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Case report

Indocyanine green angiographic findings in seven eyes with vasoproliferative retinal tumor

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ABSTRACT

Purpose: Vasoproliferative tumors (VPTs) are rare benign tumors, and detailed indocyanine green angiographic (ICGA) findings in eyes with VPTs have not been reported. We present the characteristic ICGA findings in seven eyes with a VPT.

Observations: We present the fluorescein angiographic (FA) and ICGA findings of seven consecutive patients who were diagnosed with primary VPT from April 2013 to March 2015 in the Oncology Service of the Department of Ophthalmology, Tokyo Medical and Dental University. We reviewed the demographics of the seven patients with VPTs. Abnormal vessels within the tumor were observed in three cases with active tumors. These vessels were hypofluorescent in the ICGA images in the scar phase. On the other hand, three cases in which the exudation remained from the initial visit to the last examination had abnormal vessels in the ICGA images. The remaining case had one straight vessel in the tumor from the initial to the last examination in the scar phase. FA in the active phase changed from hyperfluorescent leakage to staining in one eye, and the remaining six eyes continued to show hyperfluorescent leakage throughout the examination period.

Conclusions: The leakage of fluorescein continued from the initial to the final examination even after the activity of the tumor had decreased. In the active phase, ICGA showed abnormal vessels with or without leakage, and the tumors at the scar phase show a hypofluorescent lesion.

Importance: ICGA supported the ophthalmoscopic findings, and can be used as a diagnostic aid to confirm a regression of the VPTs.

1. Introduction

A vasoproliferative tumor (VPT) of the retina is a rare benign tumor that resembles a retinal hemangioma. It occurs most frequently in the peripheral retina especially in the inferotemporal quadrant. Ophthalmoscopically, it appears as a globular or dome-shaped mass whose color varies but is mainly yellowish or pinkish.[1,2] The size of the feeder vessels to a VPT is normal or slightly enlarged, and patients with VPT have no systemic or neurological abnormalities and no family history of VPT.[2–5]

The VPTs are classified as primary or secondary ocular tumors.[3] Even though they are usually benign, a reduction in the visual acuity can occur from their associations with exudations, vitreous hemorrhages, and epiretinal membranes (ERMs).[3]

When a VPT is considered to be a risk for visual reduction, it is usually treated by cryotherapy or laser photocoagulation.[3] Shields et al. reported that 64% of patients with VPT required treatment[3] but there are still no guidelines on the best treatment protocol mainly because they are so rare.

We used color fundus photographs, fluorescein angiograms (FA), and indocyanine green angiograms (ICGA) that were recorded with a conventional camera and a widefield camera with a horizontal width of 200° from seven eyes to obtain images of VPTs. This new widefield device allowed us to observe the peripheral retina more clearly, and we were able to analyze the VPTs more accurately because of the wider field of view and improved resolution. The images of FA showed that the

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Table 1
Summary of clinical data.

Case							
	1	2	3	4	5	6	7
Gender	M	F	M	M	F	M	F
Age	44	29	38	45	28	61	50
Eye	OD	OS	OS	OD	OD	OD	OS
Visual Acuity	2.0	1.2	1.2	2.0	0.4	1.2	1.5
Spherical equivalent	0.125	−14.125	−1.5	−8.125	−1.75	−0.75	−0.375
Location	Inferotemporal	Temporal	Temporal	Superotemporal	Inferotemporal	Inferotemporal	Inferotemporal
Follow-up time	39	33	36	40	30	31	23
Macular abnormality	None	None	None	None	ERM	None	None
Treatment	Observation	Observation	Observation	Observation	Observation	Observation	Observation
Initial ophthalmoscopic finding	Hemorrhage and exudation	Hemorrhage and exudation	Hemorrhage and exudation	Hemorrhage and exudation	Hemorrhage and exudation	Exudation	Scarring
Last ophthalmoscopic finding	Scarring	Scarring	Scarring	Exudation	Hemorrhage and exudation	Exudation	Scarring
FA	Leakage→Leakage	Leakage→Staining	Leakage→Leakage	Leakage→Leakage	Leakage→Leakage	Leakage→Leakage	Leakage→Leakage
ICGA	Abnormal vessels→Hypofluorescence	Leakage→Hypofluorescence	Leakage→Hypofluorescence	Abnormal vessels→Abnormal vessels	Leakage→Abnormal vessels	Abnormal vessel→Abnormal vessels	Abnormal vessels→Abnormal vessels

OD = right eye; OS = left eye; ERM = epiretinal membrane; FA = fluorescein angiograms; ICGA = indocyanine green angiograms.

VPTs had mildly-dilated hyperfluorescent feeder vessels[4] and often had leakages in the late phase of FA.[3] FA also showed leakage and tissue staining even after the activity of the VPT had decreased after treatment.[5] As best we know, there are no reports on the ICGA findings in eyes with VPTs.

Thus, the purpose of this study was to determine the ICGA findings of VPTs and to determine whether the ICGA findings were indicators of VPT activity. To accomplish this, we recorded color fundus photograph, FA, and ICGA from 7 consecutive patients with primary VPT and examined whether there were any changes that indicated that interventions were needed.

2. Methods

This was a retrospective, observational case series study. The procedures used in this study were approved by the Tokyo Medical and Dental University Ethics Committee, and they conformed to the tenets of the Declaration of Helsinki. A signed informed consent was obtained from all participants to undergo the standard ophthalmological examinations, FA, and ICGA.

Eight consecutive patients were diagnosed with primary VPT between April 2013 to March 2015 in the Oncology Service of the Department of Ophthalmology of the Tokyo Medical and Dental University. One patient was excluded because of allergy to fluorescein, and the remaining seven patients were studied. The decimal best-corrected visual acuity (BCVA) was measured with a Landolt C chart, and the fundus was examined by ophthalmoscopy, color fundus photography, pseudo-color fundus photography, FA, and ICGA. The color fundus photographs of 50° horizontal width were recorded with the TRC 50DX retinal camera (Topcon Medical Systems Co, Tokyo, Japan) or with the VX-10i fundus camera (Kowa Co, Nagoya, Japan). Pseudo-color fundus photographs with a horizontal width of 200° were recorded with the Optos P200T (Optos PLC, Dunfermline, Scotland). FA and ICGA were performed with the KOWA VX-10i fundus camera with a horizontal width of 50° (Kowa Co, Nagoya, Japan) from April 2013 to August 2014. Fundus photographs were also recorded with the Heidelberg Spectralis (HRA, Heidelberg, Germany) fundus camera with a non-contact ultra-widefield lens from September 2014 to March 2015. The fundus images had a horizontal angular width of 102°.

The diagnosis of VPT was made by the FA findings and color photographs. Three retinal specialists (SM, MU, and TI) examined the color photographs, pseudocolor photographs, FA, and ICGA independently to make the diagnosis. They judged the activity of the VPT by the degree of hemorrhaging and exudation in the color and pseudocolor photographs. FA and ICGA were performed at each examination.

The activity of the VPT was classified by the color photographs into: an active phase VPT with hemorrhage and exudation; an intermediate phase VPT with only exudations; and a scar phase VPT with whitish scar without hemorrhage and exudations.

3. Results

The demographics of all seven eyes of the seven patients are presented in Table 1. Four of the patients were men and three were women, and the VPTs were solitary in all eyes. The average age of the patient was 42 ± 10.8 years with a range of 28–68 years, and the average follow-up period was 33.1 ± 5.4 months with a range of 23–40 months.

The tumor was located in the inferotemporal area in four eyes, in the temporal area in two eyes, and in the superotemporal area in one eye. Only one patient had a reduction of the decimal visual acuity to 0.4 at the initial visit, and the reduction was caused by an ERM. The visual acuity in this patient improved to 1.0 after 1 month because the ERM spontaneously detached. The visual acuity in the remaining six patients was within the normal range. At the initial visit, five eyes were in the active phase, one eye in the intermediate phase, and one eye was in the scar phase of VPT.

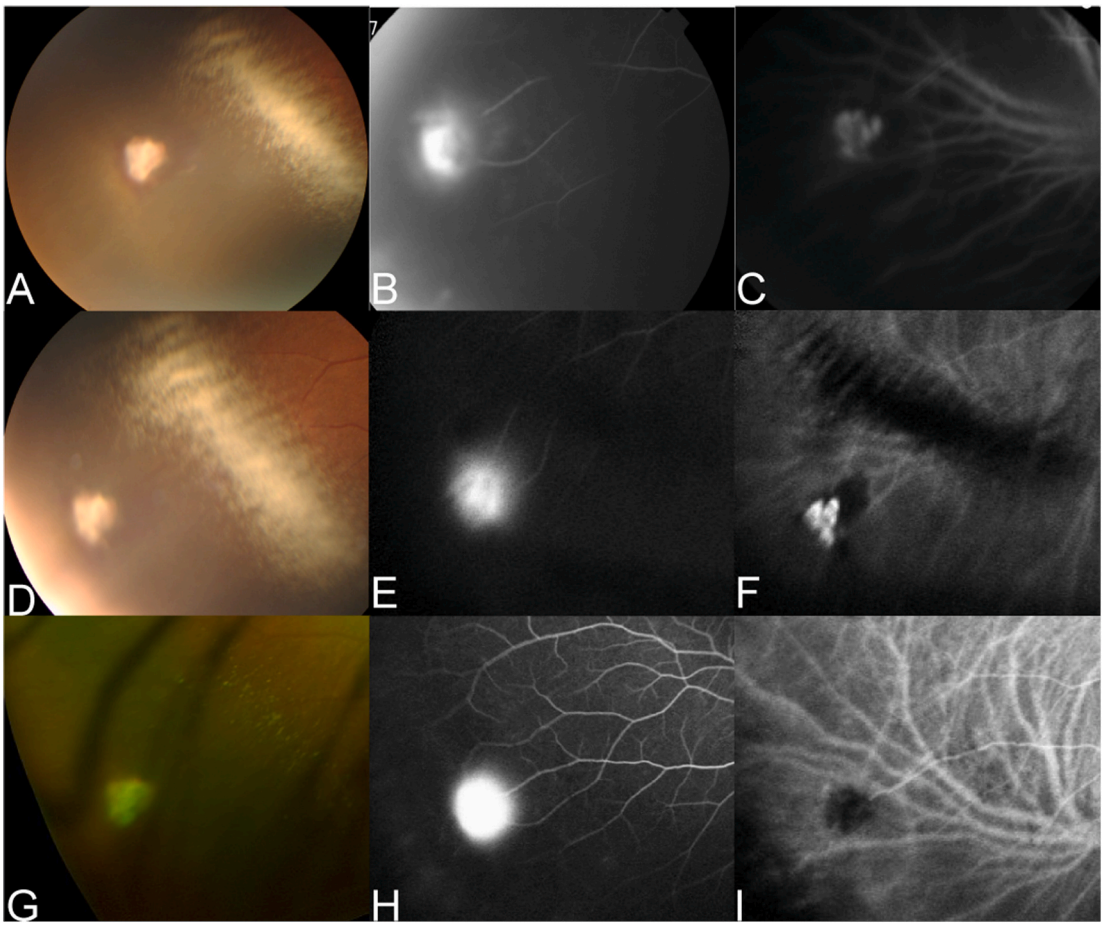

Fig. 1. Case 1. Fundus photograph of inferotemporal area of the right eye of a patient diagnosed with a vasoproliferative tumor (VPT)
A: Color fundus photograph at initial examination. The VPT is surrounded by retinal hemorrhage and exudations in the vitreous.
B: Late phase fluorescein angiogram at the initial examination showing the VPT as a hyperfluorescent mass with leakage.
C: Indocyanine green angiogram (ICGA) at the initial examination showing that the VPT is a hyperfluorescent tufted lesion.
D: Fundus photograph at 11 months. The appearance of the VPT has not changed.
E: Late phase FA image at 11-months showing leakage from the VPT similar to that at the initial visit.
F: ICGA at 11 months shows the hyperfluorescent tufted lesion.
G: Pseudocolor fundus photograph at 23-months. Hemorrhages are not present but the vitreal exudations remain.
H: FA shows leakage from the VPT at 23-months
I: ICGA shows the VPT as a hypofluorescent lesion at 23-months. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.1. Findings and changes of five eyes with VPT in active phase (Cases 1–5)

Five of the seven eyes had retinal hemorrhages and exudations around the VPT at the initial visit, i.e., the active phase. In three of these eyes, the VPT progressed to a white scar without hemorrhages and exudations, i.e., the scar phase, during the experimental period. In one of the eyes, the hemorrhage was resorbed but the exudation remained, i.e., the intermediate phase. In the remaining eye, the hemorrhage and exudation around the VPT remained, and the tumor did not progress to the scar phase.

In the three eyes that had progressed to the scar, the FA findings changed from hyperfluorescent leakage to hyperfluorescent tissue staining in one eye, and the hyperfluorescent leakage continued in the other two eyes. The ICGA findings changed from hyperfluorescent leakage to hypofluorescence in two eyes, and from hyperfluorescence of the abnormal vessels to hypofluorescence in the remaining eye. It could not be determined whether the hypofluorescence was caused by a blockage of the fluorescence or a blood flow defect.

In one eye in which the VPT changed from the active phase to the intermediate phase, and in one eye in which the tumor remained in the active phase from the initial to the final examination, FA showed leakage from the tumor at the initial visit which did not change to the end. In both eyes, ICGA showed abnormal vessels at the initial visit which also had not changed at the final examination. The two eyes that did not progress to the scar phase did not show hypofluorescence on ICGA.

3.2. Findings and changes in one eye with VPT in intermediate phase (Case 6)

In one of the seven eyes, the retina around the tumor had exudations continuously from the initial visit to the final visit, and fluorescein leakage from the tumor was present at the final visit. ICGA showed an abnormal vascular network without leakage from the initial visit to the final visit.

3.3. Findings and changes in one eye with VPT in scar phase (Case 7)

In the remaining eye, the tumor was a whitish scar without hemorrhages and exudations at the initial visit. The FA leakage was present

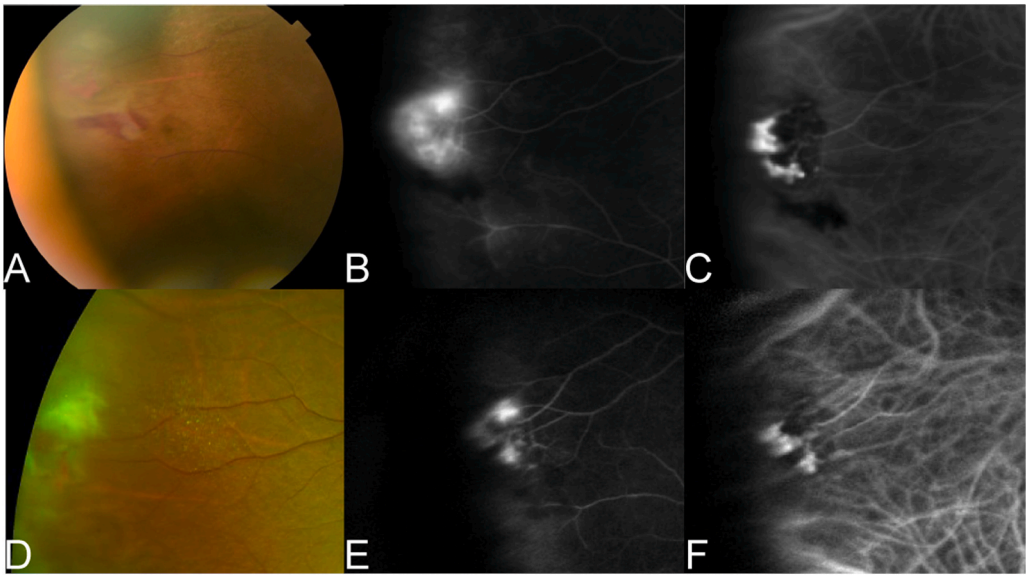

Fig. 2. Case 5. Fundus photographs of the inferotemporal area of the right eye.
A: Color fundus photograph at the initial visit. The VPT consists of mild gliosis and abnormal blood vessels of orangish-red color. Hemorrhage can be seen beneath the VPT.
B: FA at the initial visit shows a hyperfluorescent massive lesion with abnormal vessels with leakage
C: ICGA at the initial visit shows a hyperfluorescent lesion with tufted abnormal vessels.
D: Color fundus photograph at 18 months. Scar tissue is observed around the small red abnormal vessels of the VPT. A small amount of exudation is present temporal to the VPT.
E: FA at 18 months shows that the leakage from the VPT is still present but decreased.
F: ICGA at 18 months shows tufted abnormal vascular network. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

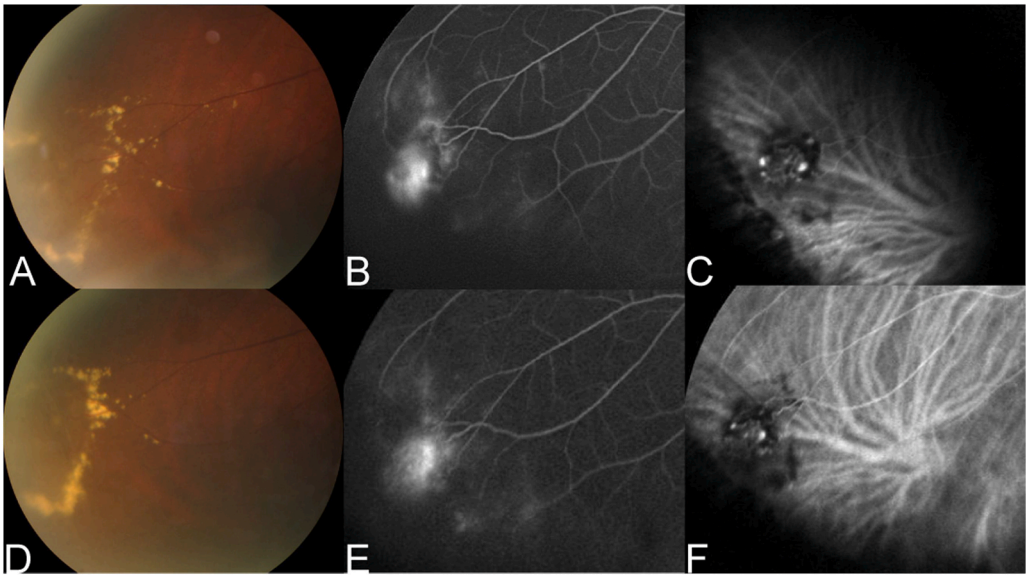

Fig. 3. Case 6. The VPT is seen in the inferotemporal sector of the fundus of the right eye.
A: Color fundus photograph at the initial visit shows yellowish white VPT with exudation.
B: FA at the initial visit shows leakage from the VPT.
C: ICGA at the initial visit shows abnormal vascular network.
D: Fundus photograph after 31 months shows that the exudation has increased.
E: FA after 31 months shows leakage is still present.
F: ICGA after 31 months shows hypofluorescence and abnormal vascular network is still present. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

from the first to the final visit. ICGA showed one straight abnormal vessel in the tumor at the initial visit and it was present at the final examination.

3.4. Case reports

Case 1 (Fig. 1). At the initial visit, a yellowish-white VPT with hemorrhages and exudation into the vitreous was seen at the inferotemporal region of the right eye. Both FA and ICGA showed that the VPT was hyperfluorescent with leakage. This eye was followed without treatment, and the FA leakage continued for at least 23 months. The ICGA leakage was not present at 11 months after the initial visit, and FA and ICGA showed only abnormal vessels. After 23 months, the VPT changed to hypofluorescence in the ICGA images. Color fundus photographs showed there was a decrease in the hemorrhages with exudations after 17 months. There was a spontaneous regression of the tumor after 23 months.

Case 5 (Fig. 2). At the initial visit, a VPT with an ERM was seen at the inferotemporal quadrant of the right eye, and the decimal visual acuity was reduced to 0.4 due to the ERM. Color fundus photographs showed that the appearance of the VPT was due to gliosis of the retina and the presence of abnormal blood vessels. A hemorrhage was seen beneath the VPT. FA showed leakage, and ICGA showed the presence of abnormal vessels. After 1 month, the ERM spontaneously resolved and the visual acuity recovered to 1.0. After 18 months, the beaded hyperfluorescence decreased, and ICGA leakage was not detected but the abnormal vessels remained. After 29 months, the FA leakage remained, and scar tissue had formed around the abnormal blood vessels. The size of the hemorrhage decreased but exudation had not decrease in the color fundus photographs.

Case 6 (Fig. 3). At the initial visit, a yellowish-white VPT with exudation was seen at the inferotemporal sector of the right eye. A

leakage on FA was observed, and abnormal vessels were seen in the ICGA images. After 31 months, the FA leakage remained, and the ICGA findings did not change to hypofluorescence and the abnormal vessels remained.

4. Discussion

Our results showed the ICGA findings of 7 cases with a VPT. The abnormal vessels within the tumor could be observed in the three cases with active tumors. These vessels progressed to hypofluorescence in the ICGA images in the scar phase. On the other hand, the other three cases, in which the exudation did not disappear, had abnormal vessels in the ICGA images from the initial to the last examination. The remaining case in the scar phase showed one straight vessel in the tumor from the initial to the last examination.

Shields et al. reported that VPTs could be an expression of vascularization, and the tumor is due to proliferation of the pigment epithelial cells and a reactive gliosis around them.[6] Histopathological studies showed that VPTs are composed of both glial and vascular elements but reports on VPTs are limited.[1]

It is difficult to show the vascular structure in the FA images because of leakages and staining in the early phase even in the ultra-widefield images. Shields et al. reported that a capillary network that appeared to come from the retinal circulation was present in the tumor in the FA images in 1995. A later FA study (2013) showed that the tumor was hyperfluorescent in the arterial phase and remained hyperfluorescent or had leakages in the late phase.[3]

In our cases, we were able to clearly observe the vascular structure of the VPT in the ICGA images because indocyanine green was less likely to leak due to its high molecular weight.[7] The ICGA findings of VPT showed that the activity of the abnormal vessels within the tumor was associated with the tumor activity. This supports the hypothesis that a VPT is not a real tumor but an abnormal vascularization with gliosis.

Unfortunately, we did not observe a reduction of activity of the abnormal vessels in the ICGA images, and a regression of the bleeding and exudation by ophthalmoscopy at about the same time. We believe that ICGA did not help predict the VPT activity but supported the ophthalmoscopic findings. Thus, ICGA can be used as a diagnostic aid to confirm a regression of the VPTs and may provide a basis for extending the follow-up period.

This was a case report of 7 consecutive patients with VPT, and none required treatment. One patient had symptoms from an ERM but all others were asymptomatic. In Japan, medical examinations are improving, and asymptomatic diseases may become more easily detected. Because we do not perform surgery in the oncology service at our hospital, patients who need surgery are referred to another surgical hospital. We believe that patients with VPT who did not require surgery were referred to our hospital for more detailed examination, and thus, the patients were biased in severity. This resulted in a report of seven consecutive eyes that resolved spontaneously. ICGA findings of VPT in patients requiring surgery are unknown. In the future, examination on ICGA findings of VPT with various activities at multiple centers may improve the understanding of the state of a VPT.

Patient consent

Informed consent in writing from patients for use their information and fundus photographs for research was obtained.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: Saya Matsuura, Tomoka Ishida, Miho Tobe, Minami Uchida, Ryoko Souma, Kyoko Ohno-Matsui.

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