also responsible for the occasional presentation of "pigment showers" where AC pigment circulating can be mistaken for white blood cells as found in uveitis. Other findings associated with the flow and current include circumferential deposition of pigment on the posterior lens surface at the junction of zonules and posterior capsule (known as either a Zentmayer line or Scheie strip), and the heavy deposition of pigment on the TM.1

This heavy trabecular pigmentation is the hallmark gonioscopic finding in the disease and may be the most impactful clinical sign that is ultimately causative of PG.126 Trabecular pigmentation in PDS and PG is uniformly dense and diffuse, involving all 360° of the TM (inferior angle may be slightly denser due to gravity), unlike the patchy pigmentation found in its secondary open angle glaucoma colleague exfoliation syndrome. Although multiple histological evaluations of the TM have shown that pigment is phagocytosed, it is thought that the extreme amount of pigment in PDS and PG causes phagocytic stress with resultant alterations to TM extracellular matrix. This chronic phagocytic stress causes the TM cells to reach phagocytic overload, signaling their death and subsequent local necrosis. Trabecular beams, devoid of TM cell support, collapse and fuse resulting in loss of inter trabecular spaces/ diminished aqueous outflow channels and under-perfusion to outflow tissues. This leads to increasing outflow obstruction and increasing IOP, ultimately increasing the risk of developing and/or causing the development of PG.1,4,26 Although this mechanism seems intuitive, the amount of pigmentation in the angle does not correlate directly with the risk of converting from PDS to PG. The amount of pigment is, however, directly related to the severity of the glaucomatous optic neuropathy when it occurs.4 A recent study on experimentally induced PG showed that IOP elevation actually preceded phagocytosis decline, calling additionally into question our actual understanding of the disease process.31 These findings may implicate other factors, as first proposed by Kaiser-Kupfer, possibly genetic, that are likely involved in who does and does not develop PG in PDS cases.32

In 1979 Campbell noted that characteristic radial mid-peripheral iris transillumination defects in PDS corresponded with the underlying zonular bundles. On average he found 65 to 80 bundles of zonules attached to the anterior capsule with the same number of radial iris transillumination defects. These were caused by zonules rubbing against the iris pigment epithelium, with subsequent migration of the released pigment. He additionally proposed that the aforementioned rubbing was due to the posterior bowing of the peripheral iris which he observed in many of his PG patients. He suggested that a “reverse” pupillary block mechanism might be at play and proposed that performing a LPI would convert the posterior iris contour to a more planar contour, thus eliminating the interface of zonules and pigmented iris pigment epithelium.33,34 A later study employing UBM confirmed this proposal as LPI was able to restore a normal iris contour and normal iridolenticular contact in PDS patients.35

More recently a case report showed that AS-OCT can also confirm the normalization of iris contour post LPI.36 Karickhoff confirmed the concept that the posterior bowing elucidated by Campbell causes a “reverse” pupillary block mechanism and elevated IOP.37 He suggested that the abnormal irido-lenticular touch in PDS works like a ball-valve/flap-valve mechanism where aqueous is allowed to travel unidirectionally from the posterior chamber (PC) to the AC – but not opposite – with the induced pressure gradient forcing the iris posteriorly, resulting in the “reverse” pupillary block.4,38 “Reverse” pupillary block is not unique to PDS and can be induced by exercise, accommodation, blinking or eye movements in normal. However, it likely occurs more easily in PDS due to these patients having increased iris concavity, a more posterior iris insertion and possibly larger irides which all create greater irido-lenticular contact.4,18,39 Liebmann’s group previously confirmed mid-peripheral concavity in both PDS and PG using UBM.40 Karickhoff suggested that employing LPI would equalize the pressure gradients between the PC and AC, preventing further dispersion of pigment and thus reducing phagocytic stress and decreasing likelihood of increased IOP.38 Further discussion of LPI’s role in PDS/PG will be discussed in the management section.

Once PG is induced it uniquely tends to enter a quiescent “burnout” phase as the patient ages. Typically occurring after 10 years, this “burnout” phase is characterized by reversal of iris transillumination defects, reduction in TM pigmentation, and IOP normalization, sometimes permitting reduced aggression
in management. The inferior angle tends to clear prior to the superior angle, known as the "pigment reversal sign" where the superior angle appears markedly darker than its inferior counterpart. It has been proposed that the clearance of pigment from the angle may restore some normalcy to aqueous outflow reducing the previously pathological IOP. The practitioner must exercise caution in categorizing glaucoma in new patients with "pigment reversal sign" and a population based normal IOP as these patients may have burned out PG rather than POAG. This reality may also result in a generalized underestimation of the true prevalence of PDS/PG.

The cause of burnout in PG may be multifactorial and multiple theories have been proposed. With aging accommodative power diminishes, relative miosis increases, and lenticular axial length increases possibly causing a relative pupillary block in which iris bombe might lift the peripheral iris away from its underlying zonules and reduce friction and pigment release. Some speculate about the possibility that all the pigment from the posterior iris epithelium has been rubbed off by the zonules and no additional pigment exists to slough, giving the TM the opportunity to potentially recover as it is no longer under the assault of pigment. Lastly, reduced IOP may result from age-related ciliary body shut-down and reduced aqueous production. Figure 8 shows the "burnout" phase with reversal of pigment in the TM of the inferior angle.

Long Anterior Zonules (LAZ)
Recently a new mechanism has been proposed for liberation of pigment which causes a variant of pigment dispersion that is distinct from traditional PDS. Known as the LAZ trait, it represents radially-oriented zonule fibers that insert more centrally than usual on the anterior capsule. Pigment dispersion results from the posterior iris chafing against these centrally located zonules, creating pigmented lens striae (PLS) and increased trabecular pigment. The prevalence of PLS has been estimated at 2.2% in African American patients and these findings are typical in patients over 50 years of age. PLS are strongly associated with Krukenberg spindles in an African American population and can be associated with glaucoma related to pigment dispersion. LAZ patients are also associated with higher IOP than non-LAZ patients. These multiple associations make the reasonable hypothesis that the LAZ trait is a marker for mechanisms that elevate the risk of glaucoma. Minimally, practitioners should be aware of the prevalence of LAZ trait and its potential to confound accurate diagnosis in patients appearing to have classic PDS.

Genetics in the Pathogenesis of PDS/PG
As stated above it has been proposed that the disease process in PG may involve not only basic mechanical tenets but also genetic predispositions. Past studies suggest a hereditary basis for the PDS/PG spectrum with as high as 26% of patients with PDS and/or PG having family members with glaucoma. A 2019 study in Iowa found the risk of PDS in a first degree relative of a patient with PDS was 10.10%. PDS/PG is, at present, considered to have an autosomal dominant transmission, however its penetrance is incomplete and does not necessarily behave in a Mendelian pattern. Haplotypes of LOXL1 were recently found to be associated with an increased risk of PDS and PG with the suggestion that mutations in this gene could alter the elasticity of iris stromal fibers in these cases. LOXL1 has also been implicated in exfoliation glaucoma (XFG). In reality, multiple genes are most likely involved in both PG and PDS and their individual interactions with each other and the environment may create the ultimate phenotype of the disease that is expressed. Although no specific PDS/PG gene has been consistently isolated, a genetic locus for PDS has been mapped to chromosome 7q35-q36 and may be related to an increased likelihood of the condition. This genetic linkage has not, however, been replicated. In general, the risk of developing PDS/PG in the genetic line of patients with these conditions is low. Further research and increased understanding of the genetic basis of this spectrum of disease will potentially elucidate the complete mechanism of the disease and how to prospectively manage these patients in the future.

Treatment/Management
Treatment and management of each patient with PDS or PG should be customized to that individual. Richter, Richardson and Grant in a prospective study on the natural history of PDS and PG, found that patients generally fall into one of four stages: 1) Inactive pigment dispersion with stable IOP 2) Active pigment dispersion with stable IOP 3) Active pigment dispersion with progressive glaucoma and elevated IOP; and 4) Inactive pigment dispersion with progressive glaucoma and normal or elevated IOP. Undoubtedly preventing patients from converting from PDS to PG, if possible, would be the ultimate goal of treatment.

As mentioned previously, Campbell's initial assertion that LPI would be effective in normalizing the pressure between the PC and AC was compelling. A substantial amount of research efforts have been placed into assessing the value of LPI in the management of PDS, in the context of preventing PG. LPI's preventative role is considered controversial. In fact, the American Glaucoma Society Pigmentary Glaucoma Iridotomy
study, which involved Campbell assessing long-term IOP control in PG patients undergoing uniocular LPI compared to their fellow untreated eyes, failed to demonstrate support LPIs benefit in these cases, when subjected to rigid statistical analysis. A recent Cochrane review showed there was a lack of high quality evidence to support or refute LPIs use in PG. This partly stemmed from the lack of consistency in the methodology employed in the five randomized controlled trials (RCTs) included in this particular review, specifically the lack of disease staging and variability of baseline patient characteristics.

Underscoring the controversy and inconsistencies on the subject are two recent studies assessing the role of LPI in the natural history of PDS. Scott et al. tested the hypothesis that Nd:YAG LPI reduced the incidence of conversion to PG in PDS patients with established OHT. One hundred sixteen patients were randomly assigned to LPI or to a control group of no LPI and then monitored for conversion to PG over three years. They found that 15% of patients having undergone laser and 6% of the control group converted to PG in the study period and that a similar percentage of patients in each group had to be placed on medications (15% LPI, 17% control). They concluded there was no benefit to LPI in PDS patients with OHT. They did propose that the development of OHT may have indicated established and likely irreversible TM damage. Accordingly, performing LPI to minimize the release of pigment at the OHT stage might be completely ineffective when that pigment release had already caused substantial damage to outflow. They admitted a possible imprecision in the study was how they characterized iris concavity as an inclusion criterion – it was estimated subjectively, not using UBM. They ultimately suggested that LPI might be effective in younger patients without irreversible TM damage.

Gandolfi et al., in a prospective long-term analysis of the role of drug-induced mydriasis and laser LPI in the identification and management of patients with PDS at risk for OHT, assessed the 10-year incidence of increased IOP in both eyes – one undergoing LPI and the other a control. The diagnosis of PDS was confirmed by the gonioscopic evaluation of the iris root configuration and then confirmed by UBM. Patients were separated into low- and high-risk of developing OHT based on the phenylephrine provocative test, where the successful liberation of at least 10 pigment particles in a single light beam post instillation of 10% phenylephrine was considered high-risk. The high-risk patients were then randomized to receive LPI in one eye and no treatment in the fellow eye. Low-risk patients were left untreated. Over follow-up, an IOP of 5mmHg over baseline daily phasing (six in-office readings between 8:00am and 6:00pm) was considered to be significant. After 10 years of follow-up 14.3% of patients in the high-risk group undergoing LPI experienced an increase of 5mmHg or more, whereas 61.9% of their fellow, untreated eyes, experienced that increase. Only 11.4% of the low-risk, untreated eyes had a significant IOP increase. The authors concluded that in PDS patients with low baseline IOPs (under 18mmHg) using the phenylephrine provocative test identified patients at high-risk for developing IOP elevation and that LPI, when performed on high-risk eyes, reduced the rate of IOP elevation to the same level as the low-risk eyes. The authors noted that the conclusions are based on the assumptions that the development of OHT is secondary to pigment liberation and that increased IOP will lead to PG, as well as the assumption that pharmacologically induced release of pigment successfully identifies patients that are more likely to develop PG.

Not all patients with PDS will develop increased IOP. For those that do it is reasonable to start with medical therapy prior to considering surgical options. Choices include medications that enhance uveoscleral outflow, trabecular outflow, or reduce aqueous production. The selection of the individual medication will depend on the stage of disease and presumed extent of trabecular damage. In theory pilocarpine is an ideal therapy for PG cases. Its parasympathomimetic activity stimulates the smooth muscles of the ciliary muscle to contract, increasing tension on the scleral spur, which widens the TM and increases outflow. Its effect to the iris sphincter causes miosis, reversing posterior iris bowing and pupillary block, as well preventing dilation reducing further risk of irido-zonular interaction. It has also been shown to inhibit exercise induced increased IOP likely due to the aforementioned iris configuration changes. Given that most patients with PG are young the miotic side effects of pilocarpine may be unacceptable given the accommodative spasm and blurred vision that accompanies, as well as the known risk of retinal detachment with pilocarpine. There is a known increased prevalence of lattice degeneration and retinal breaks in patients with PG. Although Scheie et al did not find an increased incidence of these occurrences when pilocarpine was used, a careful retinal evaluation would be warranted prior to considering its use. Independent of the possible side effects, the use of pilocarpine would be contingent on the extent of TM damage. If contracture due to pigment induced damage is significant, attempting to open the TM with pilocarpine may be a moot point.

The same applies for the recently commercially available netarsudil, which has been proven to enhance conventional trabecular outflow in patients with POAG. What is compelling about netarsudil is its inhibition of rho kinase (ROCK). ROCK-1 and ROCK-2 decrease TM outflow by increasing the contractility of TM cells through alteration of the cell shape and extracellular matrix. The ROCK inhibitors may induce a retraction of some of the damage created by ROCK-1 and -2, subsequently improving outflow facility. It is possible that if the TM cells are not excessively damaged by pigmentation in PG that a ROCK inhibitor might successfully alter TM cells and limit damage. The difficulty is in knowing whether increased IOP is truly a surrogate for TM damage. If it is not, the use of a ROCK inhibitor in these patients may have value. Studies on netarsudil in patients with PDS and OHT, as well as those with PG would be valuable. What is known is that targeting uveoscleral outflow and suppressing aqueous production should circumvent the damage in the conventional pathway and successfully lower IOP.
Generally prostaglandin analogues, which enhance uveoscleral outflow, are considered first-line in PDS and PG, although they have no specific anti-PDS/PG activity. They have been shown to have more effective in lowering IOP in patients with PG than aqueous suppression by beta-blockers, specifically timolol. Alpha adrenergic agonists (brimonidine) and carbonic anhydrase inhibitors (brinzolamide, dorzolamide) can also effectively suppress aqueous and lower IOP in PG spectrum patients. It has been proposed that selective α2-agonists such as brimonidine may actually be more useful in PG than in other forms of open angle glaucoma (OAG), as these patients may have hypersensitivity of their adrenergic receptors. If medical therapy is insufficient more aggressive therapy is required.

Laser trabeculoplasty in PDS/PG spectrum, much like with LPI, is considered controversial and has not been studied as extensively as it has in POAG and even XFG. Ritch et al. retrospectively reviewed the results of argon laser trabeculoplasty (ALT) in patients with medically uncontrolled PG over an average of 33 months. They found a cumulative success for all eyes of 80% at one year, 62% at two years, and 45% at six years. Notably, close to 33% of patients undergoing ALT still required trabeculectomy with incisional surgery taking place between one week and 37 months after ALT. Younger patients were more likely to have successful outcomes with ALT alone whereas older patients were more likely to require trabeculectomy for IOP control.

When compared to ALT, selective laser trabeculoplasty (SLT) employs less energy over a shorter duration, which is thought to selectively target pigmented TM cells, gently stimulating their metabolic state and improving aqueous outflow without collateral thermal damage. Ayala retrospectively reviewed the success rate of 180° treatment by SLT in patients with PG, defining failure of SLT as <20% IOP reduction, change in the medical treatment, performance of a further SLT treatment, or the patient being sent for surgery. He found the average time to failure to be 72.4 months. The success rate dropped from 85% at 12 months to 14% at 48 months. The initial success rate may have been due to the intense absorption of energy by the heavy amount of TM pigmentation, but that effect was not sustainable. Ayala concluded the long-term success rate of SLT in PG cases was low. When compared to similar 48-month success rates with SLT in POAG, Ayala's results with PG were substantially less. Koucheki and Hashemi did find a significant initial reduction in IOP after SLT in PG patients. However, they found inflammation and IOP spikes commonly occurred when SLT was performed 360° degrees and the overall complication rate and need for further surgical interventions was much greater in their PG patients vs the PXG and POAG patients involved in the study. This is consistent with Harasymowycz et al. report on four patients with heavily pigmented TMs who had IOP spikes post SLT (highest post SLT IOP of 65mmHg in a patient whose preop IOP was 27mmHg). Three of the four patients went on to require trabeculectomy. They recommended that physicians performing SLT on patients with heavy TM pigment be aware of a possibly increased likelihood of IOP spikes, necessitating more rapid incisional surgeries. Therefore laser trabeculoplasty's value in PG may be most significant in younger patients, but is likely a stopgap in management that has diminishing returns beyond that typically expected in other forms of OAG.

When medical and laser intervention is unsuccessful the standard surgical management for PG has involved filtration surgery employing ab externo trabeculectomy. However, given PG relative rarity there has been very little meaningful research about the long-term effectiveness of trabeculectomy in these patients. Qing et al, in a prospective observational case series, followed 18 patients over eight years to determine the long-term efficacy and safety of trabeculectomy in PG patients. Eight years after surgery they found a substantial and sustainable reduction of IOP over baseline (13.7±2.5mmHg post-op vs 34.5±4.7mmHg pre-op). Fifteen out of 18 eyes had stable BCVA, VF and optic nerve findings, and functional blebs remained in 12 out of 18 eyes. No patients required additional glaucoma surgery during the study period. The authors admitted that study limitations included a small sample size and no control group for comparison. Although they concluded in their study trabeculectomy was a safe and effective treatment for PG eyes, their results may not be generalizable due to the small sample size.

Although there has been a recent surge in the use of microinvasive glaucoma surgeries (MIGS) there is not an abundance of studies involving MIGS and PG. Klamann et al. retrospectively investigated the effectiveness and complication rate of the iStent inject among different open angle subgroups. The iStent inject is a second-generation trabecular micro-bypass device inserted into the TM into Schlemm's canal under intraoperative gonioscopic guidance. This device works to augment aqueous outflow through bypassing the TM, which is the greatest site of resistance to that outflow. Thirty-five patients were included in the Klamann et al study, only three of which had PG. In the three PG patients IOP prior to bypass was 28.3±3.21mmHg and the number of preoperative medications averaged 3.66±0.57. One day post-surgery the IOP was reduced to 12.33±0.57mmHg. However, after four weeks all three patients' IOPs were above 30mmHg. The authors speculated that stent obstruction from pigment may have occurred and they even attempted to Nd:YAG laser the opening of the stent, without success. Trabeculectomy had to be performed in all three patients. The small sample size, short duration of follow-up and retrospective nature all limit the generalizability of this study, but minimally raises awareness of the potential substantial IOP elevation in these patients if attempting trabecular micro-bypass.

In 2004 Ab interno trabeculectomy (Trabectome) was the first MIGS procedure to meet FDA approval. This procedure involves the ablation of a strip of TM and the inner wall of Schlemm's canal using a handheld electrode, guided by intraoperative gonioscopy. To date there has been only one major prospective study comparing the efficacy of ab interno trabeculectomy using...
Trabectome in patients with PG to patients with OAG. Out of 101 POAG and 101 PG cases Akil et al. found that at 12 months post operatively Trabectome provided similar safe and successful outcomes in both POAG and PG patients. Specifically, PG patients had an average baseline IOP of 24.4±7.7mmHg and were on 2.8±1.2 glaucoma medications. At the 12-month postoperative visit PG patients average IOP was 17.1±5.0mmHg and they were on 2.1±1.4 medications. Further longitudinal data would be beneficial in understanding the long-term implications of surgery, but the authors concluded that ab interno trabeculectomy is a good choice for early surgical intervention in young, myopic patients with mild to moderate PG.57

In November 2016 the FDA approved the XEN® glaucoma gel microstent (XEN-GGM) for patients with refractory glaucoma who failed previous surgeries or in patients with POAG, PXG, or PG with open angles who are unresponsive to maximum tolerated medications. The XEN-GGM is a transscleral gelatin stent placed through a clear cornea incision using a preloaded injector which acts as a shunt between the AC and subconjunctival space. It is meant to work like a traditional trabeculectomy without the conjunctival incision.58 Although early data shows promising results with XEN-GGM in refractory forms of OAG, there is a dearth of information specifically on its use in PG.59 Multiple studies include PG cases but there is no specific data available on those cases from which to evaluate.58,60–62 It seems reasonable given its surgical mechanism that XEN-GGM could be a viable option in the surgical management of PG. However, specific studies will need to be carried out on patients with this form of secondary OAG. Ultimately ab externo incisional trabeculectomy remains the standard for refractory PG at present until further research proves less invasive methods are superior.

Conclusion
PDS and PG comprise opposite ends of a spectrum of disease that can be visually devastating to those who suffer from the condition. Fortunately for the patient described in this case report his PG has been functionally benign with minimal progression occurring and his PDS has not converted to PG. Accordingly, although his condition was appropriately categorized with the subsequent assumption of potential high velocity, intensified management has not been necessary. Ultimately, PDS/PG can be an aggressive condition that practitioners need to respect and requires a low threshold for surgical intervention. At present there is no consensus on preventive management in these cases and it is therefore incumbent on the managing OD, much like in the care of all glaucomas, to analyze the behavior of the disease in the individual patient to optimize care.

References


