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Progressive retrocorneal pigmentation in dogs: A clinical report of 34 cases

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Abstract

Objectives: To describe the signalment, ophthalmic examination findings, and follow-up of dogs affected with a previously unreported retrocorneal pigmentary lesion.

Materials and Methods: Retrospective record evaluation spanning 2009-2019.

Results: Retrocorneal pigmentary lesions were described in 34 patients (46 eyes). German Shepherds (n = 7), Jack Russel terriers (n = 5), and terrier crosses (n = 4) made up 16/34 (47.1%) of the cases. The mean age was 13.5 years (range 1.4-14.2 years), and 16/30 (53.3%) dogs were female. Most dogs were affected unilaterally (22/34 (64.7%)), the others bilaterally, and 5/34 (14.7%) were referred for it while the others were incidentally diagnosed. The lesions affected the ventral, peripheral, inner cornea and had a round/undulated leading edge. The number of corneal clock hours affected was known for 41/46 (89.1%) eyes and involved 1-3 clock hours in 32/41 (78.1%) eyes, 4-6 in 6/41 (14.6%), 7-9 in 2/41 (4.9%), and 10 in 1/41 (2.4%). The central cornea was affected in 9/46 (19.6%) eyes, and in 5/9 (55.6%), the median corneal clarity score was G2 (scale: G0-G4). The commonest additional findings included free-floating uveal cysts (11/34 dogs, 32.4%), cataracts (6/34 dogs, 17.6%), and primary glaucoma (5/34 dogs, 14.7%). Gonioscopy was available in 16/34 (47.1%) dogs and was normal except in primary glaucoma cases. Follow-up was documented in 13/34 (38.2%) dogs with a mean follow-up of 17 months (range: 5-26 months). Lesion progression was documented in 6/13 (46.2%) dogs.

Conclusions: Retrocorneal pigmentation occurs as a slowly progressive lesion of older dogs that could impact vision. Histological studies of affected eyes are warranted.

KEYWORDS

corneal clarity, corneal pigmentation, endothelial pigmentation, limbal pigment, pigment dispersion, progressive pigmentation

1 | INTRODUCTION

The cornea is a transparent and highly specialized part of the anterior surface of the eye that permits the passage of light into the ocular media and plays an important role in optically modifying it.[1,2] Therefore, a change in the transparency and/or integrity of the cornea, such as corneal pigmentation, is potentially relevant to veterinary ophthalmologists because it could affect vision and/or visualization of intraocular structures.

Corneal pigmentary lesions containing melanin have been described before in dogs, such as pigmentary keratitis, which is generally associated with inflammation of the cornea,[3-10] and with medial entropion of the lower eyelid in Pugs.[11] These pigmentary changes typically affect the corneal epithelium and superficial corneal stroma,[10,12-14] and in some cases can lead to significant visual impairment, even blindness.[1,4,9,11,15] Spontaneous development of free-floating pigmented iris cysts can occur in a variety of breeds, and the cysts can rupture and lead to anterior lens capsule and endothelial corneal staining.[16-18] Pigmentary cystic glaucoma is a condition seen mainly in Golden Retrievers that present with thinned walled cysts in the posterior chamber, proteinaceous exudation, and melanin dispersion in the aqueous humor.[19-22] Corneal pigmentation is not an obvious clinical characteristic of pigmentary cystic glaucoma, though a study reported the presence of retrocorneal membranes that sometimes contain a sparse amount of melanin.[19] Limbal melanocytoma is a neoplastic proliferation of melanocytes that arises at the limbus and can affect the adjacent peripheral cornea of dogs.[23,24] Lastly, ocular melanosis, as typically seen in Cairn terriers, affects several layers of the eye, including the perilimbal sclera.[25-27] The cornea is not as heavily affected as other ocular tissues are, although one case with stage 3 ocular melanosis was shown to have pigment lining a part of the ventral corneal endothelium.[26]

One of the authors of the present study (RFS) noticed that dogs were occasionally referred with pigmentary lesions of the cornea that did not fit the clinical characteristics of the pigmentary changes described above that affected the posterior corneal surface to varying degrees, and that had not been reported before in the veterinary literature. As a result, it was theorized that this undescribed presentation was likely to be infrequently diagnosed, infrequently referred, and only occasionally reported in ophthalmic examinations. It was also theorized that the condition was likely to be progressive and that in some cases, the lesions might affect the visual axis and therefore could potentially affect vision.

The aims of the present study were to describe the clinical presentation of dogs affected with retrocorneal pigmentary lesions that the authors refer to as progressive retrocorneal pigmentation (PRP), and to report the analysis of patient signalment, and ophthalmic clinical findings, gonioscopy, corneal clarity scoring, and follow-up when available.

2 | MATERIALS AND METHODS

The authors performed a retrospective review of the medical records of dogs that were diagnosed with PRP by one of the authors between 2009 and 2019 at 3 ophthalmic referral centers (2 from the United Kingdom and 1 from the Netherlands) and by the other authors in the year 2019 in 3 separate ophthalmic referral centers (1 in the United Kingdom and 2 in the Netherlands).

Inclusion criteria included animals referred to an ophthalmologist and with a complete ophthalmic examination performed and/or directly supervised by a diplomate of the ECVO that included Schirmer tear test I (Schering-Plough Animal Health Corporation, Union), menace response, palpebral, dazzle and pupillary light reflexes, slit lamp biomicroscopy (Kowa SL15 or SL17, Kowa Company, Ltd), rebound tonometry (TonoVet® or Tiolat, Icare or Tonopen Vet®), indirect ophthalmoscopy (Keeler Vantage Plus or Omega 500, Heine) with a hand-held 30D lens (Volk Optical Inc) when not precluded by other ocular pathology and fluorescein testing (Minims® Fluorescein sodium 1% w/v, Bausch & Lomb). Depending on the presentation and at the clinician's discretion, gonioscopy and corneal clarity scoring of the central cornea were also included as part of the ophthalmic examination. Gonioscopy was performed using a hand-held slit lamp (Kowa SL15 or SL17, Kowa Company, Ltd) and an 18mm Koeppe gonio lens (Ocular Instruments). Corneal clarity scoring of the central cornea was based on a clarity scale of G0-G4 described by Sanchez et al (2015).[28]

Data collected included signalment, history, side affected, localization and extent of the PRP lesion, other findings of the ophthalmic examination, as well as gonioscopy results, corneal clarity scoring, and follow-up if they were available.

3 | RESULTS

Thirty-four patients with a total of 46 affected eyes were included. There were 28 patients seen by the same clinician between 2009 and 2019. Six additional cases were seen by other clinicians in other participating referral practices in the EU in the year 2019. A total of 12/34 (35.3%) patients were affected bilaterally (n = 24 eyes) and 22/34 (64.7%) patients were affected unilaterally (n = 22 eyes), including 8/22 (36.4%) right eyes and 14/22 (63.6%) left eyes.

A total of 16 breeds or breed-crosses were represented. There were 6 breeds/breed-crosses with 2 animals or more including German Shepherds (n = 7), Jack Russel Terriers (n = 5), Terrier crosses (n = 4), Staffordshire Bull Terrier

(n = 3), Labrador Retriever (n = 3), and Border Terrier (n = 2). A total of 10 breeds had only one affected animal each (Bohemian Shepherd, Border Collie, Cavalier King Charles Spaniel, Chow-chow, English Cocker Spaniel, English Bull Terrier, Flat Coated Retriever, Maltese, Pekingese, and Shih-Tzu). The three most commonly affected breeds accounted for 16/34 (47.1%) of the cases, and terrier breeds and terrier crosses together accounted for 15/34 (44.1%) of the patients.

The sex was not specified in the records of 4/34 (11.8%) dogs and was known for 30/34 (88.2%) animals. There were 14/30 (46.7%) males, of which 10 were neutered, and 16/30 (53.3%) females all of which were neutered. The age was not specified in the record of 2/34 (5.9%) dogs and was known for 32/34 (94.1%) animals. The mean age was 13.5 years (range 1.4-14.2 years).

A total of 5/34 (14.7%) animals were referred for examination of the corneal lesion that was later diagnosed as PRP. The rest of the PRP cases (29/34, 85.3%) were incidentally diagnosed.

Grossly, all the PRP lesions presented as a dark, translucent, opacity of the perilimbal inner corneal surface that on slit lamp examination had a speckled pattern that was consistent with pigment (Figure 1A-C). The lesions had a round or undulating leading edge that resembled the shape of a sea fan (Figure 2A-C). All of the lesions affected the inner-most part of the cornea between the 4 and the 8 clock hours (eg, the ventral, ventrolateral, and ventromedial inner cornea), as seen with the 0.1 mm slit of the slit lamp biomicroscope, independent of whether the lesion also extended to other clock hours or not. The number of clock hours affected per eye was described in 41/46 (89.1%) eyes and was not known in 5/46 (10.9%) eyes. When more than one clock hour was affected, they were always contiguous clock hours independent of the number of clock hours affected, except in one eye of one animal that was affected twice in two single but separate clock hours. As the clock hour count was used to describe the extent of the individual lesions, the small lesions in the eye of that patient were counted as if they affected only 1 clock hour. In a total of 32/41 (78.1%) eyes, the PRP lesion affected from 1 to 3 clock hours, in 6/41 (14.6%) eyes it affected 4 to 6 clock hours, in 2/41 (4.9%) eyes it affected 7 to 9 clock hours, and in 1/41 (2.4%) eyes, it affected 10 clock hours. The presence or extent of the lesions did not appear to be correlated to the presence of obvious limbal pigment.

The lesions extended toward the central cornea and affected part of the pupillary axis in 9/46 (19.6%) eyes (8/34 (23.5%) dogs) (Figure 3A,B). The corneal clarity score based on a clarity scale of G0-G4[28] was known for a total of 5 of those 9 eyes (55.6%) (case 1: G2, case 2: G1, case 3: G2, case 9: G2 and case 13: G0). The median value for the corneal clarity score was G2. The PRP lesion did not reach the central cornea in 37/46 (80.4%) eyes (26/34 (76.5%) dogs).

Other ophthalmic findings included free-floating anterior uveal cysts in 11/34 (32.4%) patients, one of which had a ruptured cyst that left a pigment patch on the cornea (Figure 4), cataracts in 6/34 patients (17.6%), and primary glaucoma in 5/34 patients (14.7%). In addition, there were dogs with spontaneous chronic corneal epithelial defects (4/34, 11.8%), keratoconjunctivitis sicca (3/34, 8.8%), lens luxation (2/34, 5.9%), stromal hemorrhage (2/34, 5.9%), and one animal each (1/34, 2.9% each) with meibomian gland adenoma, entropion, retinal detachment, systemic hypertension, or a history of "suspected glaucoma" that was later diagnosed as clinically normal. A total of 6/34 animals (17.6%) had more than one ophthalmic finding in addition to PRP.

A total of 8/34 patients presented with poor vision. A total of 6/34 (17.6%) had cataracts, 1/34 (2.9%) had a retinal detachment, and 1/34 (2.9%) presented with retinal hemorrhages and swelling associated with systemic hypertension and immature cataracts. None of these cases had PRP lesions that reached the pupillary axis.

Gonioscopy was performed in 16/34 (47.1%) cases and 360 degrees of the circumference of the pectinate ligament were assessed in each case, as none of the PRP lesions were large enough to interfere with the test. Gonioscopy revealed that the areas of the pectinate ligament adjacent to where the PRP lesion was present looked similar to the other parts of the iridocorneal angle in each eye that was assessed. The PRP

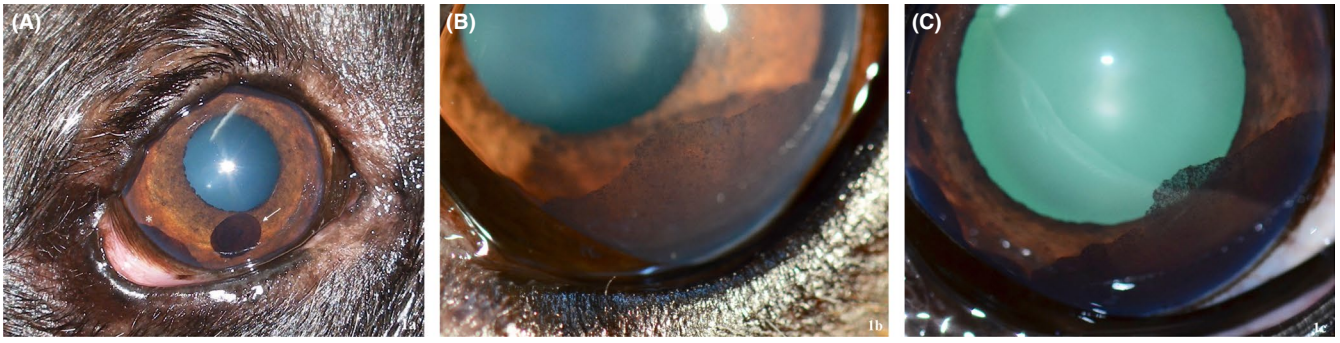

FIGURE 1 (A-C). Gross appearance of a small PRP lesion (asterisk) in the right eye of a labrador retriever that also has a dark, free-floating anterior uveal cyst (arrow) (A). Detail of an PRP lesion in the left eye of a German Shepherd dog as seen with direct illumination (B) and retroillumination (C)

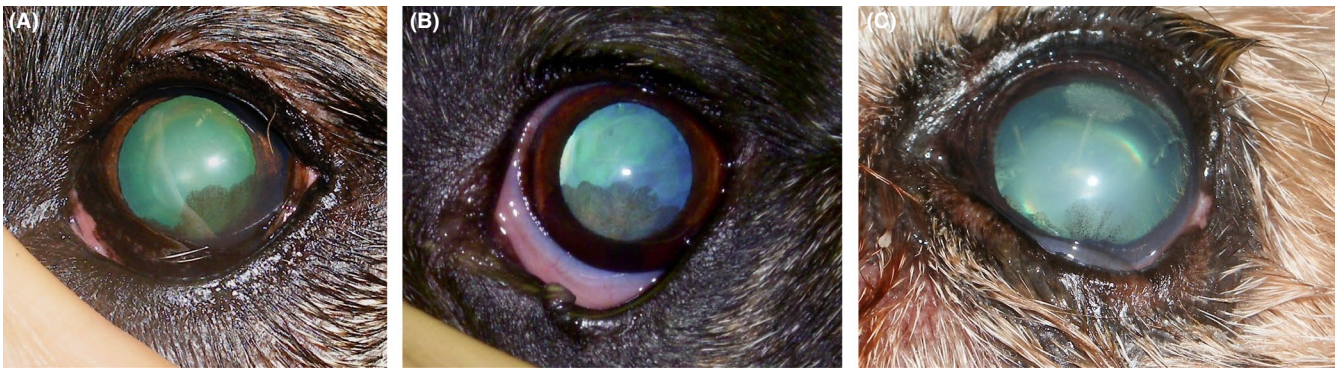

FIGURE 2 (A-C). PRP lesions with a round or undulating leading edge giving the appearance of a sea fan in a German Shepherd dog (A), Staffordshire Bull terrier (B), and Jack Russell terrier (C). The first two (A and B) affected the ventral pupillary axis

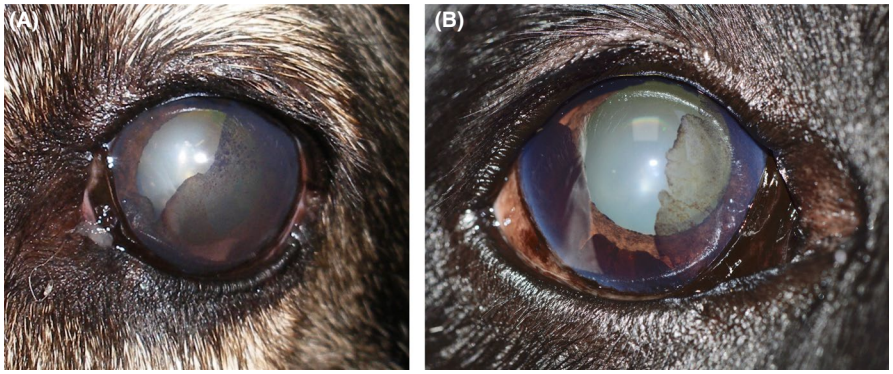

FIGURE 3 (A, B). Examples of PRP lesions that affected part a large part of the central pupillary axis in a German Shepherd dog (A) and in a Flat Coat Retriever (B)

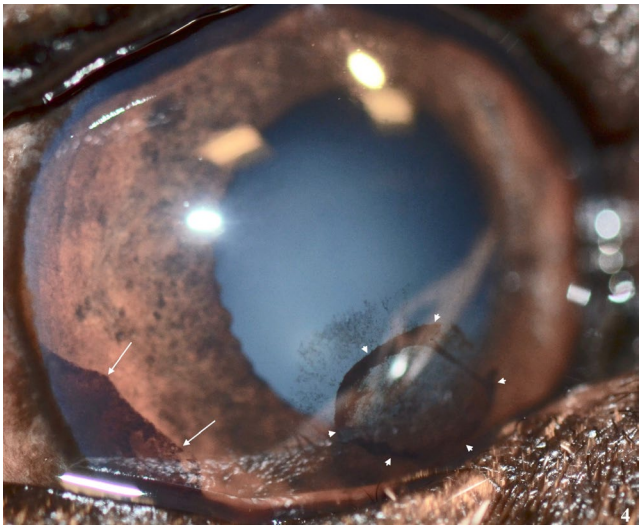

FIGURE 4 Cornea of a Staffordshire Bull Terrier with an PRP lesion (arrows) and a pigment splotch from a ruptured free-floating anterior uveal cyst (arrow heads)

lesions did not extend to the pectinate ligament strands of the iridocorneal angle in any of the cases. A total of four cases were diagnosed with severe goniodysgenesis, and all were the patients that had been referred for possible glaucoma. Gonioscopy was not repeated in any of the animals without glaucoma, and no additional animals developed new clinical signs that were consistent with glaucoma during the follow-up period.

There was a documented follow-up of the PRP lesions in 13/34 (38.2%) of the dogs included in the study, although the follow-up time was only recorded for 12/34 (37.5%) of these dogs. The mean recorded follow-up time was 17 months (range: 5-26 months). Lesion progression was documented in a total of 6/13 (46.2%) dogs (Figure 5A-B).

4 | DISCUSSION

The present study describes a condition of the inner corneal surface of older dogs that has not previously been described in the veterinary literature and might show a predisposition for terriers and terrier crosses as well as German Shepherds. Grossly, the PRP lesions presented as dark opacification in the ventral, ventrolateral, and/or ventromedial perilimbal inner corneal surface and had an undulating leading edge resembling that of a sea fan. On slit lamp examination, the PRP lesions were translucent, had a speckled pattern, and appeared to be consistent with melanin pigment. The lesions extended toward the axial cornea in a slowly progressive manner and in very advanced cases reached the central and even the dorsal half of

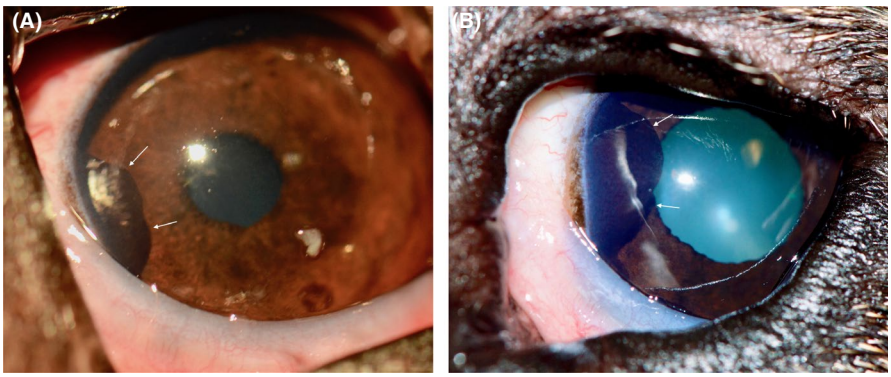

FIGURE 5 (A, B) PRP lesion progression in an English Bull terrier. Image (B) was taken 2 y after (A)

the cornea. Gonioscopy, when available, revealed no obvious changes in the pectinate ligament strands near the PRP lesions.

The total number of patients seen by each of the ophthalmologists in their respective centers was not known and, therefore, the prevalence of PRP lesion also remains unknown. However, these were busy referral practices with at least one full-time ophthalmologist solely dedicated to ophthalmic practice. Despite this, the total number of animals diagnosed with this condition was low. In the majority of cases, the condition was found as an incidental finding of the ophthalmic examination and only a small number of animals were referred because of it. The low number of cases seen most probably reflects that the condition is infrequently encountered in practice. However, had this lesion been thoroughly described in the veterinary literature, it is possible more animals would have been incidentally diagnosed or referred for it. The authors hope that by raising awareness of the condition and offering an example of how these lesions were described and followed over time, others will document this finding as well.

Generally speaking, the PRP lesions included in this study did not appear to lead to obvious ocular problems. However, a small number of the eyes had lesions extensive enough to affect the visual axis though none presented for poor vision. When available, the corneal clarity score of those cases was low. Therefore, it is reasonable to assume that PRP could affect vision, at least in principle. Extensive lesions could also potentially affect visualization of the intraocular structures during ophthalmic examination, but this was never reported in any of the cases included. A proportion of the animals included also had cataracts. None of the animals with extensive PRP underwent phacoemulsification, but it would be reasonable to also expect extensive PRP lesions to affect visualization of the intraocular structures during intraocular surgery.

One of the hypotheses of the present study was that the endothelial discoloration observed in the affected cases was consistent with the presence of melanin pigment. The source of the pigment remains unknown. There are several pathologies describing anterior corneal pigmentation in the veterinary literature,[3-14] but only ruptured free-floating anterior uveal cysts are described to lead to obvious retrocorneal pigmentation.[16-18] Ruptured cysts might leave an obvious pigment splotch residue on the inner cornea that is often round.[16] However, the PRP lesions observed in the present study were morphologically different. They were always connected to the limbus, had a round to undulating leading edge and often were more extensive than that described for ruptured cysts. Two studies of Golden Retrievers with Pigmentary Cystic Glaucoma have reported the presence of retrocorneal membranes,[19,21] with only one of the two studies reporting the membranes could contain a sparse amount of melanin.[19] However, visible retrocorneal pigment has never been reported as a clinical characteristic of this disease.[19-22] Histologic studies of eyes with PRP are required to confirm if the PRP lesions contain melanin as suspected through direct, gross observation, and to determine the exact localization of the lesion with relation to the corneal endothelial cells and the inner corneal stroma of affected animals.

Pigment dispersion syndrome is a condition of the human eye that can lead to secondary glaucoma.[29] It is characterized by dispersion of iris melanin secondary to posterior iris contact with the anterior lens and by posterior epithelial defects of the iris that lead to visible transillumination defects.[29] Some cases with pigment dispersion syndrome develop pigment deposition on the posterior surface of the central cornea in a vertical, spindle-shaped pattern, known as Krukenberg spindles, in addition to pigment deposits on the anterior lens capsule and the iris surface.[29] Krukenberg spindles are thought to occur secondary to aqueous convection currents within the anterior chamber and consist of melanin granules on and within endothelial cells.[29] A preliminary study of changes in the anterior segment of healthy canine eyes presented at the 41st Annual ACVO conference in San Diego suggested that pigment dispersion occurred in older dogs and that evidence of melanophagia could be found in the ciliary cleft, ciliary process, and base of the iris.[30] A histologic study of eyes with goniodysgenesis-related glaucoma showed that melanin dispersion occurred in affected eyes though there was also no mention of melanin being phagocytized by corneal endothelial cells.[31] The presentation of PRP lesions in the animals included in this study did not resemble Krukenberg spindles but might also be explained by the presence of melanin that

comes to rest on endothelial cells or that might, over time, be phagocytized by them. Pigment dispersion syndrome in humans is thought to be caused by the posterior bowing of the midperipheral iris, which contacts the anterior lens and liberates pigment in the process.[29] Dogs with pectinate ligament dysplasia are theorized to develop relevant pressure differential changes between the anterior and posterior chambers due to a sigmoid configuration of the iris, and this also leads to contact between the posterior iris and the anterior lens.[32] A study of dogs with goniodysgenesis-related glaucoma theorized that this iris to lens contact might lead to the loss of posterior epithelium and the presence of free melanin observed in the affected eyes, 84% of which also had melanin in the gravity-dependent part of the anterior chamber structures.[31] It is possible that a similar mechanism for melanin dispersion leads to the development of the PRP lesions described in the present study independent of other mechanisms that lead to glaucoma. This would explain, at least in part, why the PRP lesions in the present study always affected the ventral half of the eye, which is the gravity-dependent part of the eye. In addition to investigating the exact localization of the melanin in PRP lesions with respect to the inner-most corneal layers, future histologic studies could also study the potential source of the pigmentation including the evaluation of criteria for melanin dispersion, as previously done in eyes with goniodysgenesis-related glaucoma.[31]

The presence of free melanin and inflammatory changes in the iridocorneal angle was theorized to play a key role in the pathogenesis of goniodysgenesis-related glaucoma in canines.[31] The dogs with high intraocular pressure in the present study underwent gonioscopy of the normotensive eye that confirmed the presence of goniodysgenesis and the diagnosis of primary glaucoma. If melanin dispersion was confirmed to be associated with the development of PRP lesions, it could be considered a negative prognostic indicator in the presence of goniodysgenesis. Eyes with PRP that are enucleated due to glaucoma would arguably be easier to find for study than eyes with PRP lesions but without glaucoma. However, secondary changes related to elevated intraocular pressure could interfere with the study of the RPP lesions. Therefore, canine eyes with PRP lesions but without glaucoma would be better suited to study the pathogenesis of these lesions, though eyes with PRP lesions and glaucoma would also be of interest.

Another cause of the PRP lesion could be neoplasia, though in the absence of thickening of the lesions in any of the cases included in this study and in the absence of an obvious blood supply reaching the lesions, neoplasia seems unlikely.

The limitations in this study are those of a retrospective multicenter study, such as the potential of lack of detail in medical records that could be prevented with a prospective study design, and the fact that re-examination periods were performed at different times due to differences in personal preference between clinicians. Lastly, the number of animals affected was relatively low and, therefore, caution is advised when speaking of potential breed predispositions.

5 | CONCLUSIONS

Progressive retrocorneal pigmentation in dogs is a rare, slowly developing lesion that affects older animals and could impact vision and/or visualization of intraocular structures. Histologic studies of affected eyes are warranted to further the understanding of this condition and its possible implications in clinical disease.

CONFLICT OF INTEREST

The authors declare there are no potential conflicts of interest with respect to the research, authorship, and/ or publication of this article.

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