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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Short title: VKH-like uveitis then MAR from Melanoma

Summary/Precis: A case of Vogt-Koyanagi-Harada-like uveitis followed by melanoma-associated retinopathy with focal chorioretinal atrophy and choroidal neovascularization in a patient with metastatic cutaneous melanoma

Abstract

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

Observation: A 68-year-old man with a history cutaneous melanoma presented with VKH-like uveitis. Work up revealed a pelvic mass, which was excised and found to be metastatic melanoma. Two years later, the patient developed MAR with focal chorioretinal atrophy and adjacent CNV.

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

Keywords: Choroidal neovascular membrane; cutaneous melanoma; melanoma associated retinopathy; paraneoplastic retinopathy; Vogt-Koyanagi-Harada disease
Introduction

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 Vogt-Koyanagi-Harada (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 Presentation

A 68-year-old Caucasian man presented for evaluation of decreased vision and floaters affecting both eyes. Past medical history was notable for cutaneous melanoma of the right ankle diagnosed one year prior to 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 prior two months, and the occurrence of a diffuse skin rash, three months prior to presentation, which on biopsy was found to be consistent with dermatomyositis. On examination, best-corrected visual acuity (BCVA) was 20/60 in the right eye and 20/80 in the left. There was diffuse poliosis of 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 2 A). Fluorescein angiography revealed disc leakage and diffuse staining of the large retinal vessels, without retinal pigment epithelium (RPE) leaks, choroidal neovascularization (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 cytoplasmic antibodies, erythrocyte sedimentation rate, C-reactive protein, and serologic testing for exposure to Hepatitis B and C, human immunodeficiency virus, 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 (CT) and positron emission tomography (PET) 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 BCVA had recovered to 20/20 OD and 20/25 OS one year following initial presentation.

Two years later, the patient returned for evaluation of progressive nyctalopia. The BCVA 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 PET-CT 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 greyish 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 4A, B). Fluorescein
angiography (not shown) revealed late leakage from the CNV in the right eye. OCT angiography showed flow signal within type 2 CNV in the right macula (Figure 4C). Intravitreal bevacizumab (0.125mg/0.05ml) induced regression of CNV in the right eye, with BCVA improving to 20/40.

Discussion

A 68-year-old man with metastatic cutaneous melanoma that was not treated with checkpoint inhibitor medications developed VKH-like uveitis that resolved with corticosteroid treatment. Two years later he developed progressive nyctalopia 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 patients also had a diffuse rash that was found on biopsy to be consistent with dermatomyositis, yet another known systemic paraneoplastic complication of metastatic melanoma. Other reported non-ocular 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 computer tomography, and eosinophilia. 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 hyper-reflective 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. Electroretinographic 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 prior to 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 CT was otherwise unremarkable. Gass published this case prior to 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 disc edema, macular edema, and localized choroidal depigmentation and RPE atrophy.

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 thought 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 ten 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 following 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 following 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 ranibizumab, with resolution of subretinal fluid and regression or stabilization of the CNV.

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 following metastatic cutaneous melanoma tended to show better than expected overall outcomes.

References


9. Cunningham ET, Moorthy RS, Zierhut M. Immune Checkpoint Inhibitor-Induced Uveitis, Ocular Immunology and Inflammation. 2020 Sep 1;28(6):847-49.

10. Elwood KF, Pulido JS, Ghafoori SD, et al. CHOROIDAL NEOVASCULARIZATION AND CHORIORETINAL ATROPHY IN A PATIENT WITH MELANOMA-ASSOCIATED
RETINOPATHY AFTER IPILIMUMAB/NIVOLUMAB COMBINATION THERAPY. Retinal Cases & Brief Reports. 2019 Jun 25.

Figures

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

Figure 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 optical coherence tomography shows a serous detachment of the macula with obscuration of normal choroidal anatomic features. Similar imaging findings were present in the right eye.

Figure 3 - Electroretinogram showing normal a-wave amplitudes and markedly decreased b-wave amplitudes bilaterally.

Figure 4 – Color fundus photograph of the right (A) and left (B) eyes showing several focal areas of chorioretinal atrophy. Greyish subretinal material and subretinal hemorrhage is visible at the foveal margin of two atrophic lesions in the inferior macula of the right eye. A magnified view of the right fundus photograph with a superimposed en face optical coherence tomography (OCT) angiography projection of the outer retina (C) shows type 2 neovascular flow signal corresponding to the clinically visible choroidal neovascularization.
(CNV). A 20µ thick *en face* structural OCT slab taken 40µ anterior to retinal pigment epithelium shows subretinal hyperreflective material corresponding to CNV (D).