Pathologic study of early manifestations of polypoidal choroidal vasculopathy and pathogenesis of choroidal neo-vascularization

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ABSTRACT

Purpose: To describe the histopathologic features of an early case of presumably bilateral polypoidal choroidal vasculopathy (PCV) in two eyes obtained at autopsy from a patient with no prior ocular therapy.

Observations: The choroid of both eyes at the macular and peripapillary regions was greatly thickened with dilated, thin walled choroidal venules interwining with arteriosclerotic arterioles in the Sattler's layer of the choroidal vasculature. At the temporal and nasal equatorial regions of both eyes many of these congested vascular channels abruptly disappeared and were replaced by loose connective tissue with loss of the normal choroidal stromal tissue and uveal melanocytes. A few remaining venules showed intraluminal sloughing of endothelial cells and deposition of fibrinous material networks suggesting occlusion of these choroidal venules. At this equatorial location, serous detachment of retinal pigment epithelium (RPE) appeared and a thin neovascular membrane with cords of endothelial cell invaded into the sub-RPE space. Anteriorly, the neovascular membrane expanded and bulged into the sub-retinal space with dilated neovascular capillaries in a “grape like” or polypoidal configuration.

Conclusion and importance: Polypoidal Choroidal Vasculopathy is a disease of the dilated and multi-layered choroidal venules. Occlusion of these choroidal vascular channels might give rise to choroidal stasis and ischemia leading to serous RPE detachment and a sub-RPE neovascular membrane. Gross dilatation of the choroidal venules and capillaries in the sub-RPE neovascular membrane leads to the characteristic “grape like” structures, a unique clinical feature in this disease entity. These pathologic features of PCV are different from the pathologic changes of neovascular age-related macular degeneration (nAMD). Consequently, PCV and nAMD are two distinct diseases. However, in the late stage of both entities, choroidal ischemia in both diseases, lead to sub-RPE neovascularization and subsequent sub-RPE and/or sub-retinal hemorrhage. These results in both entities showed comparable clinical and pathologic features that are frequently mistaken PCV as a sub-type of Neovascular AMD.

1. Introduction

Idiopathic polypoidal choroidal vasculopathy (PCV) is a clinical term suggested by Yannuzzi et al.1 Previously, PCV was described in the literature as multiple recurrent serosanguineous retinal pigment epithelial detachments or as posterior uveal bleeding syndrome.2–7 Clinically, in the macular, peripapillary or peripheral fundus regions, nodular orange-red vascular lesions bulge from the choroid into the sub-retinal space. This is associated with serosanguineous detachment of the retinal pigment epithelium (RPE) and choroidal neovascularization (CNV). Fluorescein angiography shows patterns of classic and occult CNV. The classic features of the abnormal choroidal vasculature are best seen by indocyanine green (ICG) angiography. The polypoidal lesions appear as localized hyperfluorescent spots, associated with branching networks of dilated vascular channels. As the disease advances, sub-retinal hemorrhage and fibrosis occur. Published reports show a broad spectrum of clinical presentations for PCV,6–15 and some authors suggest the disease may be a subtype of neovascular age-related macular degeneration (nAMD). Previous histopathologic studies of this entity mostly come from examination of surgical specimens obtained from excision of choroidal neovascular tissue.13–15 Enucleated eyes have shown the late stage of the disease after multiple complications, and various forms of therapy.6,20 As a result, the early histopathologic features of this disease entity have not been clearly defined. This report describes the histopathologic features in two eyes obtained at autopsy of a patient who had no history of ocular symptoms and had not received prior medical or surgical ocular treatment. The histopathologic features of the early manifestation of this disease are distinctive, and
are different from neovascular age-related macular degeneration. We suggest that a more appropriate name for this entity may be venous stasis choroidopathy.

2. Case report

A 60 year-old African American woman had a history of systemic hypertension, hypothyroidism, morbid obesity, and sleep apnea. She had previous surgeries of cholecystectomy, uterine myomectomy, and thyroidectomy. She underwent L4-L5 laminectomy, for lumbar stenosis and spondylolisthesis. Post-operatively, the patient complained of intermittent dyspnea and was found unconscious in the bathroom. Resuscitation efforts were unsuccessful. Autopsy showed pulmonary arterial and right ventricular thrombi. The patient had no visual eye complaints or history of previous eye examination or treatment.

Gross examination of the left and right eyes showed globes of normal size with 11 and 17 mm of optic nerve attached respectively. The eyes were opened horizontally. The anterior segment, vitreous cavity, choroid, retina and macula were unremarkable in both eyes.

Histopathologic examination of the left eye showed an unremarkable anterior segment with a few Hassel- Henle’s warts in the peripheral Descemet's membrane and a wide-open chamber angle. In the macular and peripapillary regions, the posterior choroid was significantly thickened. Dilated and congested multi-layered thin-walled choroidal venules intertwined with choroidal arterioles, which exhibited a markedly thickened and hyalinized muscular layer (Figs. 1 and 2). These vascular channels were tightly packed in the choroid with little extravascular space. (Fig. 2). No transudate or proteinaceous extravascular fluid suggesting autolytic changes were seen. The choriocapillaris was engorged and drained into the dilated choroidal venules in multiple sites. This was a distinct pathologic finding (Fig. 1B). At the temporal equatorial region, most of the dilated and congested choroidal venules of the posterior choroid abruptly disappeared (Figs. 3 and 4). The remaining choroidal venules exhibited empty lumina or filled with fibrinous material with a sloughing-off of endothelial cells. The normally compact choroidal stroma with abundant uveal melanocytes in the posterior choroid was replaced by loose edematous connective tissue with marked loss of stromal uveal melanocytes. Some of the choroidal venules were surrounded by lymphocytes and mononuclear cells. At the equatorial location, the RPE was shallowly detached with serosanguineous fluid (Fig. 4). The choriocapillaries were decreased in number and widely separated by intercapillary pillars. Anterior to the equator, the sub-RPE fluid was infiltrated by a new vascular membrane consisting of endothelial cell cords, with and without lumina in a loose and serosanguineous matrix (Fig. 5). A few engorged choroidal venules which were lost at the equatorial region reappeared in this location.

**Fig. 1.** A. The posterior choroid is much thickened with a network of interlacing dilated choroidal venules and arterioles (hematoxylin and eosin stain, ×100 magnification). B. The choriocapillaris is drained by a thin-walled venule (arrow) (hematoxylin and eosin stain ×200 magnification).

**Fig. 2.** Arteriosclerotic choroidal arteries intertwine with dilated choroidal venules with no exudation in the choroidal stroma (hematoxylin and eosin stain ×200 magnification).

**Fig. 3.** At the equatorial region there is abrupt disappearance of (double arrows) the dilated choroidal venules which are seen in the posterior choroid (single arrow) (hematoxylin and eosin stain ×40 magnification).

**Fig. 4.**
Farther anteriorly, the capillaries of the sub-RPE neovascular membrane were grossly dilated, bulged into the sub-retinal space in a nodular fashion (Fig. 6), and became tortuous in an edematous fibrovascular connective tissue matrix (Fig. 7). In the choroid, grossly dilated choroidal venules reappeared and extended forward to the pars plana and pars plicata regions.

Similarly, the nasal equatorial choroid was also abruptly thinned with loss of the congestive choroidal venules from the posterior pole. There was a serous RPE detachment and a neovascular membrane spreading anteriorly to the ora serrata region. The retina and photoreceptors throughout these different regions of the eye appeared intact. The optic disc and optic nerve were unremarkable with a few scattered corpora amylaceae.

Histopathologic examination of the right eye showed similar features as observed in the left eye. The anterior segment was unremarkable. The choroid in the macular and peripapillary areas showed similar thickening with dilated thin-walled choroidal venules intertwining with arteriosclerotic arterioles.

In the temporal and nasal equatorial regions of the right eye, thinning of the choroid and disappearance of the dilated choroidal venules were also observed. The compact choroidal stroma was replaced by loose connective tissue with loss of uveal melanocytes. Similarly in this region, serosanguineous detachment of the RPE and a neovascular membrane were also observed. At the pars plana and pars plicata regions, choroidal venules were dilated. The optic nerve and retina were unremarkable with scattered corpora amylaceae.

3. Discussion

In 1990, Yannuzzi and colleagues described a syndrome consisting of polypoidal choroidal vascular lesions associated with serous and hemorrhagic detachment of retinal pigment epithelium, and named the entity idiopathic polypoidal choroidal vasculopathy (IPCV). Subsequently many clinical investigators including Yannuzzi and colleagues expanded the clinical spectrum of the disease and examined patients with scanning laser ophthalmoscopy - indocyanine green
angiography (SLO-ICGA) in association with fluorescein angiography (FA) and optical coherence tomography (OCT). Additional clinical manifestations such as choroidal network of branching vessels of varying dimension, choroidal aneurysmal enlargement, pulsation of the vascular channels and choroidal, sub-RPE and sub-retinal hemorrhages and fibrosis occurring in the late stage of the disease. Yannuzzi et al.4 further described that while the idiopathic polypoidal choroidal vasculopathy were mostly seen in the posterior pole and the peripapillary region, isolated peripheral lesions were also observed. The histopathologic feature of this disease were described in clinical pathologic correlative studies.13,15–20 Histopathologically this disease is composed of dilated secular vascular channels consisting of thin wall venules intertwined with arteriosclerotic choroidal arterioles. Other prominent histopathologic feature of the disease is a serosanguineous RPE detachment associated with extensive sub-RPE choroidal neovascularization breaking through Bruch's membrane into the sub-RPE and/or the sub-retinal space. In advanced cases subretinal hemorrhage and fibrosis involving Bruch's membrane, RPE and photoreceptor cells were observed. These pathologic features have been observed in surgically excised specimens or enucleated eyes with this disease.

The case reported here showed histopathologic features comparable to those reported in the literature. In the macular and peripapillary choroid, dilated secular vascular channels intertwined with arteriosclerotic arterioles (Figs. 1 and 2). These vascular channels aggregated in 3–4 layers in the posterior choroid and there was little extra vascular space and no exudate and transudate were observed in between the choroidal vascular channels (Fig. 2). These proliferated vascular channels were definitively much more than normal adult choroidal vasculature and were different from post mortem autolytic choroidal vascular dilation. Furthermore these dilated choroidal vascular channels abruptly disappeared at the equatorial region (Figs. 3 and 4) and replaced with scattered venules (Fig. 4) which exhibited sloughing of endothelial cells with intraluminal fibrous deposit, suggesting venous stasis. The dense choroidal stroma was replaced by edematous loose connective tissue with loss of the uveal melanocytic population. The abrupt loss of dilated choroidal vascular channels, dense choroid stroma and uveal population were distinctive and was not seen in post mortem autolytic changes of choroidal vascular tissue.

The most significant pathologic changes of these two eyes were the RPE detachment from Bruch's membrane. The resulting sub-RPE space was filled with serous serosanguineous fluid (Fig. 4). More anteriorly a neovascular membrane consisted of endothelial cell cords that crept into the sub-RPE space (Fig. 5). Still further anteriorly, the sub-RPE neovascular capillaries were grossly dilated, approaching a nodular fashion between the Bruch's membrane and the RPE (Figs. 6 and 7). Such extensive sub-RPE neovascular pathologies are not seen as post mortem changes of choroid. Even though most CNV in the polypoidal choroidal vasculopathy occurred in the posterior pole and peripapillary region, three cases of the idiopathic polypoidal vasculopathy were described in the retinal periphery by Yannuzzi et al.8 In like manner, sub-RPE neovascularization was also observed in the retinal periphery in this case.

The above histopathologic observations in both eyes of this patient, provided strong evidences to suggest that this is an early case of polypoidal choroidal vasculopathy. However since this case was presented at such an early phase of the disease without choroidal and sub-RPE hemorrhage, the patient had no ocular complaints to lead her to seek ophthalmic care and a clinical eye examination. Consequently, no clinical findings were recorded in this case. Our following hypothesis of the pathogenesis of PCV and choroidal neovascularization needs choroidal circulatory studies in future clinic-pathologic correlative cases to confirm our proposed pathogenetic mechanism of this disease.

Most previous histopathologic studies of PCV describe the primary lesion of the disease consisting of saccular dilated vascular channels in the choroid.13,15–20 The origin of these vascular channels is uncertain. Kuriwa et al21 reported that the PCV composed of large choroidal arteriosclerotic arterioles and thin-walled venules. Rosa et al.22 reported branches of the short posterior ciliary arteries supplying the PCV. However Lafault et al.23 described the thin walled vascular channels to be venular in origin. Other authors described these dilated channels without stating their nature. In our case, these dilated vascular channels were definitely venular in origin because we observed that the choriocapillaris drained into the dilated vascular channels in multiple sites.

In previous pathology reports, advanced choroidal arteriosclerosis was a prominent histopathologic feature but the relationship between the choroidal arteriosclerotic arterioles and the dilatation of the choroidal venules was uncertain. Okubo et al.16 in their study of a surgically excised lesion, described a tortuous dilated venule adjacent to an arteriosclerotic arteriole. These authors suggested that this histopathologic feature might represent an arteriovenous (AV) crossing in the choroid. In our study we observed that the arteriosclerotic arterioles intertwined with the dilated choroidal venules. The close approximation of the choroidal arterioles and venules might represent an AV crossing which might induce obstructive effect on choroidal venous circulation.

In our previous study of human choroidal vascular plastic casts,21 we observed venular dilatation at the choroidal AV crossing obstructive sites suggesting that the AV crossing does induce circulatory disturbance in a similar way that retinal arteriovenous crossing induces retinal venous obstruction. Okubo et al. reported a clinical case of venous pulsation of a vascular “polyp” at arteriovenous crossing with leakage of ICG dye.22 The pulsation and dye leakage disappeared after photodynamic therapy. The authors suggested that venous stasis and fluctuation of blood flow at the choroidal arteriovenous crossing were causing the pulsation of the venule. Their clinical finding supports our observation of venular dilatation in plastic vascular casts21 and possible circulatory disturbance in choroidal venous circulation inducing vascular polyps.

One of the unusual pathologic observations in our study of the autopsy eyes was the abrupt disappearance of the congested choroidal venules at the equatorial region in both eyes. The few remaining venules exhibited sloughing of endothelial cells associated with intra-luminal fibrinous deposit suggesting venous occlusion. The normal compact choroidal stroma was replaced by edematous loose connective tissue with loss of uveal melanocytes, suggesting choroidal venous stasis of a chronic nature. Farther anteriorly, shallow serous detachment of the RPE appeared suggesting that the extensive venous stasis of choroidal venous circulation. Anteriorly to the equator, the neovascular membrane exhibited grossly dilated capillary vascular channels. We hypothesize that at this location, the loss of the tight choroidal stroma allowed the neovascular capillaries to dilate bulging anteriorly into the sub-retinal space. These sub-RPE capillaries were dilated to the size of the venules seen of the posterior choroid (Figs. 6 and 7). The venular saccular channels of the posterior choroid and the dilated capillaries of the neovascular membrane may account for the polypoidal images seen with ICG angiography.

At the peripheral fundus region the dilated choroidal venules reappeared suggesting that the extensive venular and arteriolar anastomoses of the choroid had provided retrograde blood flow to the choroidal venular occlusive area.

Outer retinal ischemia may be induced by arterial, capillary or venous pathologies of the choroidal circulation. Choroidal arteriolar ischemia may be exemplified by malignant hypertension such as seen in toxemia of pregnancy, which causes severe choroidal arteriolar constriction leading to occlusion of choriocapillaris and necrosis of RPE known clinically as Elschnig's spots25. Choroidal capillary stasis may be
exemplified by choroidal capillary hemangioma’ which at times leads to cystoid degeneration of the outer retinal layers and serious retinal detachment. Both choroidal arteriolar ischemia as observed in malignant hypertension’ and choroidal capillary stasis as seen in choroidal hemangioma do not induce choroidal neovascular membranes in the sub-RPE and sub-renal regions as described in PCV.

The pathologic manifestations of choroidal ischemia may be compared with those of retinal ischemia. Retinal arteriolar occlusion gives rise to retinal infarct. Retinal venous occlusion, as seen at retinal AV crossing induces retinal venous stasis and retinal neovascularization similar to the choroidal neovascularization of PCV.

Based on the pathologic features described above, PCV appears to be a distinct clinical entity and not a sub-type of neovascular AMD. This suggestion is further supported by different demographic findings between PCV and AMD. PCV occurs much more frequently in non-Caucasian populations such as in Asians and African American women. The variable location of PCV in the macular, peripapillary or peripheral retinal regions contrast sharply with neovascular AMD occurring mostly in the macular area. Genetic studies also show marked differences between PCV and nAMD. While neovascular AMD appears to be much more responsive to repeated anti-VEGF intravitreal injections, Yannuzzi and Coscas et al. have also suggested that PCV and neovascular AMD are different clinical entities. However, both neovascular AMD and PCV eventually lead to sub-RPE detachment and choroidal CNV, resulting in sub-RPE and sub-retinal hemorrhage as a final common pathologic pathway between PCV and neovascular AMD.

Because of the pathologic features of our case, we hypothesize that choroidal venular stasis is one of the primary pathogenetic mechanisms. Future choroidal venous circulatory study in clinic-pathologic correlative cases may help to confirm this proposed pathogenetic mechanism.

Patient consent

We hereby acknowledge ethical and patient consent has been authorized by the spouse of the deceased in writing, thereby granting examination, removal, imaging, and retention of organs, tissues, implanted devices, and fluids as deemed necessary for diagnosis, education, and research and quality improvement.

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Conflict of interest

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Authorship

We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

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References

1. Yannuzzi LA, Sorenson J, Spaide RF, et al. Idiopathic polypoidal choroidal vasculopathy (IPCV). Ophthalmology. 1999;106:1080-1087.
2. Stern RM, Zakon ZN, Zegarra H, Gutman FA. Multiple recurrent serosanguineous retinal pigment epithelial detachments in women. Am J Ophthalmol. 1985;105:560-569.
3. Klein RC, Brucker AJ, Johnston RL. The posterior uveal bleeding syndrome. Ophthalmology. 1993;100:109-117.
4. Klein RC, Brucker AJ, Johnston RL. Posterior uveal bleeding syndrome (abstract). Ophthalmology. 1984;91(suppl 9):100.
5. Yannuzzi LT, Zakon ZN, Zegarra H, Gutman FA. Multiple recurrent serosanguineous retinal pigment epithelial detachments in women. Ophthalmology. 1999;106:1080-1087.
6. MacCumber MW, Dastghieb K, Brensler NM, et al. Clinicopathologic correlation of the multiple recurrent serosanguineous retinal pigment epithelial detachments syndrome. Ophthalmology. 1994;111:143–152.
7. Yannuzzi LA, Ciardella A, Spaide RF, Rabb M, Freund KB, Orloch DA. The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. Arch Ophthalmol. 1997;115:478–485.
8. Yannuzzi LA, Nogueira FB, Spaide RF, et al. Idiopathic polypoidal choroidal vasculopathy: a peripheral lesion. Arch Ophthalmol. 1998;116:382–383.
9. Moorby RS, Lyon AT, Rabb MD, Spaide RF, Yannuzzi LA, Jumpol LM. Idiopathic polypoidal choroidal vasculopathy of the macula. Ophthalmology. 1998;105:1380–1383.
10. Spaide RF, Yannuzzi LA, Slakter JS, Sorenson J, Orlach DA. Indocyanine green video angiography of idiopathic polypoidal choroidal vasculopathy. Ophthalmology. 1995;102:100–110.
11. Yannuzzi LA, Wong DWK, Sforzolini BS, et al. Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. Arch Ophthalmol. 1999;117:1503–1510.
12. Tan CS, Ngo WK, Lim LW, Lim TH. A novel classification of the vascular patterns of polypoidal choroidal vasculopathy and its relation to clinical outcomes. Br J Ophthalmol. 2014;98:1528–1533.
13. Honda S, Matsuyama W, Negi A. Polypoidal choroidal vasculopathy: clinical features and genetic predisposition. Ophthalmologica. 2014;321:59–74.
14. Coscas G, Lupidi M, Coscas F, et al. Toward a specific classification of polypoidal choroidal vasculopathy: idiopathic disease or subtype of age-related macular degeneration. J Ophthalmol. 2015;2015:318-3195.
15. Nakajima M, Yuzawa M, Shimada H, Mori R. Correlation between indocyanine green angiographic findings and histopathology of polypoidal choroidal vasculopathy. Jpn J Ophthalmol. 2004;48(3):249–255.
16. Okuho A, Sameshima M, Umemura A, Kanda S, Ohba N. Clinicopathological correlation of polypoidal choroidal vasculopathy revealed by ultrastructural study. Br J Ophthalmol. 2002;86(10):1093–1098.
17. Kurisu S, Tateiwa H, Hisanomi T, Ishibashi T, Yoshimura N. Pathological features of surgically excised polypoidal choroidal vasculopathy membranes. Clin Exp Ophthalmol. 2004;32(3):297–302.
18. Nakashizuka H, Mitsumata M, Okuho A, et al. Clinicopathologic findings in polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci. 2008;49(11):4720–4723.
19. Laflat RA, Asenberg S, Van Den Broecke C, Bartz-Schmidt K, Heimann K. Polypoidal choroidal vascular pattern in age-related macular degeneration: a clinicopathologic correlation. Retina. 2009;29:650–654.
20. Ross Jr RH, Davis JL, Elifig CW. Clinicopathologic reports, case reports, and small case series: clinicopathologic correlation of idiopathic polypoidal choroidal vasculopathy. Am J Ophthalmol. 2005;140:502–508.
21. Yoneya S, Tso MOM. Angiographic architecture of the human choroid. Arch Ophthalmol. 1987;105:681–687.
22. Okubo A, Sameshima M, Sakamoto T. Choroidal venous pulsations at an Arteriovenous crossing in polypoidal choroidal vasculopathy. Korean J Ophthalmol. 2013;27(5):384–387.
23. Tso MOM, Jampol LM. Hypertensive retinopathy, choroidopathy, and optic neuropathy of hypertensive ocular disease: a clinical and pathophysiologic approach to classification. In: Laragh JH, Brenner BM, eds. Hypertension: Pathophysiology, Diagnosis, and Management. New York, NY: Raven Press; 1990:433–465.; vol.1.
24. Witschel H, Font RL. Hemangioma of the choroid. A clinicopathologic study of 71 cases and a review of the literature. Surv Ophthalmol. 1976;20:415–431.
25. Uyama M, Wada M, Nagai Y, et al. Polypoidal choroidal vasculopathy natural history. Am J Ophthalmol. 2002;133(5):639–648.
26. Tan CSH, Miyake Y, Suzuki T, Nakamura M, Nagasaka T. Polypoidal choroidal vasculopathy treated with macular transplantation: clinicopathological correlation. Br J Ophthalmol. 2002;86:321–327.
27. Lim TH, Laude A, Tan CSH. Polypoidal choroidal vasculopathy an angiographic discussion. Eye. 2010;24:483–490.
28. Chen H, Liu K, Chen LJ, Hou P, Chen W, Pang CP. Genetic Associations in Polypoidal Choroidal Vasculopathy. Invest Ophthalmol Vis Sci. 2014;55:3842–3855.