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Case Report

Two Cases of Proliferative Diabetic Retinopathy with Marked Sheathing of the Retinal Arteries following Vitrectomy

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Keywords
Calcification · Diabetic retinopathy · Retinal detachment · Retinal arterioles · Sheathing · Vitrectomy

Abstract
Purpose: The aim of this paper was to report 2 patients (3 eyes) with proliferative diabetic retinopathy (PDR) who showed marked sheathing of the retinal arterioles that was ultimately attributed to calcification following vitrectomy. ***Cases:*** Case 1 involved a 65-year-old female with PDR who underwent bilateral vitrectomy for traction retinal detachment. Postoperatively, bilateral retinal redetachment (reRD) was observed. Sheathing of the retinal arterioles was observed at the same time, yet was not apparent preoperatively. Case 2 involved a 71-year-old female with PDR who underwent vitrectomy for vitreous hemorrhage. Postoperatively, reRD was observed, and fundus findings showed sheathing of the retinal arterioles. In both patients, silicone oil tamponade and retinopexy were performed at reoperation, but sheathing of the retinal arterioles persisted postoperatively. Fluorescein fundus angiography showed that retinal blood flow was maintained, and no vessel leakage occurred. In addition, no sheathing of the retinal veins was observed. Optical coherence tomography (OCT) showed a higher intensity for retinal arterioles with sheathing than for normal retinal arterioles. ***Con-***

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clusion: Vessel sheathing in our 2 patients (3 eyes) differed from the sheathing seen in vasculitis. Based on the hyperintensity on OCT, this sheathing may have been due to retinal artery calcification induced by hypoxia and inflammation associated with reRD.

Introduction

Diabetic vascular disease is characterized by vascular calcification, and coronary artery calcification, in particular, is considered important in terms of the effects on long-term survival. Vascular calcification has traditionally been regarded as a process involving degeneration and necrosis of arterial walls, but new studies have suggested that vascular wall cells (mainly vascular smooth muscle cells [VSMCs]) undergo transformation due to hypoxia and inflammation that ultimately leads to calcification [1]. Reportedly, cartilage-like tissue has been found in vascular calcified lesions, suggesting that the process of vascular calcification may be quite similar to osteogenesis [2]. Various studies have reported an association between vascular calcification with changes in oxidative stress, inflammation, and hypoxia [3, 4]. In the field of ophthalmology, retinal artery calcification in a patient with chronic renal disease has been reported [5]. However, to the best of our knowledge, retinal artery calcification in diabetic patients has not been described.

Here, we report 2 patients with proliferative diabetic retinopathy (PDR) who showed marked sheathing, thought to be caused by retinal artery calcification, after retinal redetachment (reRD) following vitrectomy.

Cases Reports

Case 1

Case 1 involved a 65-year-old female with highly active, untreated PDR in both eyes. She had a history of diabetes (hemoglobin [HbA1c, 5.9%]), hypertension, and cerebral infarction, yet no history of hyperlipidemia. Upon initial examination, visual acuity was 20/100 (uncorrectable) in her right eye and 20/70 (uncorrectable) in her left eye, and intraocular pressure was 15 mm Hg in her right eye and 13 mm Hg in her left eye. Examination of the anterior eye segment and the optic media showed no abnormalities. Funduscopy showed neovascularization of the optic disc in both eyes and preretinal hemorrhages around the optic disc in her right eye. In her left eye, fibrovascular membranes of the optic disc extended inferiorly, and partial traction retinal detachment (TRD) was evident (Fig. 1a). No retinal artery sheathing was observed at this time.

Vitrectomy and cataract extraction was later performed for her left eye, and the fundus visualization was improved and the retina was reattached. However, after 1 month following the initial surgery, reRD due to reproliferation occurred from the posterior pole toward the midperiphery of 4 quadrants. At the time of this reRD, some well-demarcated sheathing of the retinal arterioles was intermittently observed, primarily at the posterior pole (Fig. 1b), yet no retinal vein abnormalities were seen. Silicone oil tamponade was performed at reoperation, but the sheathing persisted for more than 1 year after surgery (Fig. 1c).

Fluorescein fundus angiography (FA) before the reoperation showed that blood flow was maintained at the sites of sheathing, with no dye leakage (Fig. 2a, b). Optical coherence tomography (OCT) after the reoperation showed high reflectance and remarkable acoustic

shadows of the vessel walls corresponding to the areas of sheathing (Fig. 2c). Approximately 1 year later, TRD of the patient's right eye had also progressed, so vitrectomy was performed. However, after 2 months following the initial surgery, reRD due to reproliferation occurred from the posterior pole toward the midperiphery of 4 quadrants. Findings similar to those of her left eye were observed postoperatively.

Case 2

Case 2 involved a 71-year-old female with highly active, bilateral PDR who developed a vitreous hemorrhage in her right eye. She had a history of poorly controlled diabetes (HbA1c, 10.1%) and hypertension, yet no hyperlipidemia. Upon initial examination, visual acuity was reduced to light perception (uncorrectable) in her right eye and 20/70 (uncorrectable) in her left eye, while intraocular pressure was 16 mm Hg in her right eye and 11 mm Hg in her left eye. Examination of the anterior eye segment showed no abnormalities, and examination of the optic media showed bilateral cataracts. The fundus of her right eye could not be visualized because of the vitreous hemorrhage, but B-mode ultrasonography showed no clear evidence of RD. Her left eye showed some mild preretinal hemorrhages.

Vitrectomy and cataract surgery were performed in her right eye. After removal of the vitreous hemorrhage, fibrovascular membranes were seen extending from the optic disc to the vascular arcade, and localized tractional RD around the upper vascular arcade was detected. Following surgery, the fundus could clearly be observed (Fig. 3a). However, proliferation of the retinal surface was again seen 2 months later, the same as in Case 1, and RD occurred. The extent of reRD was from the posterior pole toward the midperiphery of 4 quadrants.

Fundus findings at this time showed marked sheathing of the retinal arterioles, which had not been observed after the initial surgery (Fig. 3b). Silicone oil tamponade and retinopexy were performed at reoperation, but sheathing persisted, the same as in Case 1 (Fig. 3c, d). The FA and OCT findings were similar to those in Case 1 (Fig. 4a–c).

The concentration of serum calcium was 9.5 mg/dL in Case 1 and 9.2 mg/dL in Case 2. Hypercalcemia was not detected by the blood test in both cases.

Discussion

The pathogenesis of the sheathing of retinal arterioles may involve retinal arteritis, arterial occlusion, and lipemia retinalis. However, our 2 patients (3 eyes) had no underlying diseases, and the FA findings revealed no leakage from blood vessels, thus ruling out vasculitis. Retinal artery occlusion was also ruled out because FA showed that blood flow was maintained. Lipemia retinalis was not likely because of normal lipid levels.

A common feature in our patients was highly active PDR in which marked retinal artery sheathing had not been seen previously but was observed after RD. Blood flow was maintained in both patients, and OCT showed high reflectance and strong acoustic shadows of the vessel walls. Moreover, the lumens of the blood vessel were consistently hypointense. These findings suggest that the sheathing was due to vascular calcification.

Vascular calcification is thought to be preceded by degeneration and apoptosis of VSMCs due to oxidative stress. The matrix formed with the destruction of SMCs may act as a scaffold, and differentiation of vascular wall cells to osteochondrogenic cells is involved. Inflammation, hypoxia, receptors of advanced glycosylation end-products (RAGE), and hyperglycemia can cause transformation of VSMCs to osteoblast-like cells, ultimately leading to ossi-

fication [6]. Mesenchymal stem cells that can differentiate into osteocytes, chondrocytes, and adipocytes also exist in the perivasculature, and differentiation to osteocytes is more likely to occur under a hypoxic state. Vascular wall cells also display mesenchymal stem cell characteristics and may be able to differentiate into osteoblasts. In our patients, blood vessels with sheathing were seen in areas of retinal arterioles where VSMCs and vascular wall cells were present, and retinal artery calcification probably occurred following hypoxia and inflammation due to RD.

Medial arterial calcification is reportedly often seen in diabetes and chronic kidney disease. This medial arterial calcification is not due to passive calcium deposition, but is instead an active process associated with osteogenic transformation of VSMCs.

RAGE expression, which promotes ossification, is upregulated in the SMCs of retinal arterioles in PDR. Increases in the RAGE ligands of advanced glycosylation end-products (AGE), HMGB1, and S100 protein have also been reported in PDR [7]. Hyperglycemia also promotes ossification of VSMCs, thus leading to calcification [6].

BMP-2, an osteogenic cytokine, is increased in the eye [8], and retinal artery SMCs are in an environment where osteogenic transformation can easily occur in diabetic retinopathy. If TRD develops, HMGB1 and S100 protein are released, and RAGE effects are expected to be enhanced. Thus, when mechanical stretching of retinal arterioles occurs due to proliferative membranes, osteogenesis of SMCs is increased via the action of BMP-2, which then leads to retinal artery calcification [9].

Histopathological analysis is necessary to confirm that the vessel sheathing in our patients was due to vessel calcification, but this is difficult. However, OCT is thought to be useful for examining retinal pathology. OCT of calcified coronary arterioles shows well-defined areas of high intensity and heterogeneous low intensity within vessels [10]. In the retinal arterioles with sheathing in our patients, OCT also showed high intensity, with somewhat lower intensity within the vessels. This was probably due to calcification, similar to that in coronary arterioles.

In conclusion, we encountered 2 patients with PDR who displayed extensive retinal artery sheathing after reRD following vitrectomy. Similar findings may also be seen in patients with DR who are on blood dialysis. Further investigation using OCT and FA is necessary in the future for an improved understanding.

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Statement of Ethics

This case study has been approved by the Ethics Committee of the Osaka Medical College.

Disclosure Statement

There are no conflicts of interest to report for all authors.

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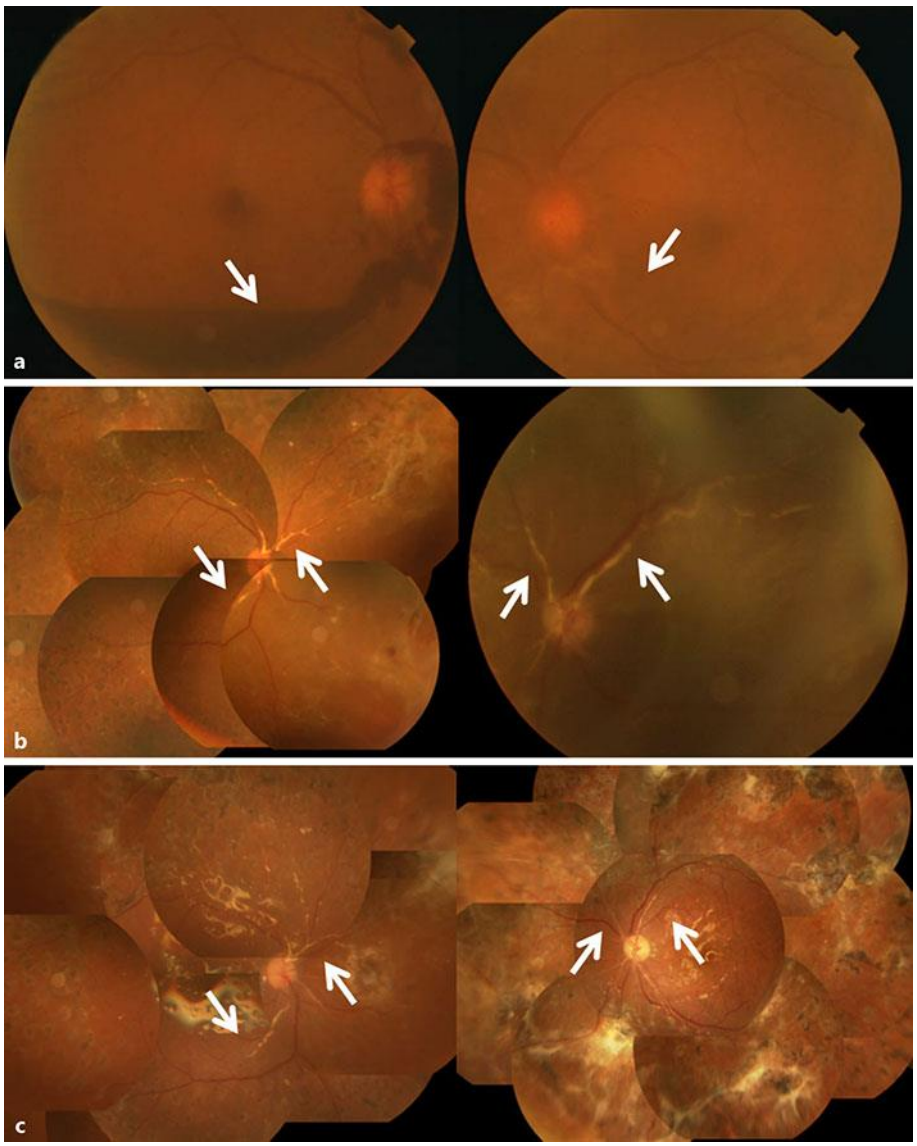

Fig. 1. Fundus photography images in Case 1. **a** Image obtained at initial evaluation. Preretinal hemorrhages can be seen around the optic disc in the patient's right eye (arrow). In the left eye, fibrovascular membranes and a traction retinal detachment around the optic disc (arrow) are seen. **b** Image obtained at the time of retinal detachment after the initial surgery. Intermittent, well-defined sheathing of the retinal arterioles (arrow) is apparent in both eyes. The retinal veins appear normal. **c** Image of silicone oil after reoperation. Persistent sheathing of the retinal arterioles (arrow) is apparent more than 6 months after surgery.

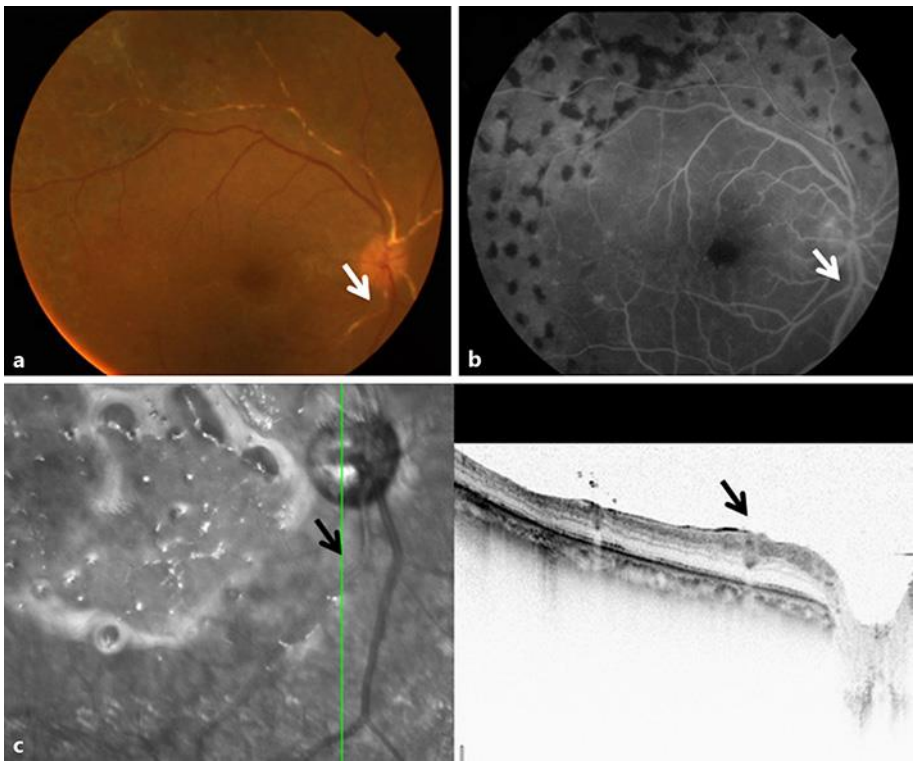

Fig. 2. Fundus angiography (FA) and optical coherence tomography (OCT) images of the right eye in Case 1. **a**, **b** FA of the right eye. Blood flow is maintained at areas of retinal artery sheathing (white arrows). **c** OCT image of the same area. High reflectance and acoustic shadows of the vessel walls (black arrows) are evident.

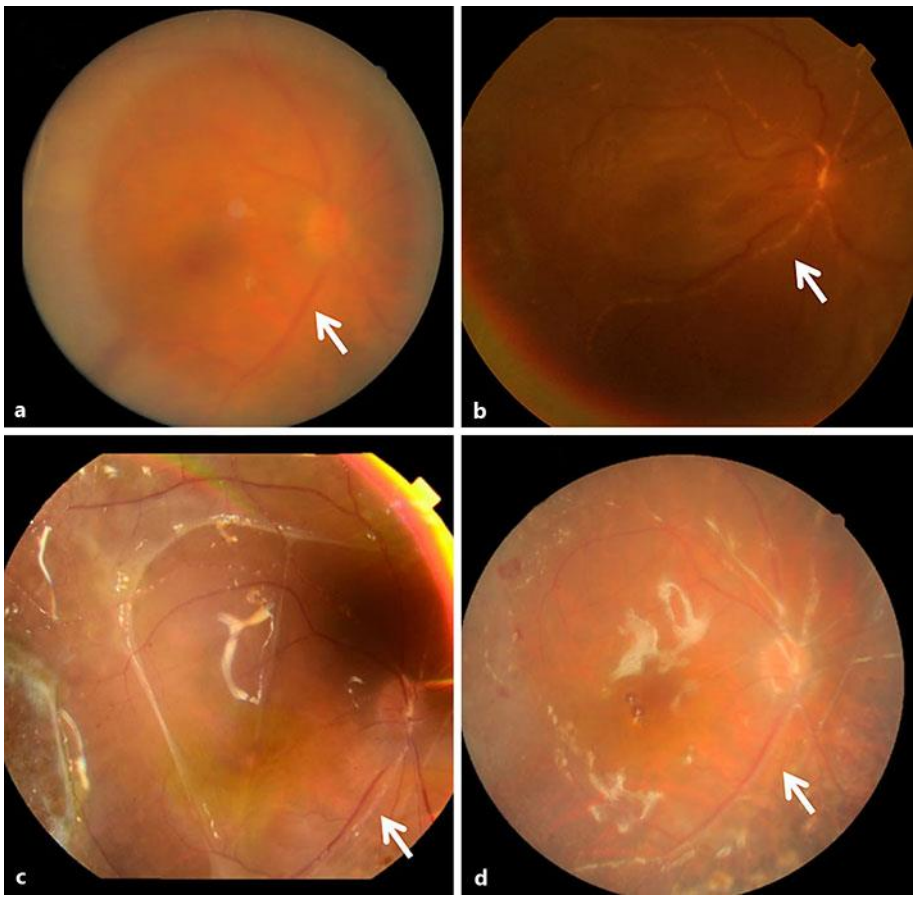

Fig. 3. Fundus photography images in Case 2. At initial evaluation, the fundus could not be visualized because of the vitreous hemorrhage. **a** Image obtained after the initial surgery. No retinal artery sheathing (arrow) is seen immediately after surgery. **b** At the time of retinal detachment, marked sheathing of the retinal arterioles (arrow) is apparent. **c** Image obtained at the time of retinal redetachment shows persistent sheathing (arrow). **d** No changes in findings are seen (arrow).

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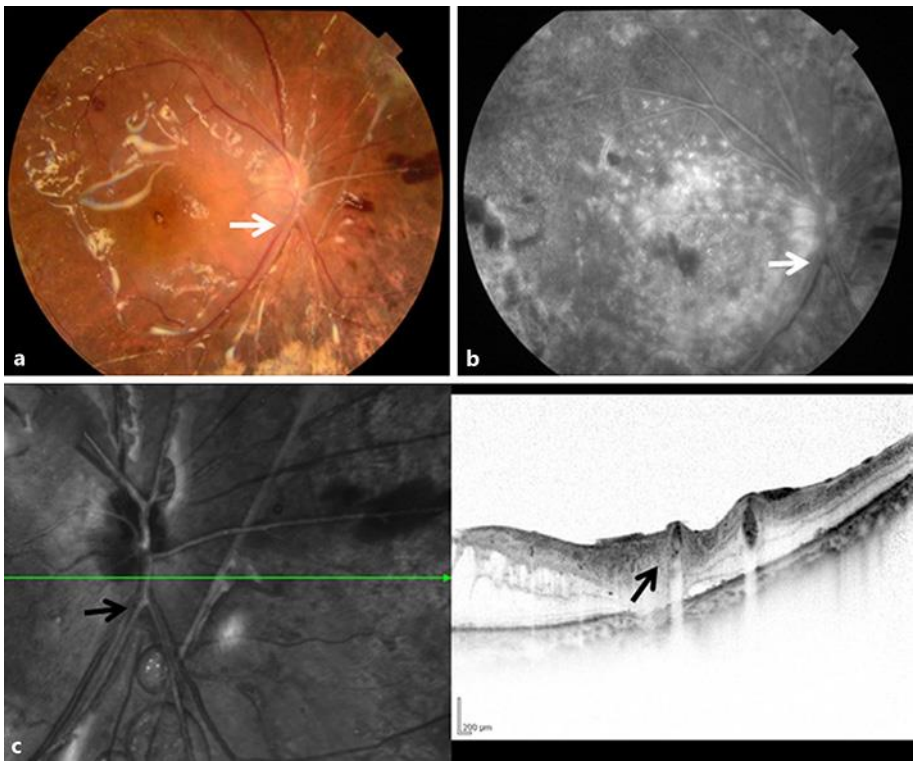

Fig. 4. Fundus angiography and optical coherence tomography images of the right eye in Case 2. **a**, **b** Blood flow is maintained at the areas of retinal artery sheathing (white arrows), the same as in Case 1. **c** High reflectance and acoustic shadows of the vessel walls (black arrows) are apparent.