Case Report

Unilateral Multiple Evanescent White Dot Syndrome-Like Reaction Following the CyberKnife Stereotactic Radiotherapy for Choroidal Malignant Melanoma

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Abstract

A 58-year-old otherwise healthy man received a diagnosis of choroidal malignant melanoma (CMM) in June 2021 and underwent a single session of (21 Gy) CyberKnife stereotactic radiotherapy (SRT). Eleven months later, we noticed 3+ anterior chamber cells with occasional vitreous cells in the left eye. Though the tumor looked regressed, there were mild optic disc leakage, early hypofluorescent and late hyperfluorescent punctate lesions scattered 360 degrees, and late staining of the mass on fluorescein angiogram. The findings were compatible with a unilateral multiple evanescent white dot syndrome (MEWDS)-like reaction that was most likely related to CyberKnife SRT-induced tumor necrosis, and a dexamethasone implant was administered intravitreally into the left eye together with topical steroids. A second intravitreal injection of dexamethasone was given three months later due to remittance of the angiographic features. As there are only a few reports on CyberKnife SRT for the treatment of CMM, we wanted to share our interesting observation of a post-treatment MEWDS-like reaction likely related to tumor necrosis syndrome with the ophthalmic community.

Keywords: Choroidal malignant melanoma, CyberKnife stereotactic radiotherapy, dexamethasone implant, fluorescein angiography, multiple evanescent white dot syndrome

Introduction

Multiple evanescent white dot syndrome (MEWDS) is an acute, multifocal, mostly unilateral, self-resolving inflammatory chorioretinopathy that affects young adults (predominantly females, at a ratio of 5:1).[1] Lesions are typically indistinct, yellowish white in color, and occur at the level of the retinal pigment epithelium (RPE) or outer retina. They are predominantly located in the perimacular area and may extend into the mid-peripheral retina. Foveal granularity, optic disc edema, and vitreous cells may also be present.[2,3] The lesions routinely resolve within weeks to months and recurrence is rare.[4]

A MEWDS-like reaction can be seen with or after various clinical entities, including multifocal choroiditis, macular neovascularization, angioid streaks, retinal detachment surgery, *Toxoplasma* chorioretinitis, Best vitelliform dystrophy, retinopexy, traumatic subretinal hemorrhage, pseudoxanthoma elasticum, acute zonal occult outer retinopathy, peripapillary subretinal neovascularization, hepatitis A and yellow fever vaccination, rabies vaccination, tuberculosis, optic neuritis in multiple sclerosis, coloboma of optic papilla, cryotherapy, radiotherapy for the treatment of retinoblastoma, and idiopathic neovascularization/atrophic scar.[2,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19]

Here we report a patient with a MEWDS-like reaction most likely associated with tumor necrosis syndrome that was noticed 11 months after CyberKnife (Accuray, Sunnyvale, CA, USA) stereotactic radiotherapy (SRT) for the treatment of a left choroidal malignant melanoma (CMM). Our aim was to share our observations and experience related to the diagnosis and our management strategy.

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Case Report

A 58-year-old man presented in June 2021 with visual loss in the left eye of 1 month duration. His medical and family histories were unremarkable. Upon examination, his best-corrected visual acuity (BCVA) on Snellen chart was 1.0 (decimal) in the right eye and 0.2 in the left eye. Color vision was 21/21 with the Ishihara pseudoisochromatic plates and there was no relative afferent pupillary defect (RAPD) in either eye. On slit-lamp examination, both anterior segments were unremarkable. While the right fundus was normal, there was a markedly elevated amelanotic mass temporal to the macula in the left eye (Figure 1A). On fluorescein angiogram (FA), multiple irregular pinpoint foci of fluorescein leakage together with discrete hypofluorescent patches corresponding to the lesion were observed (Figure 1B). Optical coherence tomography (OCT) (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) sections demonstrated massive subretinal fluid involving the fovea in the left eye. Ultrasonography (USG) revealed a hyperechogenic choroidal lesion with low to medium internal reflectivity and choroidal excavation (Figure 1C). The tumor size was 13.27 mm x7.34 mm on B-mode ophthalmic USG. Orbital computed tomography conducted to aid in the planning of CyberKnife SRT revealed a CMM with enhanced contrast, accompanied by related subretinal fluid accumulation (Figure 1D). After discussing the therapeutic options and possible outcomes, a single session of CyberKnife SRT (21 Gy) was administered for tumor treatment.

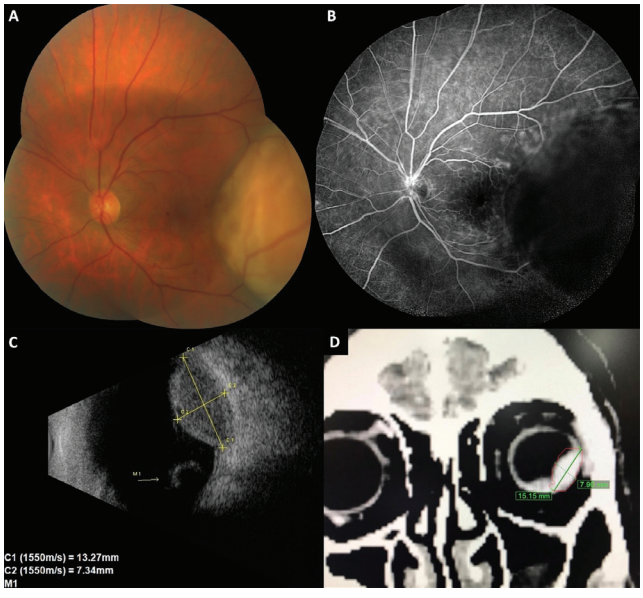

Figure 1. At the first presentation (June 2021), left eye: A) Color fundus photograph depicting the markedly elevated amelanotic mass temporal to the left macula. B) Composite venous phase of fluorescein angiogram exhibiting the multiple irregular pinpoint foci of fluorescein leakage together with discrete hypofluorescent patches corresponding to the mass area. C) B-mode ultrasonography demonstrating a hyperechogenic choroidal lesion (13.27 mm x7.34 mm) with low to medium internal reflectivity and choroidal excavation. D) Contrast-enhanced orbital computed tomography obtained for CyberKnife stereotactic treatment planning showed a contrast-enhanced choroidal melanoma along with the associated subretinal fluid

Eleven months after treatment, left eye BCVA was counting fingers at 2 meters. There were 3+ anterior chamber cells in the left eye with occasional vitreous cells. Left eye intraocular pressure was 15 mmHg. Tumor size was measured as 13.24 mm x6.12 mm on B-mode ophthalmic USG. On fundoscopic examination, the right fundus was normal while the tumor in the left eye looked regressed (Figure 2A). On FA, there was mild optic disc leakage, early hypofluorescent and late hyperfluorescent dot-like lesions scattered 360 degrees in a wreath-like pattern, and late staining of the mass in the left eye (Figure 2B). OCT of the left eye demonstrated subretinal and intraretinal macular fluid with a serous retinal detachment at the temporal retina (Figure 2C). Indocyanine green angiography (ICGA) could not be performed due to reimbursement issues. The patient was put on topical prednisolone acetate drops six times a day for the left eye. The left fundus appearance suggested a diagnosis of MEWDS-like reaction secondary to CyberKnife SRT-induced toxic tumor necrosis syndrome. After reviewing the therapeutic options, an intravitreal dexamethasone implant was administered to the left eye.[20]

Two weeks after the intravitreal injection, left BCVA had recovered to 0.15 and the anterior chamber inflammation had subsided. The intravitreal dexamethasone implant could be viewed in the left inferior vitreous cavity (Figure 3A). Fluorescein angiographic appearance was dramatically improved, as the previously documented dot-like scattered lesions were less apparent, with markedly diminished punctate leakage on FA (Figure 3B). There was no apparent optic disc leakage. The amount of intraretinal fluid was dramatically reduced on OCT (Figure 3C).

In the follow-up examination 12 weeks after the intravitreal injection, color vision in the left eye was 1/21 with the Ishihara

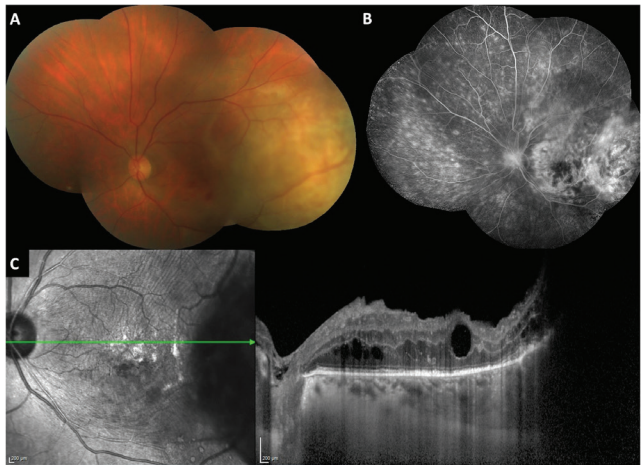

Figure 2. Eleven months after the CyberKnife stereotactic radiotherapy (May 2022), left eye: A) Color fundus photograph showing the slightly regressed tumor. B) Composite venous phase of fluorescein angiogram showing mild optic disc leakage, early hypofluorescent and late hyperfluorescent dot-like lesions scattered 360 degrees in a wreath-like pattern and late staining of the mass. C) Spectral domain optical coherence tomography section demonstrating subretinal and intraretinal macular fluid with a serous retinal detachment in the temporal retina

pseudoisochromatic plates and a left RAPD was noted. Retinal hemorrhages and exudates were noted in the inferotemporal macula. The disc edema was most likely related to the radiation retinopathy and optic neuropathy, and the dexamethasone implant was no longer visible (Figure 4A). The wreath-like pattern of scattered lesions had reappeared and there was also significant macular nonperfusion on FA (Figure 4B). Intraretinal fluid was hardly noticeable on OCT in the left eye (Figure 4C). A second dexamethasone implant was administered to the left eye.

Two weeks after the second injection, the fundus appearance looked unchanged (Figure 5A), while the dots previous seen on FA had completely disappeared (Figure 5B). OCT of the left eye showed hints of epiretinal membrane, and the fluid was diminished (Figure 5C). Left OCT angiography (Triton, Topcon Inc., Oakland, NJ, USA) depicted areas of no flow in the superficial capillary plexus (Figure 5D) and deep capillary plexus (Figure 5E) slabs (6x6 mm).

In December 2022, 12 weeks after the second intravitreal injection, left eye BCVA on Snellen chart was 0.2. There were no anterior chamber cells in the left eye. Fundus appearance of the left eye was similar except for the changes secondary to radiation retinopathy. Tumor size was measured as 11.07 mm x4.63 mm on B-mode ophthalmic USG and necrotic cystic changes were seen on the tumor surface.

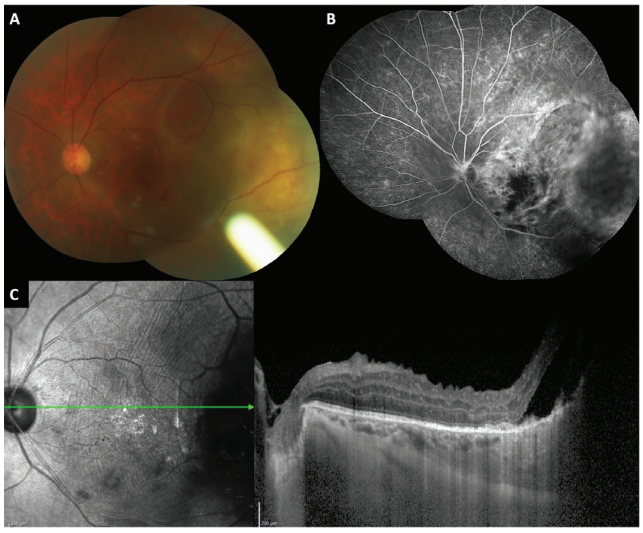

Figure 3. Two weeks after the first intravitreal injection (June 2022), left eye: A) Color fundus photograph showing the intravitreal dexamethasone implant in the vitreous cavity. B) Composite venous phase of fluorescein angiogram revealing the markedly diminished dot-like scattered lesions and punctate leakage. C) Spectral domain optical coherence tomography section demonstrating reduced intraretinal fluid

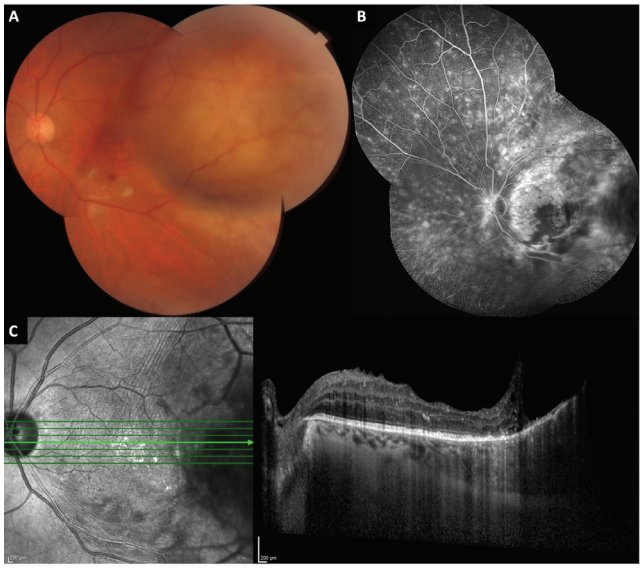

Figure 4. Twelve weeks after the first intravitreal injection (September 2022), left eye: A) Color fundus photograph showing retinal hemorrhages and hard exudates at the inferotemporal macula due to radiation retinopathy. B) Reappearance of the scattered hyperfluorescent dot-like lesions, significant macular non-perfusion, and disc hyperfluorescence on composite venous phase angiographic image. C) Spectral domain optical coherence tomography section demonstrating the reduced amount of intraretinal fluid

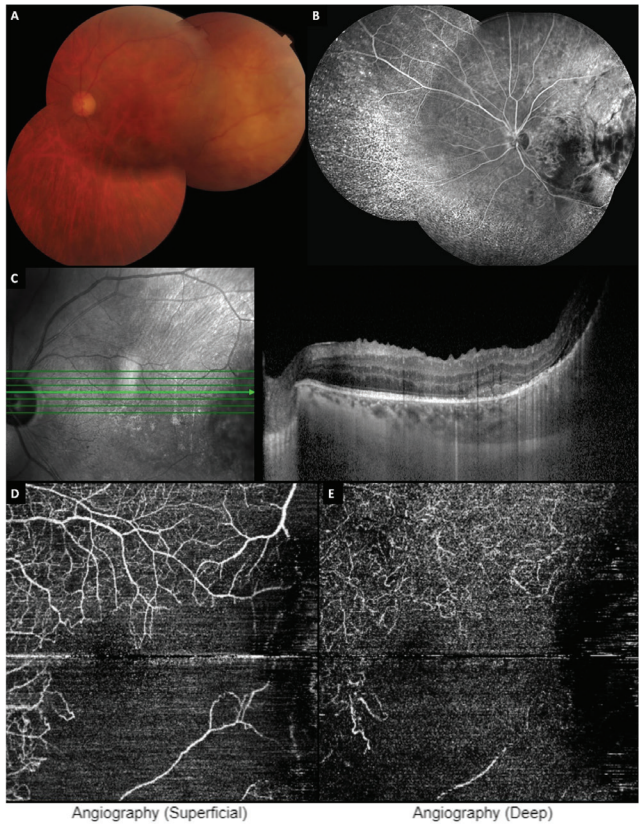

Figure 5. Two weeks after the second intravitreal injection (October 2022), left eye: A) Color fundus photograph showing the regressed tumor. B) Composite venous phase of fluorescein angiogram showing the disappearance of the previously present hyperfluorescent dots with macular non-perfusion-related hypofluorescence. C) Spectral domain optical coherence tomography section demonstrating reduced intraretinal fluid and some evidence of epiretinal membrane formation. D, E) Optical coherence tomography angiography depicting the areas of no flow in the superficial capillary plexus and deep capillary plexus slabs (6x6 mm) of the left fundus, respectively

Discussion

CyberKnife SRT is an image-guided, frameless, robotic system that comprises a focusing collimator allowing the precise application of the radiation beam in multiple directions. Retinal detachment, radiation papillopathy, radiation retinopathy, optic atrophy, radiation-induced cataract, vitreous hemorrhage, neovascular glaucoma, and loss of eye lashes are among the ocular adverse effects of CyberKnife SRT.[21,22]

CMMs derive their blood supply exclusively from the choroid. High radiation doses cause plugging of the blood vessels, depriving the tumor of its blood supply and thereby causing tumor necrosis.[23] The most common changes in irradiated RPE are atrophy, loss of melanin, accumulation of lipofuscin, and subsequent hyperplasia, which all occur partly as a direct consequence of irradiation and partly because of the vascular changes in the adjacent choroid. The uniform post-radiation response of the vasculature involves luminal irregularity, tortuosity, formation of microaneurysms, infiltration, loss of lumen, neovascularization, and fibrosis.[24] The release of inflammatory mediators and cytokines, such as tumor necrosis factor and interleukin-1, makes the necrotic tissue a potent irritant capable of inducing the clinical features of uveitis.[25]

MEWDS-like reaction appears to be an epiphenomenon that may be associated with clinical changes characterized by the disruption of the immediate subretinal anatomical tissue layers, including the choriocapillaris, Bruch's membrane, and RPE, as well as with an increased inflammatory response against the necrosed tumor.[11] Disruption of these layers may lead to destruction of the outer blood-retina barrier and subsequent loss of the immune privilege of the outer retina/ellipsoid region. Interaction between the immune system and retinal antigens may induce retinal autoantibody formation, which might lead to the transient inflammatory outer retinal changes typical of a MEWDS-like reaction.[13] Another possible mechanism of the MEWDS-like reaction may be a delayed type IV hypersensitivity.[11]

Boyd et al.[26] showed that vascular endothelial growth factor A and proinflammatory cytokines that cause impaired capillary permeability are elevated in the ocular fluids of eyes with treated and untreated CMM. Additionally, tumor irradiation induces an inflammatory response, tumor necrosis, and vessel damage.[27] Brour et al.[28] even reported a patient with CMM who was treated with proton beam irradiation and subsequently developed sympathetic ophthalmia. They claimed that proton beam irradiation could cause disruption of the uveal tissue, which enhanced the autoimmune reactions.[28] In our case, the MEWDS-like reaction might have occurred via all of the abovementioned mechanisms.

Cicinelli et al.[2] reported that MEWDS-like reaction corresponded to a transient disorder of the outer retina triggered by the local infectious or inflammatory environment. Serrar et al.[19] evaluated a total of 101 eyes of 100 patients (60 eyes of 59 patients with primary MEWDS and 41 eyes of 41 patients with secondary MEWDS) and found that the hypofluorescent lesions on late-phase ICGA were less extensive and less symmetric in secondary MEWDS than in primary MEWDS. They observed that the MEWDS lesions were mostly located in the same quadrant as the chorioretinal lesions in secondary MEWDS. Moreover, they also found that fundus autofluorescence (FAF) and ICGA showed fewer lesions, which were less likely to be centered at the posterior pole.[19] Patients with MEWDS-like reaction may not conform to the classical clinical findings, demographics, or natural history of primary MEWDS, and may not have a significant change on FAF, as in our patient.[2]

The pathogenesis of MEWDS-like reaction is uncertain, but damage at the level of RPE-Bruch's membrane and perhaps the loss of outer retinal integrity with exposure to new retinal antigens are believed to play a role and may be triggered by CyberKnife SRT or a proinflammatory environment created by the retinal tissue surrounding the CMM.

The administration of systemic corticosteroids was previously reported in a few cases of secondary MEWDS. Fung et al.[12] reported a case with ocular trauma-related subretinal hemorrhage who developed an atypical MEWDS-like reaction following the resolution of hemorrhage 10 weeks later. They administered oral prednisone with subsequent improvement in signs and symptoms. In a single-center case series of 167 consecutive patients with pseudoxanthoma elasticum, 9 patients developed secondary MEWDS and oral corticosteroid therapy was initiated in only one patient due to severe visual loss, presence of RAPD, and some vitreous cells.[13]

To our best knowledge, the present case is the first patient to receive intravitreal dexamethasone implants because of secondary MEWDS. However, unlike other MEWDS-like reactions, angiographic relapses occurred with the waning effect of the dexamethasone implant, most likely due to ongoing tumor necrosis syndrome. In light of the present case, clinicians should be aware of the development of MEWDS-like reaction following radiation therapies administered for the treatment of CMM.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: S.K., M.T., A.O.S., Design: S.K., M.T., A.O.S., Data Collection or Processing: S.K., M.T., A.O.S., Analysis or Interpretation: S.K., M.T., A.O.S., Literature Search: S.K., M.T., A.O.S., Writing: S.K., M.T., A.O.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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