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Multimodal Imaging, Including Laser Speckle Flowgraphy: A Case of Retinal Metastasis

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Abstract. *Background/Aim: Intraocular metastases of systemic cancer are most frequently located in the choroid, followed by the iris and ciliary body, while retinal metastases are extremely rare. Here we present a case of retinal metastasis and analyze multimodal imaging. Case Report: A 66-year-old woman with a medical history of breast cancer 5 years earlier was referred to our Department struggling with blurry vision in her right eye. At initial examination, her best-corrected visual acuity (BCVA) was 1.0 oculus dexter (OD). Fundus examination revealed a yellowish elevated lesion with irregular surface, measuring 2 papillary diameters, along with serous retinal detachment (SRD) on the temporal side of the optic disc. Optical coherence tomography showed SRD with an isointense nodule extending across all retinal layers. Fluorescein angiography showed hyperfluorescence and vigorous fluorescence leakage inside the tumor in the early and late phases, respectively. Indocyanine green angiography depicted feeder and drainage vessels within the mass. Laser speckle flowgraphy (LSFG) showed a cold signal inside the tumor. Based on these clinical findings, the mass was diagnosed as a retinal metastasis. Eight days after the initial visit, the patient underwent external beam radiation to the right eye. One month after the initial diagnosis, her BCVA was 0.7 OD, the tumor was localized, and SRD had decreased. LSFG indicated vascular remodeling with marginally warmer signals in the tumor. Conclusion: LSFG of the retinal metastasis showed a cold signal, suggesting low tumor blood flow velocity and that the tumor may have grown slowly. LSFG findings are likely to play a supportive role in clinical diagnosis and contribute to better understanding of pathogenesis in juxtapapillary tumors.*

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Intraocular metastases of systemic cancer are most frequently located in the choroid (88%), followed by the iris (9%) and ciliary body (2%), while retinal metastases are extremely rare (1). The rarity of retinal metastases might be explained by the fact that the choroid receives 85% of ocular blood flow, whereas the retina receives only 5% (2). In recent years, fluorescein angiography (FA) has been used for evaluating retinal blood flows in retinal metastasis (3); however, little is known about other methods, such as indocyanine green angiography (ICGA) and laser speckle flowgraphy (LSFG) findings.

LSFG is a blood flow imaging system that uses laser scattering to visualize intraocular circulation in two dimensions, which enables the noninvasive investigation of fundus circulation in various retinal and choroidal lesions. We have analyzed retino-choroidal circulation of intraocular tumor(-like) lesions, such as metastatic choroidal tumor (4), choroidal macrovessel (5), sclerochoroidal calcification (6), choroidal lymphoma (7), leukemic retinopathy (8, 9), and radiation retinopathy for choroidal melanoma (10). We previously analyzed LSFG findings on the ocular circulation in juxtapapillary tumors, such as retinal capillary hemangioblastoma (11), and optic disc melanocytoma (12). However, the details of retinal circulation and morphological changes in retinal metastasis before and after treatment are unknown.

We herein present a case of juxtapapillary retinal metastasis that underwent multimodal imaging including LSFG before and after therapy.

Case Report

A 40-year-old woman was referred to our Department complaining of decreased central vision in her right eye, especially when looking at objects close up. Her medical history included a diagnosis of breast cancer 5 years earlier, for which she had received hormone therapy and systemic chemotherapy. Four years later, bone and liver metastases had been detected and she had undergone systemic chemotherapy and partial hepatectomy, leading to partial remission after 2 years. There were no special notes on family history. At the time of initial examination, her best-corrected visual acuity was 1.0 with mild myopia and astigmatism, and her intraocular pressure was normal in both eyes. Slit-lamp microscopy did not detect any findings for either eye. Color fundus photography (CFP) showed a yellowish elevated lesion with an irregular surface, measuring 2 papillary diameters, along with serous retinal detachment (SRD) on the temporal side of the optic disc of the right eye (Figure 1A, white arrowheads). CFP also showed small intratumoral hemorrhage-like foci within the lesion (Figure 1A, green arrowhead) and hard exudates below the mass. Swept-source optical coherence tomography (OCT) showed SRD in the macula and an isointense nodule extending across all retinal layers (Figure 1B and C). Fundus autofluorescence showed hypofluorescence in the mass and hyperfluorescence in the SRD (Figure 1D). FA showed hyperfluorescence in the mass with a variety of neovascular channels in the early phase (Figure 1E), and vigorous fluorescence leakage in the late phase (Figure 1F). ICGA revealed meandering retinal blood vessels within the mass (Figure 1G). The vascular structure inside the mass showed feeder vessels (Figure 1G, red arrowheads) branching from arterial vessels and drainage vessels from venous vessels (Figure 1G, blue arrowheads), both of which were partially anastomosed at the center of the mass (Figure 1G, yellow arrowhead). Small intra-tumor hemorrhage-like foci were found within the tumor on CFP (Figure 1A, green arrowhead), corresponding with a microaneurysm on ICGA (Figure 1G, green arrowhead). B-Mode echography showed mild elevation in the area corresponding to CFP and OCT findings (Figure 1H, red arrowhead). Based on these clinical findings and her history of breast cancer, the patient was diagnosed with retinal metastasis. Furthermore, LSFG showed a cold signal in the tumor (Figure 1I, yellow arrows).

After informed consent was obtained, the patient underwent irradiation (30 Gy/10 fraction) to the right eye 8 days after the initial visit. One month after the initial diagnosis, her best-corrected visual acuity was 0.7 for the right eye, the tumor was localized, hard exudates had decreased (Figure 2A, white arrowheads) and SRD was slightly reduced (Figure 2B and C). LSFG showed marginally warmer signals in the tumor (Figure 2D, yellow arrows).

Ethics approval. The Institutional Review Board of Hokkaido University waived ethical assessment of this clinical study because it was a single case report and a non-invasive study. This study adhered to the tenets of the Declaration of Helsinki.

Consent for publication. The patient provided written, retrospective consent for publication following detailed explanation of the purpose of article and on the understanding that no identifiable information would be released.

Discussion

The prevalence of primary sites for retinal metastasis is seemingly different from that for choroidal metastasis: Tang *et al*. reviewed 42 cases of retinal metastases and reported that the most common primary sites were cutaneous melanoma followed by lung carcinoma and gastrointestinal carcinoma (13). Of the 41 patients with retinal metastasis by Ozcan *et al*. (3), 15 (36.6%) cases had lung carcinoma, 13 (31.7%) had gastrointestinal carcinoma, and 6 (14.6%) had breast carcinoma. The ophthalmic findings in the fundus consisted of yellow–white solid elevated retinal juxtapapillary mass lesions (13, 14) with or without retinal detachment or vitreous hemorrhage. However, there have been cases with poorly elevated yellowish-white lesions that were misdiagnosed as cytomegalovirus retinitis (15-17). Of eight cases of retinal metastases by Shields *et al*., seven were unilateral, and the tumors were located in the inner retina in six cases and in the entire retina in one case, with retinal hemorrhage and SRD in four cases each (18). Tumor coloration was white in two cases, yellow in four, and brown in one (18). The tumors showed morphological configurations that were smooth, cerebriform in two cases, or irregular in three cases and had intrinsic tumor vessels in two cases, but there were no cases demonstrating dilated tortuous retinal feeder vessels (18). OCT showed a hyper-reflective dome-shaped lesion with or without subretinal fluid (3, 18, 19) and retinal thinning with hyperreflective structures (20). Fundus autofluorescence examination showed hypoautofluorescence (3, 19), while FA findings were divided into cases showing early hyperfluorescence and late staining without leakage (3), or early hypofluorescence and hyperfluorescence in the venous and/or recirculation phases (18). However, as far as we are aware, there have been no reported cases clarifying ICGA and LSFG findings. In our case, there was a yellowish intraretinal lesion with irregular surface involving all retinal layers with SRD. FA showed hyperfluorescence in the mass with a variety of neovascular channels, while ICGA revealed details of the vasculature. In fact, ICGA revealed meandering of blood vessels within the mass, with feeder and drainage vessels branching from the main vessels and anastomosing in the center of the tumor. This indicates that the tumor was dependent on retinal vessels for

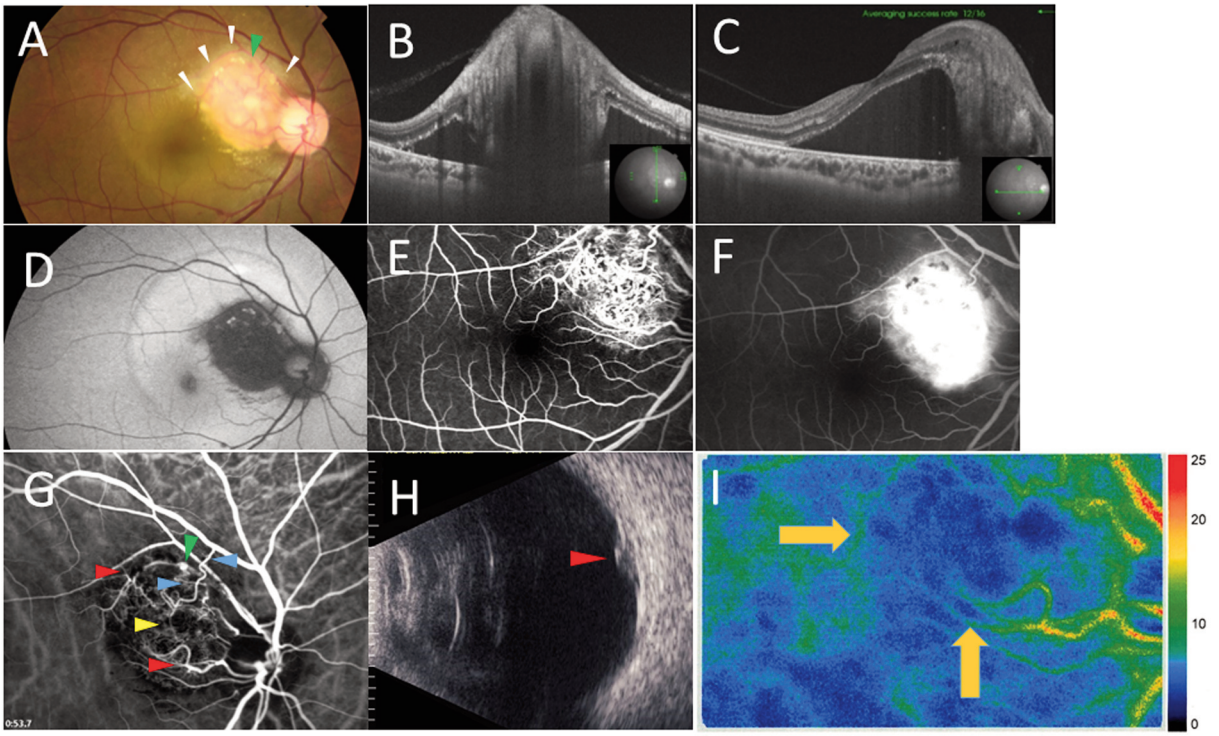

Figure 1. *Initial findings on imaging of the right eye in the present case of retinal metastasis. (A) color fundus photography showed a yellow elevated lesion measuring 2 papillary diameters with serous retinal detachment (SRD) on the temporal side of the optic disc (white arrowheads) and small intratumoral hemorrhage-like foci within the tumor (green arrowheads). (B) Swept-source optical coherence tomography (SS-OCT) at vertical scan through the mass showed nodular isointense foci extending across all layers of the retina. (C) SS-OCT at horizontal scan through the fovea showed SRD in the macular area around the mass lesion. (D) Fundus autofluorescence examination showed hypofluorescence in the mass and hyperfluorescence in the SRD. (E) Fluorescence angiography showed hyperfluorescence in the mass with a variety of neovascular channels in the early phase. (F) Vigorous fluorescence leakage in the late phase. (G) Indocyanine green angiography revealed meandering of blood vessels within the mass in the early phase. The vascular structure inside the tumor showed feeder vessels (red arrowheads) branching from arterial vessels and drainage vessels branching from venous vessels (blue arrowheads), both of which were anastomosed at the center of the mass (yellow arrowhead). (H) B-Mode echography revealed an elevated lesion (red arrowhead). (I) Laser speckle flowgraphy showed a cold signal in the mass area (yellow arrows).*

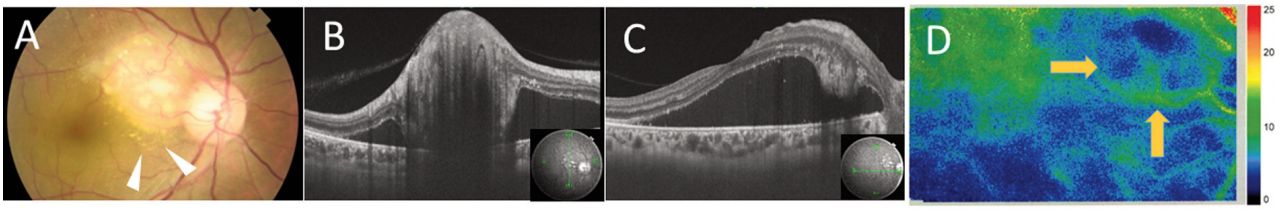

Figure 2. *Post-treatment images in the present case of retinal metastasis. (A) One month after the initial diagnosis, the tumor pallor and narrowing of blood vessels inside the tumor and hard exudates had decreased (white arrowheads). (B) Swept-source optical coherence tomography (SS-OCT) at vertical scan through the mass (upper image) showed little change in tumor size. Horizontal scan through the fovea (lower image) showed tumor shrinkage in some areas, with a well-defined retinal structure. (D) Laser speckle flowgraphy showed marginally warmer signals in the mass itself (yellow arrows).*

growth. The presence of a microaneurysm in the tumor suggested impaired blood flow within the tumor.

We previously reported a case of juxtapapillary retinal capillary hemangioblastoma in which LSFG displayed markedly warm colors, indicating fast tumor bloodstreams (11). We further demonstrated rapid choroidal blood flow velocity by LSFG in a case of metastatic choroidal tumor from breast cancer (4). In contrast, LSFG in our retinal

metastasis showed colder colors than in metastatic choroidal tumors. This suggests that tumor blood flow of the retinal metastasis may have been slower and that it had taken longer to form a mass and subretinal fluids than in the case of metastatic choroidal tumor. In fact, the mean interval from primary cancer diagnosis to retinal metastasis diagnosis was 63 months (median=33 months) according to Shields *et al.* (18), while the mean interval between the diagnoses of lung cancer and uveal metastases was 31 months (median=12 months) (21). In our case, the interval from primary cancer diagnosis to retinal metastasis diagnosis was 60 months. Despite this, the survival rate for patients with cancer metastasis to the retina is poor. Indeed, the mean survival for reported cases with retinal metastasis was only 5.7±5.2 months (3), whilst the mean survival for reported cases with choroidal metastases was 12 months (21). Although these previous reports differ in the number of cases examined and backgrounds, slow bloodstreams in tumor tissues of retinal metastases might mean that they take such a long time to grow to the point of becoming symptomatic, leading to a clinical diagnosis, thereby allowing tumor cells to disseminate and thus correlating with a poor prognosis.

In addition, retinal metastasis in this case showed a warmer signal on LSFG with a decrease in hard exudates after radiotherapy than before treatment. This may be due to vascular remodeling, with the disappearance of tumor neovascularization caused by irradiation.

In conclusion, the LSFG of metastatic retinal tumor showed cold colors, suggesting that the blood flow of the tumor was slow, and that the tumor may have grown slowly. LSFG findings are likely to play a supportive role in clinical diagnosis and contribute to the better understanding of the pathogenesis in juxtapapillary tumors.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

MM wrote the article and acquired clinical data. SK reviewed the article and interpreted the clinical data. SI performed clinical revision and supervised the data interpretation. All Authors have read and approved the article.

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