VOGT–KOYANAGI–HARADA-LIKE UVEITIS FOLLOWED BY MELANOMA-ASSOCIATED RETINOPATHY WITH FOCAL CHORIORETINAL ATROPHY AND CHOROIDAL NEOVASCULARIZATION IN A PATIENT WITH METASTATIC CUTANEOUS MELANOMA

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Purpose: To report a case of Vogt–Koyanagi–Harada-like uveitis followed by melanoma-associated retinopathy with focal chorioretinal atrophy and subsequent choroidal neovascularization in a patient with metastatic cutaneous melanoma.

Method: Case report. Main outcome measures include external photography, anterior segment photography, ophthalmoscopic examination, fundus photography, fluorescein angiography, indocyanine green angiography, spectral domain optical coherence tomography, optical coherence tomography angiography, and electroretinography.

Results: A 68-year-old man with a history cutaneous melanoma presented with Vogt–Koyanagi–Harada-like uveitis. Work-up revealed a pelvic mass, which was excised and found to be metastatic melanoma. Two years later, the patient developed melanoma-associated retinopathy with focal chorioretinal atrophy and adjacent choroidal neovascularization.

Conclusion: Patients with metastatic cutaneous melanoma can develop distinct and sequential paraneoplastic ocular complications. Onset of a Vogt–Koyanagi–Harada-like uveitis may be a good prognostic factor for survival in patients with metastatic cutaneous melanoma.

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A number of paraneoplastic ocular complications of cutaneous melanoma have been reported. These have included melanoma-associated retinopathy (MAR), paraneoplastic vitelliform retinopathy, and Vogt–Koyangi–Harada (VKH)-like uveitis with
subsequent focal chorioretinal atrophy.\textsuperscript{1–5} We describe a patient with metastatic cutaneous melanoma who developed VKH-like uveitis followed by MAR and focal chorioretinal atrophy, complications reported previously, and who then developed choroidal neovascularization (CNV) adjacent to the areas of atrophy. To the best of our knowledge, this is the first report of the sequential development these three distinct complications of metastatic cutaneous melanoma.

**Case Report**

A 68-year-old White man presented for evaluation of decreased vision and floaters affecting both eyes. The medical history was notable for cutaneous melanoma of the right ankle diagnosed one year before presentation, and treated with surgical excision, including negative regional lymph node biopsies. A review of systems was notable for patchy loss of scalp hair over the past two months, and the occurrence of a diffuse skin rash, three months before presentation, which on biopsy was found to be consistent with dermatomyositis. On examination, the best-corrected visual acuity was 20/60 in the right eye and 20/80 in the left. There was diffuse poliosis of the scalp, eyebrows, and eye lashes, and vitiligo of the forehead skin by the hair line (Figure 1). Examination of the anterior segments revealed small keratic precipitates, mild anterior chamber inflammation, and trace anterior vitreous cell in both eyes. Posterior segment examination revealed bilateral findings of moderate vitreous haze, serous macular detachments, and numerous multifocal deep yellow–orange lesions in the posterior poles (Figure 2A). Fluorescein angiography revealed disk leakage and diffuse staining of the large retinal vessels, without retinal pigment epithelium (RPE) leaks, CNV, or cystoid macular edema (Figure 2B). Indocyanine green angiography showed numerous hypofluorescent spots in both eyes (Figure 2C). Optical coherence tomography (OCT) showed bilateral serous retinal detachments involving the central macula of both eyes (Figure 2D). Purified protein derivative testing was negative. Serologic evaluation that included a complete blood count, angiotensin converting enzyme and lysozyme levels, fluorescent treponemal antibody titers, a rapid plasma reagin test, antineutrophil cytoplasmatic antibodies, erythrocyte sedimentation rate, C-reactive protein, and serologic testing for exposure to Hepatitis B and C, HIV, and Borrelia burgdorferi were all normal or negative. Chest x-ray and magnetic resonance imaging of the brain were unremarkable, but a whole body computed tomography and positron emission tomography scan detected a pelvic mass. Surgical excision and histologic examination of the mass and its adjacent lymph nodes confirmed the diagnosis of metastatic melanoma, but no ensuing treatment with chemotherapy, radiation, or checkpoint inhibitor class medications was initiated. The patient was diagnosed with paraneoplastic VKH-like uveitis in the setting of metastatic cutaneous melanoma. He was treated with prednisone and given multiple posterior sub-Tenon’s corticosteroid injections bilaterally with eventual resolution of inflammation and disappearance of the multifocal yellow–orange lesions. The patient’s best-corrected visual acuity had recovered to 20/20 in the right eye and 20/25 in the left eye 1 year after initial presentation.

Two years later, the patient returned for evaluation of progressive nystagmus. The best-corrected visual acuity had reduced to 20/50 in the right eye and 20/40 in the left eye. Examination of both the anterior and posterior segments showed no intraocular inflammation. In both eyes, there were new focal areas of chorioretinal atrophy. Fluorescein angiography (not shown) revealed hyperfluorescent window defects in areas of RPE atrophy in both eyes. Humphrey visual field testing showed central and peripheral visual field loss in the right eye and a dense ring scotoma in the left eye. Full-field electroretinography (ERG) showed symmetrically normal a-waves with markedly attenuated b-waves in both eyes (Figure 3). A serum autoimmune retinopathy panel detected antibodies against enolase, arrestin, and pyruvate kinase M2 which, in combination with the results of functional testing, were felt to be consistent with a diagnosis of MAR. A repeat positron emission tomography–computed tomography scan showed no evidence of additional metastatic disease.

The patient subsequently returned for evaluation of worsening vision in the right eye and was found to have grayish subretinal material consistent with CNV and a small amount of subretinal hemorrhage along the foveal margin of two atrophic lesions in the inferior macula of the right eye (Figure 4, A and B). Fluorescein angiography (not shown) revealed late leakage from the CNV in the right eye. Optical coherence tomography angiography showed flow signal within type 2 CNV in the right macula (Figure 4C). Intravitreal bevacizumab (0.125 mg/0.05 mL) induced regression of CNV in the right eye, with the best-corrected visual acuity improving to 20/40.

**Discussion**

A 68-year-old man with metastatic cutaneous melanoma who was not treated with checkpoint inhibitor medications developed VKH-like uveitis that resolved with corticosteroid treatment. Two years later, he developed progressive nystagmus, and subsequent ERG and autoantibody testing confirmed the diagnosis of MAR. The patient was also noted to have bilateral, focal areas of chorioretinal atrophy and later developed adjacent CNV in the right eye.

It is noteworthy that our patient also had a diffuse rash that was found on biopsy to be consistent with dermatomyositis, yet another known systemic paraneoplastic complication of metastatic melanoma.\textsuperscript{1} Other reported nonocular paraneoplastic manifestations of metastatic melanoma include development of diffuse cutaneous melanosis with dark urine, halo nevi, cachexia, hyperparathyroidism, Cushing’s syndrome from tumor secretion of adrenocorticotropic hormone, disseminated intravascular coagulation, “hot spleen” phenomenon or reversal of the liver-spleen ratio as seen on single photon emission computed tomography, and eosinophilia.\textsuperscript{1} None of these were evident in our patient, however.
Paraneoplastic retinopathies have been reported in patients with metastatic melanoma and can be divided into three distinct clinical presentations: MAR, paraneoplastic vitelliform retinopathy, and VKH-like uveitis. At presentation, patients with MAR may have a normal fundus appearance. With time, however, retinal vascular attenuation, optic nerve pallor, vitreous cells, and RPE disruption may develop. All patients with MAR either have extinguished or electronegative waveform activity on ERG, and autoantibodies against retinal bipolar cells are frequently detected. More recently, bilateral vitelliform-like lesions have been described in patients with metastatic melanoma. Typical fundus findings include multifocal, yellow–orange vitelliform lesions associated with subretinal fluid, RPE detachments, and/or deposits of hyperreflective material involving the outer retinal layers or overlying the RPE on OCT. Various autoantibodies have been detected to support a paraneoplastic etiology, most notably those directed against retinal bipolar cells. Electoretinographic results have most commonly been normal, but reports of mild reductions in a and/or b-wave amplitudes and even electronegative patterns have been reported. The least commonly reported ocular paraneoplastic presentation in patients with metastatic melanoma is a VKH-like uveitis, which has only been described three times. In 1978, Sober and Haynes described spontaneous bilateral uveitis, poliosis, hypomelanosis, and alopecia in a patient with metastatic cutaneous melanoma. In 1984, Gass described a second patient with a history of excised cutaneous melanoma three years before presentation who subsequently developed progressive loss of vision to light perception in both eyes, progressive vitiligo of the skin of the face and arms, and deafness over a two-week span. This patient was found to have bilateral panuveitis with what was described as focal choroidal depigmentation and extinguished ERG responses. Lumbar puncture revealed pleocytosis of the cerebrospinal fluid. Biopsy of inguinal lymphadenopathy revealed metastatic melanoma, but full-body computed tomography was otherwise unremarkable. Gass published this case before the recognition of MAR, and the extinguished ERG suggested the simultaneous onset of both a VKH-like uveitis and MAR. Most recently, Aisenbrey et al described a patient with a history of excised cutaneous melanoma without detectable lymph node involvement who later developed alopecia, poliosis, vitiligo, bilateral panuveitis, optic disk edema, macular edema, and localized choroidal depigmentation and RPE atrophy.

Fig. 1. A. Anterior segment color photograph highlighting poliosis of patient’s eye lashes. B. Color photograph showing diffuse poliosis involving the patient’s hair and eyebrows, with vitiligo of the forehead near the hair line.

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Fig. 2. A. Color photograph of the left eye shows that despite partial obscuration of fundus details due to vitritis, scattered deep yellow lesions are visible. B. Late phase fluorescein angiography shows hyperfluorescent leakage at the optic nerve with diffuse staining of the large retinal vessels. C. Indocyanine green angiography shows multifocal areas of hypofluorescence that are more numerous than the clinically visible yellow choroidal lesions. D. Spectral domain OCT shows a serous detachment of the macula with obscuration of normal choroidal anatomic features. Similar imaging findings were present in the right eye.
The onset of a VKH-like uveitis may be a favorable prognostic indicator for longer survival in patients with metastatic melanoma. Vitiligo, a clinical finding often associated with VKH, has been associated with longer than expected survival in patients with metastatic melanoma and believed to be a reflection of the body’s successful immunologic suppression of the metastatic melanoma cells. Patients with metastatic melanoma treated with checkpoint inhibitors have also been reported to develop a VKH-like uveitis, again supporting the notion that this particular paraneoplastic presentation may represent a robust host immune response against the malignant cells. Aisenbrey et al postulated that long-term use of methotrexate to treat VKH-like disease in their patient may have contributed to the development of metastatic melanoma, which was diagnosed five years after initiation of immunomodulatory therapy and 10 years after initial diagnosis of cutaneous melanoma. All other reports of VKH-like uveitis were described in patients who were either known to have, or were concurrently diagnosed with, metastatic melanoma. The patient in our report was treated with long-term oral corticosteroid therapy and remains without signs of recurrent malignancy six years after presentation. Three of the four reported patients with metastatic melanoma and VKH-like uveitis have survived longer than expected for their diagnosis. The one patient who expired 15 months after diagnosis of metastatic melanoma appeared to possess both MAR and VKH-like uveitis at the time of presentation.

In addition to a VKH-like uveitis, patients who have received treatment with checkpoint inhibitor class medications for metastatic melanoma have also been reported to develop focal RPE or chorioretinal atrophy with or without subsequent CNV formation. The pathogenesis of the chorioretinal atrophy and subsequent CNV in this report likely resulted from a similarly potent immune response directed against melanocytes. Other reports have shared our observation that the resultant CNV responds well to intravitreal injections of bevacizumab or

Fig. 3. Electroretinogram showing normal a-wave amplitudes and markedly decreased b-wave amplitudes bilaterally.
ranibizumab, with resolution of subretinal fluid and regression or stabilization of the CNV.10

In summary, paraneoplastic ocular manifestations of metastatic cutaneous melanoma may present in three distinct forms: MAR, vitelliform retinopathy, or VKH-like uveitis. In addition, patients who present with VKH-like uveitis may develop later complications of focal chorioretinal atrophy with or without CNV. Our patient appears to have been the first to develop several sequential and distinct ocular paraneoplastic complications of metastatic cutaneous melanoma, including VKH-like uveitis with focal chorioretinal atrophy, MAR, and secondary CNV. Those few reported patients who did develop VKH-like uveitis after metastatic cutaneous melanoma tend to show better than expected overall outcomes.

Key words: choroidal neovascular membrane, cutaneous melanoma, melanoma-associated retinopathy, paraneoplastic retinopathy, Vogt–Koyanagi–Harada disease.

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