Pyogenic Granuloma of the Retina: A Case Series

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Novel Insights and Established Facts

- Retinal granulation tissue proliferation (pyogenic granuloma) may occur in the setting of endophthalmitis. This differs from the established facts of retinal neovascularization in the setting of diabetic retinopathy, vein occlusion, and other diseases.

Keywords

Retinal disease · Tumors · Retina · Granulation tissue · Pyogenic granuloma

Abstract

Aim: To describe the clinicopathologic features of pyogenic granuloma (granulation tissue proliferation) extending from the retina. **Methods:** We describe 3 patients who underwent enucleation for endophthalmitis. The eyes were processed routinely for histopathologic examination. **Results:** All 3 enucleated eyes contained granulation tissue with reactive vascular channels and intervening stroma infiltrated with inflammatory cells. The vascular channels were arranged in a fan-like configuration and the tissue was classified as representing pyogenic granulomas. **Conclusions:** Pyogenic granulomas (granulation tissue) may emanate from the retina in cases of endophthalmitis. This is distinct from neovascularization that may occur in proliferative diabetic retinopathy, central retinal vein occlusion, or other etiologies.

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Introduction

Neovascularization of the retina may result from ischemic etiologies. These etiologies include proliferative diabetic retinopathy and central retinal vein occlusion, both of which are associated with other complications, including vitreous hemorrhage and traction retinal detachment [1]. Other common etiologies of retinal neovascularization include sickle cell disease and retinopathy of prematurity [2]. Proliferative diabetic retinopathy occurs secondary to microvasculature disruption from hyperglycemic changes and loss of retinal blood supply. Loss of vascular autoregulation can lead to nutrient and oxygen deprivation of the inner retina; capillary nonperfusion leads to retinal ischemia. Hypoxia and hypoxic tissues activate the hypoxia-inducible factor-1 α cascade. This factor upregulates endothelin-1 and vascular endothelial growth factor (VEGF). These proangiogenic cytokines drive pathologic intraretinal and intravitreal neovascularization. These new vessels occur at the vitreoretinal interface and penetrate the inner limiting membrane into

the vitreous. These vessels are typically fenestrated, brittle, and leaky, which can result in vitreous hemorrhage [1–4]. Retinal vein occlusion is usually a complication of systemic hypertension or hypercoagulability, as retinal blood supply is compromised from thrombosis or obstruction of a retinal vein branch from an overlapping rigid, sclerosed arteriole, leading to disorganized neovascularization. Ischemic retina releases angiogenic factors such as fibroblast growth factor-1 and VEGF, both responsible for retinal neovascularization. Growth of new vessels occurs at the interface between perfused and non-perfused retina [2, 4].

Neovascularization may also be part of granulation tissue proliferation, a repair process that may be a reaction to trauma or inflammation, and most commonly occurs in the conjunctiva when the eye is involved. This process is also known as pyogenic granuloma, a complication of irritation or breach of the ocular surface by trauma, surgery, or inflammation of the eyelids [5]. Pyogenic granulomas often occur in well-vascularized regions of epithelial or mucosal tissue; ocular pyogenic granulomas tend to present in the conjunctiva, eyelid skin, and rarely on the cornea [6, 7]. Herein, we present 3 cases of granulation tissue formation of the retina resembling pyogenic granulomas which were found in eyes enucleated for endophthalmitis.

Case Descriptions

Case 1

A 65-year-old male with a history of open globe trauma, traumatic aphakia, secondary glaucoma, and trabeculectomy on the left eye more than 30 years before was evaluated initially for acute endophthalmitis secondary to bleb infection. At initial visit his visual acuity was hand movements on the left eye and 20/20 on the right eye. Slit lamp examination for the right eye was unremarkable; on the left eye there was conjunctival injection, the filtering bleb was opaque, there was purulent discharge, and the cornea appeared hazy with Descemet's folds and hypopyon that filled >50% of the anterior chamber, thus occluding the pupil and impeding fundus examination. The patient was managed initially with intravitreal, systemic, and topical antibiotics with poor response; 21 days after the initial visit his vision had decreased to no light perception developed, corneal melting with perforation, and uncontrollable intraocular pressure. On B-scan, dense vitritis and serous retinal detachment were noted. It was decided to proceed with enucleation. Gross examination of the enucleated left eye revealed a thickened cornea with an inferior perforation, a distorted iris and ciliary body, an attached choroid, and a completely detached retina. Microscopic examination of the eye noted the perforation in the cornea with an associated infiltration of inflammatory cells including neutrophils, lymphocytes, and macrophages. Chronic inflammatory cells were present in the pupillary space and the ciliary

body was detached. A retinal detachment was present and the detached retina was surrounded by fibrovascular tissue containing vascular channels arranged in a fan-shaped configuration with an associated inflammatory infiltrate. This process extended from the retina to the vitreous and under the retina, although it did not disrupt the retinal pigment epithelium. A hemorrhage including erythrocytes and erythrocytic debris was noted in the subretinal area and vitreous. Inflammatory cells and necrosis were present in the vitreous. A glial fibrillary acidic protein (GFAP) immunostain was negative in the granulation tissue but positive in the adjacent retina. A trichrome stain demonstrated some collagen fibrils in the granulation tissue. These findings were interpreted to represent granulation tissue proliferation, or pyogenic granuloma, surrounding the retina (Fig. 1).

Case 2

A 65-year-old male presented with several months of eye pain of his right eye. Ocular history included proliferative diabetic retinopathy and macular edema treated with bevacizumab injections. He also had a remote history of endophthalmitis of the right eye. At presentation, his vision was 20/200 in the right eye; he had severe eye pain, high intraocular pressure, and vitreous opacities unresponsive to treatment with topical atropine, glaucoma drops, and prednisolone acetate. Over the course of several months, his vision had deteriorated to no light perception and he was given a diagnosis of chronic endophthalmitis and secondary glaucoma, likely as a complication of his intravitreal injections. Due to the chronic endophthalmitis and uncontrollable glaucoma, now resulting in a blind painful eye, he underwent enucleation of the right eye. Gross examination of the enucleated eye was notable for a hemorrhage in the anterior chamber and collapse of the vitreous. A funnel-shaped retinal detachment was present and there was subretinal proteinaceous material. Microscopic examination of the eye showed an intact cornea, with scarring and edema of the stroma. There was necrosis of the inner layers of the detached retina. Fibrovascular tissue with intervening stroma, consistent with granulation tissue, extended from the detached retina into the vitreous. This tissue was classified as granulation tissue (pyogenic granuloma). Inflammatory cells and necrotic material were also present in the vitreous. A GFAP immunostain was positive in the adjacent retina and negative in the pyogenic granuloma, whereas a trichrome stain demonstrated collagen in the pyogenic granuloma (Fig. 2).

Case 3

An 82-year-old female underwent enucleation of her right eye after developing endophthalmitis and a blind painful eye related to an open globe trauma with corneal perforation, traumatic aphakia, and retinal detachment. Gross examination of the enucleated eye showed a circumferential wound at the limbus from 9 o'clock to 6 o'clock, an atrophic iris with 360° of posterior synechiae, and a pupillary membrane. The vitreous cavity was filled with necrotic material that obscured the remaining structures. Microscopic examination showed disruption of all layers of the cornea and stromal edema, a full-thickness disruption at the limbus, disruption of the iris, and a ciliary body with an inflammatory infiltrate and fibrovascular proliferation in the anterior chamber. The retina was detached, disorganized, and surrounded by fibrovascular tissue composed of reactive vascular channels with an associated inflammatory cell infiltrate in the area of the optic nerve head. This tissue

Fig. 1. Case 1. **a** The retina (R) was surrounded by the pyogenic granuloma. Hematoxylin and eosin, $\times 5$. **b** The pyogenic granuloma consisted of fibrovascular tissue arranged in a fan-like configuration with associated inflammatory cells. Hematoxylin and eosin, $\times 10$. **c** A GFAP immunostain demonstrated reactive glial cells in the retina and was negative in the pyogenic granuloma (asterisk). Peroxidase anti-peroxidase, $\times 25$. **d** A trichrome stain showed some collagen (blue) in the pyogenic granuloma. Masson trichrome, $\times 25$.

was considered to be granulation tissue proliferation (pyogenic granuloma). The vitreous was filled with neutrophils and necrotic material. The choroid contained a chronic inflammatory cell infiltrate, and there was a mild thickening of the sclera. A GFAP immunostain was positive in the adjacent retina and negative in the pyogenic granuloma, whereas a trichrome stain demonstrated abundant collagen in the pyogenic granuloma (Fig. 3).

Discussion

Pyogenic granuloma, also termed lobular capillary hemangioma, is a benign vascular tumor formed by an exaggerated granulation tissue reaction, typically characterized by disorganized capillary growth associated with infiltration of inflammatory cells and increased stromal deposition [7, 8]. This is in contrast with neovascularization, which is composed of a vascular proliferation with

minimal if any stroma and minimal if any inflammation. The complete mechanism of pyogenic granuloma formation is not entirely known, although investigators have identified VEGF as a key factor in the development of this lesion. Cytokines from injured tissue act to recruit inflammatory cells, which produce VEGF and induce release of VEGF from other cells, causing disordered neovascularization [9]. Bragado et al. [9] studied correlating VEGF levels with the progression of pyogenic granuloma and showed that VEGF concentrations are highest during the early development of young pyogenic granuloma with poorly developed vessels, with reduction in local VEGF concentrations as endothelial cells organize into mature vasculature and stroma with identifiable lumen. This proposed pathogenesis combined helps to explain the characteristic histopathology of pyogenic granuloma: abnormal release of VEGF by infiltrating inflammatory cells,

Fig. 2. Case 2. **a** Gross appearance of the enucleated eye with funnel-shaped retinal detachment. White tissue (asterisk) corresponding to the pyogenic granuloma was present. **b** The pyogenic granuloma was present between the detached retina (R) and the necrotic material (N). Hematoxylin and eosin, $\times 10$. **c** A GFAP immunostain was positive in reactive glial cells in the retina and negative in the pyogenic granuloma (asterisk). Peroxidase anti-peroxidase, $\times 25$. **d** There was abundant collagen (blue) in the pyogenic granuloma. Masson trichrome, $\times 100$.

then vessel formation in injured tissue, classically in a fan shape, with increased interspersing stroma and fibrous tissue as the vessels develop. VEGF has also been linked to the pathogenesis of retinal neovascularization from diabetic retinopathy and central retinal vein occlusion. The identification of hypoxia-inducible factor-1 as a key transcription factor that mediates increased expression of hypoxia-regulated genes has helped to fill in more detail regarding the pathogenesis of retinal neovascularization; hypoxia-inducible factor-1 α levels are increased and show temporal and spatial correlation with excess VEGF in patients with diabetic retinopathy and in mouse models of ischemic retinopathy [2, 4, 10]. The difference is that in retinal neovascularization, diffusible VEGF forms in the ischemic retina, whereas in pyogenic granuloma, the VEGF is largely produced by an inflammatory cell in-

filtrate and is accompanied by cytokines that induce fibrocyte infiltration. Thus, pyogenic granuloma, or granulation tissue, is a more robust tissue than retinal neovascularization from ischemia.

All our patients showed histopathologic signs of pyogenic granuloma emanating from retinal tissue. This retinal lesion was distinguished from retinal neovascularization in that pyogenic granuloma included a characteristic fan shape of the proliferating vessels and an intervening fibroinflammatory stroma. We performed immunohistochemical GFAP stains in all 3 cases, which was negative in the pyogenic granulomas. A trichrome stain was performed and demonstrated varying amounts of collagen in the pyogenic granulomas. These lesions likely become more collagenized as they age. Proliferative diabetic retinopathy arises from precursor lesions, such as microan-

Fig. 3. Case 3. **a** The pyogenic granuloma containing reactive vascular channels (arrows) was adjacent to the retina (R). Hematoxylin and eosin, $\times 25$. **b** A GFAP immunostain was positive in reactive glial cells in the retina and negative in the pyogenic granuloma (asterisk). Peroxidase anti-peroxidase, $\times 25$. **c** The pyogenic granuloma was composed of reactive vascular channels in a fibrocollagenous matrix with associated inflammatory cells. A portion of the adjacent retina (R) was present. Hematoxylin and eosin, $\times 100$. **d** There were collagen fibrils (blue) present in the pyogenic granuloma. Masson trichrome, $\times 100$.

eurysms and intraretinal microvascular abnormalities. These lesions are associated with pericyte apoptosis in retinal vessels, with eventual disorganized neovascular bundles arising from existing vasculature in hypoxic areas of tissue along the blood vessels [11]. Branch retinal vein occlusion is associated with small collections of retinal neovascularization overlying visibly occluded veins [12]. In contrast, pyogenic granulomas form as an acute response to injury that will remain static as inflammation resolves, whereas diabetic retinopathy and retinopathy associated with branch retinal vein occlusion are chronic processes, with long-term increases in VEGF contributing to their progressive nature [10, 13].

To our knowledge there is only one report from Marback et al. [14] of an intraocular pyogenic granuloma arising from the optic nerve. That case was clinically con-

fused with melanoma, thus emphasizing that pyogenic granuloma is composed of more substantial/robust tissue than neovascularization. There are a few cases reported of a pyogenic granuloma arising from neural tissue, all of which developed from the spinal cord or the cauda equina [15, 16]. In most instances, pyogenic granulomas arise from oral cavity, sinus, conjunctiva, skin, endothelium of vascular tissue, or vascular malformations [17, 18]. Corneal tissue is an uncommon site of ocular involvement secondary to trauma or infectious keratitis, although a case with a prior history of trauma or infection has been reported [19].

We hypothesize that our patients developed retinal pyogenic granuloma in response to tissue injury and inflammation from endophthalmitis. In all 3 cases there was no clinical or imaging evidence of a frank retinal

mass, but a history of vitreous opacities and/or retinal detachment was documented. All 3 cases had a history of a subacute or chronic intraocular infection, and we surmise that the pyogenic granulomas developed over a period of weeks. We conclude that although rare, it is possible for pyogenic granuloma to arise from the retina, especially in cases of chronic endophthalmitis.

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References

- 1 Cho H, Alwassia AA, Regatieri CV, Zhang JY, Bauman C, Waheed N, et al. Retinal neovascularization secondary to proliferative diabetic retinopathy characterized by spectral domain optical coherence tomography. *Retina*. 2013 Mar;33(3):542–7.
- 2 Campochiaro PA. Ocular neovascularization. *J Mol Med (Berl)*. 2013 Mar;91(3):311–21.
- 3 Lechner J, O'Leary OE, Stitt AW. The pathology associated with diabetic retinopathy. *Vision Res*. 2017 Oct;139:7–14.
- 4 Jaulim A, Ahmed B, Khanam T, Chatziralli IP. Branch retinal vein occlusion: epidemiology, pathogenesis, risk factors, clinical features, diagnosis, and complications. An update of the literature. *Retina*. 2013 May;33(5):901–10.
- 5 Ferry AP. Pyogenic granulomas of the eye and ocular adnexa: a study of 100 cases. *Trans Am Ophthalmol Soc*. 1989;87:327–43; discussion 343–347.
- 6 Cameron JA, Mahmood MA. Pyogenic granulomas of the cornea. *Ophthalmology*. 1995 Nov;102(11):1681–7.
- 7 Wollina U, Langner D, França K, Gianfaldoni S, Lotti T, Tchernev G. Pyogenic Granuloma – A Common Benign Vascular Tumor with Variable Clinical Presentation: New Findings and Treatment Options. *Open Access Maced J Med Sci*. 2017 Jul;5(4):423–6.
- 8 Dahiya R, Kathuria A. Extralingival pyogenic granuloma histologically mimicking capillary hemangioma. *J Indian Soc Periodontol*. 2014 Sep;18(5):641–3.
- 9 Bragado R, Bello E, Requena L, Renedo G, Texeiro E, Alvarez MV, et al. Increased expression of vascular endothelial growth factor in pyogenic granulomas. *Acta Derm Venereol*. 1999 Nov;79(6):422–5.
- 10 Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012 Feb;44(1):1–17.
- 11 Frank RN. Diabetic retinopathy. *N Engl J Med*. 2004 Jan;350(1):48–58.
- 12 Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Trans Am Ophthalmol Soc*. 1981;79:371–422.
- 13 Vara JT, Gurudu VS, Ananthaneni A, Bagalad BS, Kuberappa PH, Ponnappalli HP. Correlation of vascular and inflammatory index in oral pyogenic granuloma and periapical granuloma – an insight into pathogenesis. *J Clin Diagn Res*. 2017 May;11(5):ZC25–8.
- 14 Marback EF, Espinheira Fonseca L Jr, Marback RL. Optic disc pyogenic granuloma. *Ocul Oncol Pathol*. 2017 Jul;3(2):110–2.
- 15 Andaluz N, Balko MG, Stanek J, Morgan C, Schwetschenau PR. Lobular capillary hemangioma of the spinal cord: case report and review of the literature. *J Neurooncol*. 2002 Feb;56(3):261–4.
- 16 Holtzman RN, Brisson PM, Pearl RE, Gruber ML. Lobular capillary hemangioma of the cauda equina. Case report. *J Neurosurg*. 1999 Apr;90(2 Suppl):239–41.
- 17 Risio D, Selvaggi F, Viola P, Lattanzio G, Legnini M, D'Aulerio A, et al. Intravenous pyogenic granuloma of the right adrenal gland: report of a case. *Surg Today*. 2013 May;43(5):569–73.
- 18 Hung CH, Kuo HW, Chiu YK, Huang PH. Intravascular pyogenic granuloma arising in an acquired arteriovenous malformation: report of a case and review of the literature. *Dermatol Surg*. 2004 Jul;30(7):1050–3.
- 19 Abateneh A, Bekele S. Corneal pyogenic granuloma: rare complication of infectious keratitis. *Ethiop J Health Sci*. 2014 Jan;24(1):85–8.

Statement of Ethics

This study received IRB exemption from Emory University based on the number of cases reported (<6 cases).

Disclosure Statement

The authors have no conflicts of interest of any kind in this article.