ELSEVIER

Gray-White, Spherical Deposition on Retinal Vessel Associated With Acute Retinal Necrosis and Diabetic Retinopathy in HTLV-I Carriers

Kumiko Nakao, Norio Ohba, Akinori Uemura,
Akiko Okubo, Munefumi Sameshima and Kayoko Hayami

Department of Ophthalmology,
Kagoshima University Faculty of Medicine, Kagoshima 890-8520, Japan

Abstract: Tiny, gray-white, spherical deposits were found on the retinal vessels and vitreoretinal interface of the fovea in a 55-year-old woman with acute retinal necrosis due to varicella-zoster virus, and in a 47-year-old man with preproliferative diabetic retinopathy. Both patients developed massive vitreous opacities due to uveal inflammation or hemorrhages that rendered the fundus difficult to visualize. A therapeutic vitrectomy revealed gray-white, tiny spherical deposits, about blood-vessel–diameter, which were scattered on seemingly intact retinal arteries and veins in the posterior fundus and over the vitreoretinal interface overlying the fovea. The deposits were loosely adherent to vessel walls and were easily aspirated, and the residual materials resolved in the early postoperative days. These characteristic retinal vascular deposits resembled those seen in patients with HTLV-I associated uveitis. The two patients reported herein were otherwise asymptomatic carriers of HTLV-I. The findings provide additional information about the etiological role of HTLV-I in the development of characteristic retinal vascular deposition, although its pathogenesis remains to be elucidated.
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Key Words: Acute retinal necrosis, diabetic retinopathy, HTLV-I, spherical vascular deposit.

Introduction

HTLV-I is a retrovirus that is involved in the etiology of a variety of diseases, including hematologic malignancy and neurological diseases. Ophthalmologically, this retrovirus has been suggested to be the underlying cause of a certain type of uveitis called HTLV-I-associated uveitis (HAU).[1–3] Previously, we reported retinal vascular deposits in 8 of 55 patients with HAU.[4] The deposits were tiny, gray-white, spherical materials that were scattered on the retinal arteries and veins in the posterior pole with no sign of vasculitis or perivasculitis. These deposits resolved spontaneously in a few weeks or in response to corticosteroids, accompanied by the regression of the anterior uveal inflammation. We report two cases of HTLV-I carriers who developed similar retinal vascular changes, associated not with HAU but with acute retinal necrosis or with preproliferative diabetic retinopathy.

Case Reports

Case 1

A 55-year-old woman, a resident of southwestern Japan, noted acute redness and visual loss in the left eye. She had otherwise been healthy, although a carrier of HTLV-I with seropositivity for its antibodies. On presentation, the best visual acuity was RE 1.5 and LE 0.6. The right eye was unremarkable with normal fundus appearance. The left eye had mutton-fat keratic precipitates, flare and cells in the anterior chamber, and mild vitreous opacities. Ophthalmoscopy revealed multifocal, yellow-white exudative patches and attenuated retinal vessels in the peripheral fundus. The posterior fundus appeared virtually intact, with normal-appearing retinal vessels (Figure

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Address correspondence and reprint requests to: Kumiko NAKAO, MD, Department of Ophthalmology, Kagoshima University Faculty of Medicine, Sakuragaoka 8-35-1 Kagoshima 890-8520, Japan

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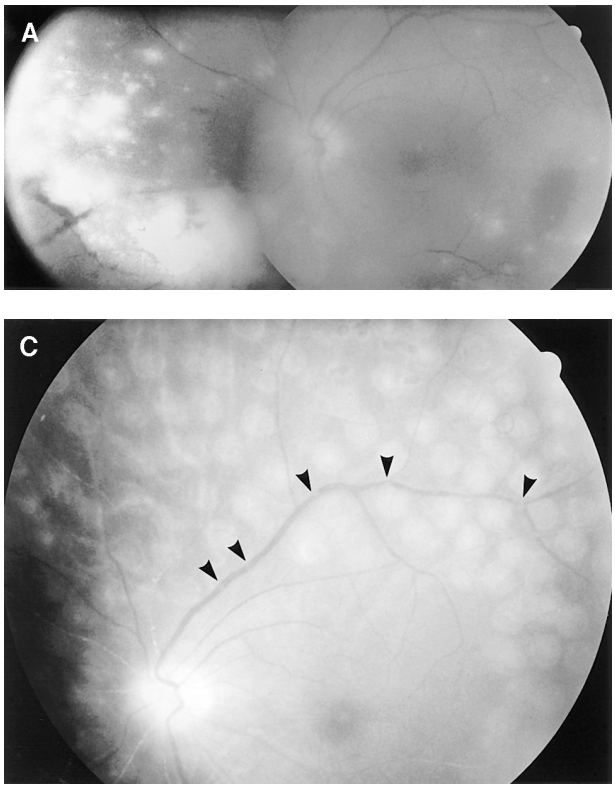

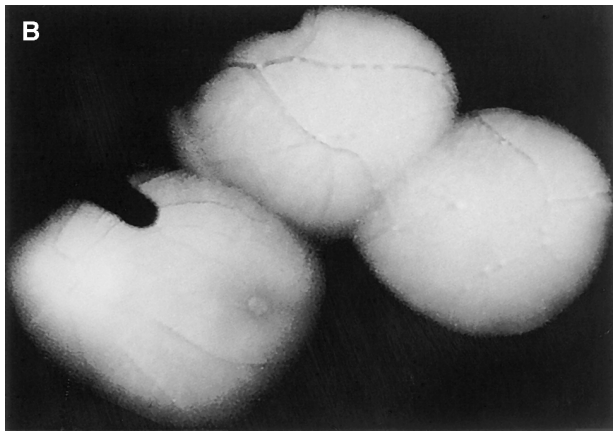

Figure 1. Case 1 (acute retinal necrosis). (**A**) Initial presentation, multifocal, yellow-white exudative patches and attenuated retinal vessels are seen in peripheral fundus. Posterior fundus appears virtually intact with normal-appearing retinal vessels. (**B**) Intraoperative posterior fundus photograph. Gray-white, fluffy material is present only on the vitreoretinal interface over fovea. Numerous gray-white, fluffy deposits are seen on apparently intact retinal vessels. (**C**) On third postoperative day, remaining deposits (arrowheads) have diminished.

1A). Diagnostic paracentesis disclosed the presence of the DNA of varicella-zoster virus (VZV) by using polymerase chain reaction, which led to a diagnosis of VZV-induced acute retinal necrosis. Two-week administration of intravenous acyclovir, interferon-β and oral corticosteroids were not effective, and the vitreous opacification became increasingly dense, rendering the fundus invisible and decreasing the visual acuity to hand motion.

A therapeutic vitrectomy was then performed by a standardized procedure. Intraoperatively, the posterior vitreous membrane was detached completely. Aspiration of membranous and granular vitreous opacities revealed the fundus and showed yellow-white necrotic patches in the peripheral fundus, which were to resolve toward retinal atrophy. Noticeably, numerous, tiny, gray-white, spherical materials approximately the size of the blood vessels were found deposited on the retinal vessels in an otherwise unremarable posterior fundus (Figure 1B). The deposits appeared loosely adherent to the retinal arteries and veins and also to the vitreoretinal interface over the fovea. They could be easily detached and aspirated by means of a fluted needle without any damage to the involved vessels. The postoperative course was uneventful and the corrected visual acuity recovered to 0.4. Residual deposits on the retinal vessels resolved spontaneously within a week (Figure 1C), although the peripheral fundus remained atrophic with obliterated retinal arteries and small retinal breaks. There was no remarkable change during a follow-up examination 1 1/2 years later, with no recurrence of the characteristic retinal vessel depositions.

Vitreous specimens obtained during the vitrectomy were examined for VZV and HTLV-I. Polymerase chain reaction of vitreous fluids demonstrated the presence of VZV DNA and HTLV-I proviral DNA. The immunoglobulin G antibody (EIA) for VZV was 128.0 in the vitreous fluids and 101.0 in the serum, and the antibody coefficient comparing vitreous and serum titers was calculated to be 4.1. These findings suggest intraocular production of the antibody to VZV. The antibody titer (PA) of HTLV-I was 512 in vitreous and 2048 in serum. The antibody coefficient was calculated to be 0.8, thus giving no evidence of local synthesis of HTLV-I antibody.

Case 2

A 47-year-old man, who had suffered since the age of 25 from insulin-dependent diabetes mellitus with continuous blood glucose control by insulin, noted floaters and visual loss acutely in the left eye.

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On presentation, he appeared in good health, and had antibodies to HTLV-I in his serum. Best visual acuity was RE 0.2 with a −10 diopter sphere and LE hand motion. The right eye showed neovascularization in the iris and anterior chamber angle, and the preproliferative stage of diabetic retinopathy with scattered retinal hemorrhages and widespread narrowing or obliteration of the small retinal vessels, which was treated with panphotocoagulation. The cornea, iris, anterior chamber, and lens of the left eye were unremarkable. There were massive hemorrhages in the vitreous cavity, which rendered the fundus invisible. Ultrasonography revealed hemorrhagic vitreous opacities and adhesion of the detached posterior vitreous membrane but no gross retinal changes. Because the vitreous hemorrhages did not resolve during the subsequent month, a therapeutic vitrectomy was performed. Aspiration of the hemorrhages and dissection of the posterior vitreous cortex adherent to a retinal vessel enabled us to evaluate the fundus. The midperiphery to the equator showed narrowing or obliteration of the retinal vessels with widespread avascular zones. The posterior fundus and optic disc were unremarkable, with no proliferated fibrovascular membrane or tractional retinal detachment, except for numerous, gray-white, small (one-to-two-vessel–diameter), spherical, fluffy materials on the apparently intact retinal arteries and veins in the posterior fundus (Figure 2). The spherical materials appeared loosely adherent to the wall of vessels, but could be readily detached and aspirated through a fluted needle without affecting the involved vessels. Intraocular retinal photocoagulation was given at the end of surgery. The postoperative course was uncomplicated, and spontaneous resolution of the residual retinal vascular deposits occurred in a few postoperative days, with return of corrected visual acuity to 0.07. A follow-up at 9 months was unremarkable, with no recurrence of the characteristic deposits on retinal vessels.

To define the features of the deposits on the retinal vessels, specimens obtained during the vitrectomy were examined by electron microscopy. As illustrated in Figure 3, the specimen contained biological structures rather than extraocular or artificial substances, and suggested debris of disrupted cellular components. The structure resembled thickened basement membrane, but it was difficult to further define the cellular features because of the limited number of specimens. Polymerase chain reaction of the vitreous specimens obtained during the vitrectomy demonstrated the presence of HTLV-I proviral DNA.

Discussion

These patients with acute retinal necrosis (ARN) and preproliferative diabetic retinopathy presented with tiny, gray-white, spherical deposits on otherwise grossly intact retinal vessels. The characteristics of these vascular lesions conform, in all likelihood, to our previous observations[4] of 8 patients with HAU. These HAU patients developed acute or subacute anterior uveitis accompanied by retinal vascular disorder, characterized by gray-white, granular deposits scattered on the retinal vessels and on the foveolar vitreoretinal interface in an otherwise unremarkable retina. These deposits were self-limited and resolved in a few weeks or were corticosteroid-responsive along with the regression of uveal inflammation.

It is of interest that the characteristic deposits over the retinal vessels were observed in patients with dis-

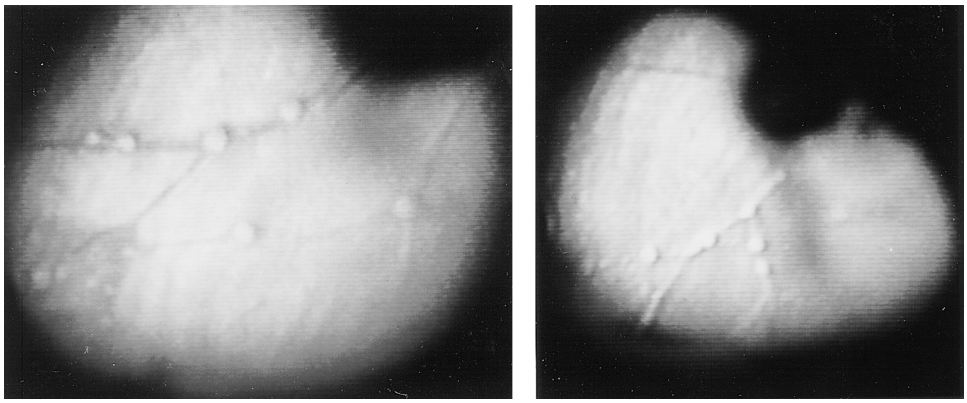

Figure 2. Case 2 (diabetic retinopathy). Intraoperative fundus photograph illustrating numerous, gray-white, fluffy, spherical materials attached to retinal arteries and veins in posterior pole.

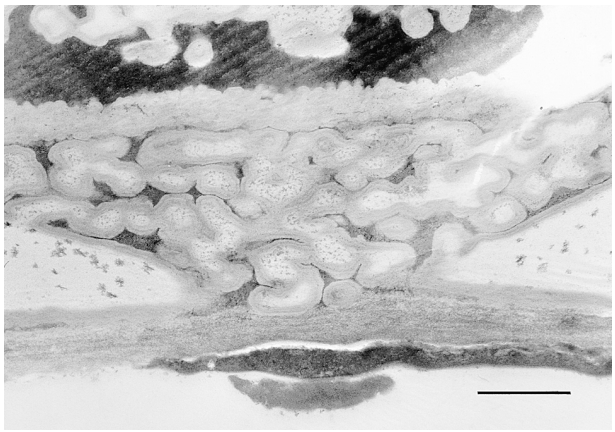

Figure 3. Electron micrograph of vitreous specimens containing gray-white materials obtained during vitrectomy for Case 2, illustrating debris of disrupted cellular components with materials resembling thickened basement membrane, ×24000. BAR: 1 μm.

eases distinct from HAU, although both patients were asymptomatic carriers of HTLV-I. The case of ARN was diagnosed on the basis of clinical and laboratory findings, including evidence of intraocular production of antibodies of VZV and detection of VZV DNA in the vitreous. The retinal involvement of ARN consists of two characteristic features, necrotizing retinitis and retinal vasculitis, and the vasculitis predominantly involves the arterial system, which is particularly striking and severe in ARN due to VZV infection.[5] To the best of our knowledge, there is no previous description in ARN of the gray-white, fluffy, spherical deposits on retinal veins as well as arteries with no other vascular change. The case of diabetic retinopathy described here developed similar vascular deposits, indicating that the characteristic change is associated not only with uveal inflammation but also with retinal vascular disease. This diabetic case presented with severe vitreous hemorrhages, and, therefore, the vascular deposits had remained undetected before vitrectomy. This type of retinal vascular involvement has not been reported in the literature regarding diabetic retinopathy.

Polymerase chain reaction of vitreous specimens in the 2 patients with ARN or diabetic retinopathy demonstrated the presence of HTLV-I proviral DNA. There is a report that HTLV-I proviral DNA is detected in the ocular infiltrating cells in the majority of HAU patients, whereas it is detected in only a few HTLV-I carriers with other uveitis.[6] Our 2 patients represent examples where the virus may also be detected in HTLV-I carriers with ocular diseases distinct from HAU. The findings indicate that the detection of HTLV-I proviral DNA in ocular fluid does not readily lead to a definite diagnosis of HAU.

In addition to the featured color, size, shape, and location, the characteristic vascular deposits described herein appeared adherent to the vessel wall so loosely that they were easily detached and aspirated without any vascular alterations. The pathomechanism for the vascular deposition exclusively in the posterior fundus remains to be elucidated. This vascular sign was invariably transient, as residual deposits resolved spontaneously in the early postoperative days. This is consistent with the observations in HAU in which the lesion resolves spontaneously in a few weeks or in response to corticosteroids.[4] The prevalence of the transient retinal vascular deposition is unknown; isolated lesions may not manifest overt clinical symptoms and may thus remain unnoticed. We have examined more than 300 asymptomatic HTLV-I carriers and identified such deposits in the present 2 cases and in 8 cases of HAU, suggesting that deposits develop only when intraocular diseases, such as uveitis and retinal vasculopathy, alter the intraocular microenvironment.

The pathomechanism of the characteristic retinal vascular deposits remain to be defined. Because the 2 patients described herein were otherwise healthy carriers of HTLV-I, and HTLV-I proviral DNA was detected in their vitreous, it is presumable that the retrovirus plays a role in the underlying etiology. It should be mentioned in this connection that there is some suggestive evidence for activated T lymphocytes being involved in the vascular events of patients with HTLV-associated myelopathy (HAM), a chronic progressive neurologic disease that is etiologically associated with HTLV-I. Histopathologic examination revealed perivascular cuffing of lymphocytes in the spinal cord.[7] Increased adherence capability of T lymphocytes to vascular endothelial cells has been shown in patients with HAM.[8,9] An increase in the spontaneous proliferative capability of the peripheral lymphocytes is also evident in HAM.[10] The increased spontaneous proliferative reaction of lymphocytes in patients with HAM in vitro suggests that extravascular HTLV-I-activated T lymphocytes are free from serum inhibitors and are able to proliferate in the central nervous system.[11] In addition, lymphocytic infiltration with a predominance of T cells has been observed in HAU patients.[6] Thus, it is tempting to speculate that activated T lymphocytes adhere to and migrate from the endothelium of retinal vessels, and proliferate in the manner of autologous or spontaneous proliferation. Eventually, this will result in the development of extravascular de-

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posits on the retinal vessels. If this hypothesis is correct, it would be expected that the retinal vascular deposits will consist of a cluster of proliferated T lymphocytes. Vitreous samples obtained during vitrectomy from 1 of the 2 patients were examined by electron microscopy, but we observed only peculiar aberrant structures with thickened basement membrane and could not establish whether the above hypothesis is correct.

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